Indolent lymphoma: diagnostic, prognostic and therapeutic paradoxes

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Indolent lymphoma

Diagnostic, prognostic and therapeutic paradoxes

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Indolent lymphoma

Diagnostic, prognostic and therapeutic paradoxes

PROEFSCHRIFT

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aan de Universiteit Maastricht,
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in het openbaar te verdedigen
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"Learns to say "I don't know." If used when appropriate, it will be often."

Donald Rumsfeld.

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Chapter 1

Introduction

Introduction

Follicular lymphoma currently represents one of the most common and easily recognized variants of lymphoma. Great strides have been made in the understanding of its pathobiology, in determination of prognostic features and in its management. This review of its history illustrates the dramatic advances that have been made in biology and medicine, starting in the mid 19th century.

1. Initial descriptions of follicular lymphoma

Rudolph Virchow, the leading German pathologist from the mid- to the late 19th century, is generally considered the founder of cellular pathology, the discipline that relates disease processes to changes in cell physiology and morphology. Virchow's numerous contributions include the original description in 1845 of leukemia, a disease characterized by an increase in the "colorless corpuscles of the blood" and often associated with splenomegaly and lymphadenopathy.¹ The first descriptions of lymphoma came approximately 20 years later when Cohnheim, a pupil of Virchow, described a case of "pseudoleukemia".² This case involved a 24 year old man who died after a short illness characterized by lymphadenopathy and massive splenomegaly, but surprisingly, without leucocytosis. At autopsy, proliferating lymphocytes were found infiltrating most organs, but, surprisingly to the authors and in contrast to leukemia, involvement of the blood was absent.

Numerous other reports followed and, it was rapidly recognized that many different types of lymphoma exist, but the normal counterparts for lymphoma cells remained elusive. This resulted in complex, contradictory and perpetually changing classification systems and a bewildering variety of nomenclature. (For an excellent overview of the evolution of concepts of lymphoma classification, we refer to the excellent book chapter by Magrath.³) It is only in the past two decades, with an understanding of T- and B-cell immunology and of cytogenetics that classifications of lymphoma have become more rooted in biology and increasingly logical. Amid the confusion of the late nineteenth and early twentieth century lymphoma classification two entities, Hodgkin's disease and follicular lymphoma were however relatively reliably recognized because of their unique morphological features.

The first systematic description of follicular lymphoma was by Brill et al in 1925.⁴ They reported two young patients, age 28 and 32 who presented with lymphadenopathy and massive splenomegaly. The lymph node biopsy showed giant follicular hyperplasia. One of the patients was icteric and might have had concomitant hemolysis. Both patients had dramatic and prolonged responses to radiation therapy, a treatment modality that had then already been in use for

about twenty years. The authors recalled seeing one similar patient ten years earlier and referred to an additional case reported in 1901. Shortly thereafter, Symmers reported three additional cases, one of them occurring in a child.⁵ Both Brill and Symmers initially considered this giant follicular hyperplasia to represent a benign entity which became widely known as Brill-Symmers disease. But over the ensuing two decades, it was recognized that Brill-Symmers disease did constitute a malignancy, and that transformation to more aggressive form of lymphoma was possible.⁶ In 1941 Gall, Morrison and Scott published the first large series of 63 consecutive cases seen at the Massachusetts General Hospital between 1917 and 1939 and thus contributed considerably to our understanding of the clinical features of follicular lymphoma.⁷ Lymphadenopathy was often widespread at diagnosis in their patients and splenomegaly was commonly present. Involvement of extranodal organs was unusual. They did not seem aware of the frequent occurrence of bone marrow involvement in follicular lymphoma, probably because bone marrow aspiration and biopsy were not a routine procedures yet.⁸ They described the indolent course of, and prolonged survival in many cases of follicular lymphoma. Twenty percent of their patients had died within two years of diagnosis as compared with 56% of patients with other types of lymphoma. Eleven percent of patients were still alive ten years after diagnosis. The same authors also emphasized the exquisite radiosensitivity of follicular lymphoma and the frequent observation of very prolonged responses after treatment with kilovoltage radiation. Finally they recognized a histologic continuum from very low grade to histologically more aggressive follicular lymphoma. They recognized four subtypes, more or less akin to our current understanding of grades I, II and III follicular lymphoma.

Rappaport reported in 1956 the next large series of 253 cases reviewed at the Armed Forces Institute of Pathology.⁹ He essentially confirmed the observations of Gall, but attempted to explain them in the framework of a classification of lymphoma that was based on cytology rather than on lymph node architecture. He questioned the concept of follicular lymphoma as a separate clinical and pathological entity, and emphasized the importance of cytological features, thus linking each cytological subtype of follicular lymphoma with a counterpart in the diffuse lymphomas. He suggested that "follicular lymphoma was not a distinct disease entity, but a variant of diffuse lymphoma of corresponding cellular composition" For every form of diffuse lymphoma, there was a nodular counterpart. His hypothesis and classification gained widespread acceptance in the US. Since then, new insights in biology have clearly established follicular lymphoma as an entity with a unique biology, quite different from large cell lymphoma.

Thus, over the first half of the twentieth century, the morphology, clinical presentation and natural history of follicular lymphoma were defined. The sensitivity of follicular lymphoma to radiation was recognized almost immediately and radiation was the treatment of choice for more than half a century. Of interest, it appears that follicular lymphoma was a much less common neoplasm in the first half of the century than it is currently. For example, it constituted only 5% of all cases of lymphoma in the series reported by Gall and Mallory.¹⁰ The relative rarity of follicular lymphoma in the Western hemisphere during the first half of the century, is reminiscent of the current incidence of lymphoma in Asia and Africa.¹¹ Its increased incidence in recent decades is likely in part related to increased recognition and to increases in life expectancy. But other unrecognized possibly environmental or dietary changes might also play a role.

2. The biology of follicular lymphoma

Our understanding of the pathobiology of lymphoma has dramatically increased over the past twenty years. This has affected diagnostic and therapeutic strategies and is starting to affect survival.

The recognition that the immune system is composed mainly of T- and B-cells and the development of monoclonal antibodies in the 1970's allowed a biological characterization of lymphomas¹² and established the germinal center B-cell as the normal counterpart of the follicular lymphoma cell.¹³⁻¹⁵ The phenotype of follicular lymphoma cells is well characterized and a number of surface antigens have been exploited as therapeutic targets for drugs such as rituximab (anti-CD20), alemtuzumab (anti-CD52), and galiximab (anti-CD 80). Cytogenetic studies documented a consistent abnormality t(14;18) in the majority of follicular lymphomas.¹⁶ Shortly thereafter, the t(14;18) breakpoint was cloned and the *bcl-2* gene described.¹⁷ *Bcl-2* turned out to be an anti-apoptotic gene, with a central function in the regulation of cell survival. The study of *bcl-2* led to a paradigm shift in the understanding of the role of apoptosis in cancer, and in follicular lymphoma in particular.¹⁸⁻²⁰ Our current understanding of follicular lymphoma is that of a clonal disorder of follicle center cells, whose expansion is driven by overexpression of *bcl-2*, resulting in increased accumulation of cells rather than increased proliferation. But several observations suggest that *bcl-2* overexpression is not sufficient, and possibly not even necessary for lymphomagenesis. First, in mouse models *bcl-2* overexpression alone leads to lymphoid hyperplasia, but additional mutations seem necessary for development of lymphoma.²¹ In humans, the presence of complex karyotypic abnormalities is the rule in follicular lymphoma.²² Translocation t(14;18) is rarely the sole abnormality. The great majority of

these secondary changes are unbalanced gains or losses of chromosomal material, with balanced translocations quite infrequent. The sequence by which these additional changes arise, whether certain alterations develop independently or in combination, and the influence these accumulating genetic changes exert individually or collectively on clinical behavior have not been determined, although certain models of karyotypic evolution have been proposed.²² Furthermore, a small number of cells carrying *bcl-2* gene rearrangements are also found in lymphoid tissues or blood of a small percentage of healthy individuals suggesting that *bcl-2* gene rearrangement does not always cause pathology. Finally, *bcl-2* rearrangement negative follicular lymphomas are not uncommon raising the possibility of alternative molecular events that may give rise to follicular lymphoma.¹¹

Much remains also to be learned about the factors underlying the marked heterogeneity in clinical course of follicular lymphomas. Some patients have an extremely indolent course and never require treatment or even experience spontaneous remissions. But others have a much more aggressive course and about ten percent of patients die within three years of diagnosis. Karyotypic, immunophenotypic or gene expression differences have only limited prognostic significance. Gene array technology has provided a novel platform for research. It was widely anticipated that specific gene expression profiles of the lymphoma cells would correlate with prognosis, as has been demonstrated in diffuse large B-cell lymphoma.^{23,24} A recent study however suggests that clinical heterogeneity in follicular lymphoma is related to gene expression signatures of the non-malignant cells that infiltrate the tumor (T-cells, dendritic cells, macrophages), rather than to differences in the lymphoma cells.²⁵ This suggests an important role for the immune system in controlling growth of follicular lymphoma and is consistent with a recent study in which a correlation was shown between the degree of macrophage infiltration into the lymphoma and patient survival.²⁶ In a recent review, a model has been proposed in which the pathogenesis of follicular lymphoma is determined by cross-talk between the malignant population and the immune system.²⁷ Different types of secondary cytogenetic lesions in the malignant population then determine specific immune response signatures.

As such, follicular lymphoma has evolved over the past twenty years from an entity defined by purely histological criteria into a malignancy with a partially elucidated biology and pathogenesis and an increasing array of disease-modifying factors. New treatments have been envisioned based on the accumulating biologic information. Those based on anti-CD20 in particular have been spectacularly successful, and the recognition of the central role of *t*(14;18) and *bcl-2* gene rearrangement has led to specific diagnostic and therapeutic strategies.

Great gaps though remain in our knowledge of etiology and of risk factors for this disorder that occurs with increasing frequency in the western world. Geographical variation in incidence and the frequent occurrence of cases without detectable bcl-2 gene rearrangement in the Far East and Africa, raise important unresolved questions regarding the biology of the disease and its causative factors.¹¹

3. Treatment for follicular lymphoma

From its earliest descriptions, follicular lymphoma was recognized as a radiotherapy sensitive disorder with an indolent course. This indolent behavior and the difficulty in predicting prognosis in individual patients have considerably complicated drug development. A substantial proportion of patients may never require treatment, and ideally, in order to demonstrate the benefit of a new approach, randomized studies are required. This is a difficult task in a rather uncommon disorder with a prolonged natural history, and nearly impossible when complex treatments such as bone marrow transplantation are concerned. In order to facilitate clinical studies, a number of surrogate markers of outcome have been proposed, but for none of them has a correlation with survival been validated.²⁸

The development of an internationally validated prognostic index, the FLIPI provides some hope for improved categorization for patients in clinical studies.²⁹ But the FLIPI is based on demographic and clinical information and is a somewhat limited instrument. Prognostic models that incorporate biologic information, such as those based on gene expression profiles, are potentially much more powerful, but require validation.

Still despite such limitations, progress has been made and in the past decade improvements in survival of follicular lymphoma patients have been repeatedly demonstrated in randomized studies and meta-analysis.³⁰⁻³² This achievement is the result of decades of formal and informal, empirical, and more recently hypothesis-driven experimentation. A large number of therapeutic agents and modalities have been utilized.

a. Radiation therapy

X-rays were discovered by Conrad Roentgen in 1896 and by 1901 were used for therapy of cancers. The sensitivity of lymphoma to radiotherapy became rapidly apparent.¹⁰ Radiation became the treatment of choice for all types of lymphoma and the older literature states that "radiosensitivity was even utilized as a diagnostic criterion for tumors not accessible for histologic study".¹⁰ In general, responses of lymphoma to radiation were incomplete and short lived,

but follicular lymphoma was remarkable because of its higher incidence of complete and prolonged responses.^{4,7} Even today, radiation remains a valuable tool in the treatment of follicular lymphoma, particularly in stage I and II disease, where radiation, sometimes combined with chemotherapy, is considered a curative form of therapy.³³⁻³⁶ Total lymphoid irradiation has also been studied in stage III disease. Five year progression-free survival rates range from 40% to 60%.³⁷⁻³⁹

b. Chemotherapy

Combination chemotherapy was initially studied in childhood ALL and many of the principles of modern day chemotherapy derive from these initial studies.⁴⁰ The first trials of combination chemotherapy in lymphoma date back to the 70's.⁴¹ Curative therapy for aggressive lymphoma and Hodgkin's disease was discovered, but in follicular lymphoma, initial optimism was followed by disappointment. With the possible exception of some small subgroups of patients, chemotherapy was not curative or did not seem to improve survival.⁴² CHOP chemotherapy did not seem much more effective than single agent chemotherapy and CVP or single agent chemotherapy did not extend life beyond what could be achieved with observation and treatment of symptoms (watchful waiting).⁴³⁻⁴⁵

Newer chemotherapeutic agents such as the nucleoside analogues have considerable activity in follicular lymphoma, but similarly were not shown to be superior in randomized studies.⁴⁶

c. Biological response modifiers

The biological response modifier interferon alpha generated considerable excitement as a potential anti-cancer agent shortly after its purification.⁴⁷⁻⁴⁹ In phase II trials, purified and subsequently recombinant interferon was found to have considerable activity in follicular lymphoma, but was not curative.⁵⁰⁻⁵³ Randomized studies were conducted with recombinant interferon in combination with chemotherapy or as maintenance therapy after completion of chemotherapy in patients with advanced follicular lymphoma. Several such trials did show a survival benefit, and interferon is approved for use in follicular lymphoma in the US as well as Europe.⁵⁴⁻⁵⁷ Negative or disappointing results of other trials,⁵⁸⁻⁶⁴ toxicity of interferon, inconvenience of administration caused a decline in interest,⁶⁵ and interferon is currently rarely used for treatment of follicular lymphoma in the US. Such a neglect may not be entirely justified as a recent meta-analysis confirms the significant survival benefit associated with appropriate interferon therapy.⁶⁶ A survival advantage was associated with interferon in those studies in which it was given in rather high doses, in

combination with intensive chemotherapy and as part of induction treatment, rather than merely as maintenance.

d. Autologous and allogeneic transplantation

High dose chemotherapy has been extensively studied in low grade lymphoma and also shows great promise. As opposed to all other types of therapy high dose chemotherapy with autologous or allogeneic transplant appears to be curative for a significant portion of younger patient with follicular lymphoma.⁶⁷ Recent investigations have focused on elucidating the mechanisms of treatment failure in autologous transplantation and on dissecting the relative contributions of GVL vs chemotherapy effects in allogeneic transplantation.⁶⁸⁻⁷⁰ The complexity of the treatment and the associated side effects have limited widespread use of transplantation, though for certain patients with recurrent disease, allogeneic or autologous transplantation represent the best treatment options and are associated with a survival benefit.³¹ The use of autologous transplantation as consolidation therapy for high risk patients in first remission has also been investigated in three large randomized studies in Europe. It consistently has improved progression free survival when compared to intensive chemotherapy followed by interferon maintenance, but until now two of three randomized studies have failed to demonstrate a survival benefit.⁷¹⁻⁷³

e. Targeted therapy

Targeted approaches, in particular humanized monoclonal antibodies directed against anti-CD20 have revolutionized the treatment of lymphoma. The development of these antibodies represents a fascinating chapter of hypothesis driven research, dating back to the late 19th century when Ehrlich formulated his theory of the magic bullet in cancer. through the development of monoclonal antibody technology by Kohler and Milstein and the design of humanized antibodies over the past decade.⁷⁴ The first murine monoclonals were used in human lymphoma patients in 1980.⁷⁵ Rituximab was approved in the late 90's and represents a great addition to the armamentarium in follicular lymphoma.⁷⁶ As a single agent, it induces complete or partial responses in a large percentage of patients.⁷⁷ In combination with commonly used chemotherapy regimens, it improves remission rates and duration of remission with minimal side-effects.⁷⁸⁻⁸⁰ It is widely expected that a considerable survival benefit will become apparent as the randomized studies mature. Rituximab may also have a role in combination with autologous or allogeneic stem cell transplantation where it may serve as a purging agent for stem cells and may prolong remissions when administered as maintenance therapy.⁸¹⁻⁸³ The radiolabelled monoclonal antibodies Tositumomab (Bexxar) and ibritumomab tiuxetan (Zevalin) also target CD 20, but cause tumor destruction by radiation.

These antibodies are currently approved for use in recurrent follicular lymphoma, but may ultimately find a role in the initial treatment of follicular lymphoma.⁸⁴⁻⁸⁶ Other antibodies at various stages of development include anti-CD22, anti-HLA DR and anti-CD80.⁸⁷⁻⁸⁹ Anti-idiotypic antibodies are based on the principle of idiotype networks. Phase I and II development has been completed.^{90,91} Two phase III studies are nearing completion.

Finally, anti-sense oligonucleotides are molecules directed against specific strands of messenger RNA. Anti-bcl-2 (genasense, oblimersen sodium) interrupts the action of bcl-2 and has activity in follicular lymphoma.⁹² It is currently undergoing testing in combination with chemotherapeutic agents and monoclonal antibodies.⁹³ In another exciting development, a peptide that specifically inhibits bcl-2 shows great promise in clinical models.⁹⁴

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Chapter 2

Allogeneic bone marrow transplantation for poor-prognosis lymphoma: response, toxicity, and survival depend on disease histology

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Abstract

Purpose

To evaluate outcomes and identify prognostic factors in allogeneic bone marrow transplantation in patients with end-stage lymphoma.

Patients and methods

Data were retrospectively analyzed of 64 patients (42 men and 22 women) 18 to 48 years of age with recurrent or refractory lymphoma who underwent allogeneic bone marrow transplantation from matched sibling donors (or in 1 case from a one antigen-mismatched relative) between May 1981 and July 1994.

Results

Twelve patients survived free of disease. They were 8 of 15 with low-grade lymphoma (disease-free survival at 2 years $59 \pm 13\%$); 3 of 25 with lymphoblastic lymphoma (disease-free survival $17 \pm 8\%$); and 1 of 10 with diffuse small non-cleaved cell lymphoma (disease-free survival $10 \pm 9\%$). Survival and disease-free survival of patients with low-grade lymphoma were significantly superior compared to any other subgroup of patients ($P < 0.01$). Only 2 patients with low-grade lymphoma had disease progression ($9 \pm 5.9\%$ actuarial risk at 2 years) as opposed to 5 of 15 with intermediate-grade lymphoma ($39 \pm 14\%$), 9 of 25 with lymphoblastic lymphoma ($28 \pm 9\%$), and 8 of 10 ($80 \pm 13\%$) with diffuse small non-cleaved lymphoma. The actuarial risk for disease progression was significantly lower for patients with low-grade lymphoma than for any other histologic subgroup ($P < 0.02$). It was significantly higher for those with diffuse small non-cleaved cell lymphoma than for other histologic subgroups ($P \leq 0.003$).

Conclusions

Allogeneic bone marrow transplantation is an effective procedure in patients with refractory low-grade lymphoma. It results in long-term remissions and should be considered in younger patients with recurrent disease who have a matched sibling donor. The late recurrence in 1 patient indicates the necessity of continued follow-up. A small fraction of patients with endstage intermediate- and high-grade lymphoma can obtain prolonged disease-free survival, but recurrence and regimen-related toxicity remain major problems. The results could be improved by the development of conditioning regimens with less toxicity and by the use of bone marrow transplantation earlier in the course of the disease.

Introduction

Fifty to 60% of patients with lymphoma achieve a complete remission with conventional treatments.¹⁻³ Approximately 40% of those with intermediate- and high-grade lymphomas and a small percentage of those with low-grade lymphomas can be cured. Salvage treatment is effective in approximately 40% of patients, and some of these cases can be successfully consolidated with high-dose chemotherapy and bone marrow or stem cell rescue.^{3,4} The majority of patients ultimately fail both front-line and salvage regimens. Such patients only rarely benefit from autologous bone marrow transplantation (BMT) and ought to be considered for more aggressive treatment strategies.

Allogeneic BMT has been extensively evaluated in the treatment of recurrent lymphomas. A substantial portion of patients with recurrent or refractory lymphoma obtain prolonged disease-free survival after treatment with allogeneic BMT.⁵⁻¹³ In three series, the incidence of recurrence was lower among patients receiving allogeneic BMT compared with those receiving autologous BMT.^{11,13,14} This has been attributed to a graft versus lymphoma effect. Unfortunately, there is a higher risk of treatment-related mortality after allogeneic BMT, which has offset the impact of this graft versus lymphoma effect and obscured the identification of patients whose disease may be susceptible to such an effect. It has also led most centers to consider allogeneic BMT mainly for patients who do not qualify for autologous BMT because of bone marrow or peripheral blood involvement or the presence of refractory disease. This review of our institutional experience with allogeneic BMT focuses on patients with such high-risk features and highlights the importance of disease histology in determining the response to and outcome of allogeneic BMT.

Patients and methods

From May 1981 until July 1994, 64 patients with non-Hodgkin's lymphoma underwent allogeneic BMT at our institutions. Eligibility criteria included age ≤ 50 years, Karnofsky performance status (KPS) $\geq 60\%$, bilirubin ≤ 2 mg/dl, creatinine < 1.5 times normal, adequate pulmonary function (forced expiratory volume in 1 second and diffusing lung capacity $\geq 50\%$ of predicted), and adequate cardiac function (left ventricular ejection fraction $\geq 50\%$). Patients with HIV-related lymphoma were not eligible. Allogeneic BMT was considered for patients with primary chemotherapy-refractory disease and for those with recurrent disease, whether responsive or unresponsive to chemotherapy. Bone marrow involvement was allowed. Refractory disease was defined as a $< 25\%$ reduction in the sum of the products of the two greatest perpendicular

diameters of measurable lesions despite treatment with combination chemotherapy regimens.

The histologic diagnosis was confirmed by review of the original biopsy specimens upon referral of the patient to our institution. Additional biopsies were performed at relapse, whenever possible, to rule out transformation.

Patients were categorized in the following histologic groups: low-grade lymphoma (Working Formulation A-C), intermediate-grade lymphoma (Working Formulation D-G; but also including H, innumoblastic lymphoma), lymphoblastic lymphoma (Working Formulation I), and diffuse small non-cleaved cell lymphoma (Working Formulation J).¹⁵ One patient with a diffuse mantle zone lymphoma was included among those with low-grade lymphoma.¹⁶ One patient with a follicular large cell lymphoma was categorized as low-grade lymphoma, based on the indolent course of the disease, the preponderance of cleaved cells, and a low DNA index.¹⁷

Conditioning regimens, donor selection, and GVHD prophylaxis

All patients provided written informed consent and were treated according to protocols approved by the institutional review boards. A number of different conditioning regimens were tested during the period covered by this report. Total body irradiation (TBI)-containing regimens included: cyclophosphamide 120 mg/kg and TBI (n=10); cyclophosphamide 120 mg/kg, etoposide 1,500 mg/m², and TBI (n=16)¹⁸; melphalan 140 mg/kg and TBI (n=4)¹⁹; cyclophosphamide 120 mg/kg, TBI, and total lymphoid irradiation (n=5)²⁰; carmustine 300 mg/m², cytarabine 800 mg/m², thioguanine 800 mg/m², cyclophosphamide 200 mg/m² and TBI (n=1); and piperazinedione 50 mg/m² and TBI (n=1).²¹ Twentyseven patients received high-dose chemotherapy without TBI. Regimens included: busulfan 16 mg/kg and cyclophosphamide (n=3)⁶; thiotepa 750 mg/kg, busulfan 10 mg/kg, and cyclophosphamide 120 to 150 mg/kg (TBC) (n=9)²²; double consolidation with high-dose cyclophosphamide 5.25 g/m², etoposide 1,200 mg/m², and platinum 135 mg/m² followed by TBC (n=12)²³; cyclophosphamide 6 g/m², carmustine 300 mg/m², and etoposide 900 mg/m² (n=2)¹³; and carmustine 300 mg/m², etoposide 1,600 mg/m², cytarabine 1,600 mg/m², and melphalan 140 mg/m² (n=1).²⁴

Donors were human leukocyte antigen-identical siblings or, in 1 case, a one antigen-mismatched relative. Fifty-nine patients received unmanipulated marrow. Five patients received a T-cell depleted marrow after conditioning with etoposide, cyclophosphamide, TBI, and total lymphoid irradiation.²⁰ Graft versus host disease (GVHD) prophylaxis consisted of cyclosporine alone (n=5); cyclosporine and short-course methotrexate (n=28),²⁵ cyclosporine and corticosteroids (n=19),²⁶ cyclosporine and T-cell depletion (n=5); and

tacrolimus (FK506) and methotrexate ($n=1$). Six patients treated in the early 1980s received combinations of corticosteroids and methotrexate.

Supportive care

All patients were treated in laminar air flow rooms or in high-efficiency, particulate-free air rooms with strict reverse isolation. Infection prophylaxis changed considerably over the period covered by this report. The initial patients received nonabsorbable antibiotics and acyclovir prophylaxis. More recently, patients received prophylaxis against *Pneumocystis carinii*, cytomegalovirus, and fungal infections.²⁷⁻²⁹ Irradiated blood products were administered to maintain a haemoglobin level >8 g/dl and platelet count $>20 \times 10^9/l$. Patients treated after 1990 received growth factor support with recombinant human granulocyte colony stimulating factor, 5 mg/kg per day subcutaneously, beginning on day 0 until recovery of granulopoiesis.

Post-transplant evaluation and response criteria

Patients were evaluated for acute and chronic GVHD, and GVHD was scored and treated according to standard criteria.^{30,31}

Response to therapy was evaluated by physical examination; blood counts; chest roentgenogram; computed tomography of the chest, abdomen, and pelvis; and bilateral marrow aspiration and biopsy.

Additional tests such as immunophenotype analysis of the blood and bone marrow, lymph node aspiration, and biopsy were performed when clinically indicated. Response was evaluated at 6 weeks, 3 months, 6 months, and 1 year after transplant, and annually thereafter.

Complete remission was defined as disappearance of all disease and symptoms related to lymphoma for more than 1 month. Partial remission was defined as greater than 50% reduction in the sum of the products of the two greatest perpendicular diameters of measurable lesions for more than 1 month. All other outcomes were considered treatment failures.

Statistical analysis

The end points included: (1) survival (interval from the day of BMT until death or end of follow-up); (2) disease-free survival (interval from the day of BMT until disease progression, death due to disease or its treatment, or end of follow-up); and (3) time to progression (interval from BMT until disease progression.) Survival curves were estimated using the method of Kaplan and Meier.³² Survival curves were compared by the log rank test.³³

The variables evaluated were: (1) histologic group, (2) conditioning (TBI versus non-TBI), (3) use of double consolidation versus single consolidation, (4)

performance status at the time of BMT (KPS <80 versus ≥ 80), and (5) decade of transplantation (BMT before 1990 versus BMT since 1990).

Because a poor performance status and the use of double consolidation were found to adversely affect survival and disease-free survival, the analysis was repeated for those patients receiving single consolidation and with a good performance status (KPS ≥ 80) at BMT (n=42).

Results

Patient characteristics, conditioning therapy, and GVHD prophylaxis are summarized in Table 2.1. As indicated, these were heavily pre-treated patients with refractory or multiply recurrent disease. The median follow-up for surviving patients is 38 months (range 10 to 171).

Figure 2.1 indicates actuarial survival and disease-free survival for patients according to histologic subtype. Ten of 15 patients with low-grade lymphoma were alive and 8 were free of disease at last follow-up (2-year survival $65\pm 13\%$; disease-free survival $59\pm 13\%$). One of 14 patients with intermediate-grade lymphoma was alive at last follow-up (2-year survival $21\pm 9\%$). He relapsed 2 years after allogeneic BMT but underwent a successful second transplantation. Four of 25 patients with lymphoblastic lymphoma were alive at last follow-up (2-year survival $21\pm 9\%$). Three were free of disease (2-year disease-free survival $17\pm 8\%$), but 1 had relapsed 38 months after BMT. One additional patient, who had central nervous system and testicular involvement at the time of transplantation, survived 6 years after BMT with mild GVHD but then died from fulminant sepsis.²⁴ One of 10 patients with diffuse small non-cleaved cell (DSNCC) lymphoma is a long-term (>14 years) disease-free survivor (2-year survival and disease-free survival $10\pm 9\%$). The survival and disease-free survival for patients with low-grade lymphoma was significantly superior to any other subgroup of patients (log rank test $P<0.01$).

Table 2.2 shows the causes of death and Figure 2.2 the probability of disease progression associated with the different histologies. Two patients with low-grade lymphoma had disease progression. One patient relapsed 6 months after transplantation with a transformed lymphoma. A second patient with chronic GVHD developed recurrent low-grade lymphoma 4 years after transplantation. Both appear to be responding to cyclosporine withdrawal.

Disease progression occurred in 5 patients with intermediate-grade lymphoma (2-year risk of progression $39\pm 14\%$), 9 patients with lymphoblastic lymphoma (2-year risk $28\pm 9\%$), and 8 patients with DSNCC lymphoma (2-year risk $80\pm 13\%$). The actuarial risk of progression was significantly higher in patients with DSNCC lymphoma than in any other subgroup of patients (log rank test $P<0.003$). Patients with DSNCC lymphoma tended to have extremely rapid

disease progression after BMT. Seven of the 8 recurrences in this group occurred within 2 months. On the other hand, the actuarial risk for progression was significantly lower in patients with low-grade lymphoma than in any other histologic subgroup ($P<0.02$).

Table 2.1 Patient characteristics, conditioning, regimens, and GVHD Prophylaxis by histologic subtype.

	Low Grade	Intermediate Grade	Lymphoblastic	DSNCC ^a
Number	15 ^a	14 ^b	25	10
Median age (y)	36	34	30	26
Range	27-45	22-48	18-45	12-43
Sex				
Men	10	11	15	6
Women	5	3	10	4
Disease state				
First relapse, untreated	-	4	-	-
First relapse, sensitive	1	1	7	1
Refractory diseases or >1 recurrence	14	13	14	9
Median # prior treatment regimens	3	3	2	3
Range	2-6	1-5	1-4	2-6
Median interval from diagnosis to BMT (m)	29	15	13	8
Range	11-89	5-182	5-36	3-21
Performance status at BMT				
80-100	13 (87%)	10 (71%)	19 (76%)	7 (70%)
≤70	2 (23%)	4 (29%)	6 (24%)	3 (30%)
Stage at conditioning				
O	-	2	6	2
II	-	2	2	-
III	2	3	-	-
IV	13	7	17	8
Conditioning regimen				
With TBI	13	5	12	7
Without TBI	2	9	13	3
GVHD prophylaxis				
Cyclosporine	13	14	16	9
Tacrolimus (FK506)	-	-	1	-
No cyclosporine	1	0	4	1
T-cell depletion + cyclosporine	1	0	4	0

^a Includes 2 diffuse well differentiated lymphocytic lymphoma, 6 follicular small cleaved cell lymphoma, 5 follicular mixed cell lymphoma, 1 follicular large cell lymphoma, and 1 diffuse mantle zone lymphoma.

^b Includes 9 diffuse large cell lymphoma, 1 diffuse mixed cell lymphoma, 3 primary mediastinal large cell lymphoma, and 1 transformed CLL.

GVHD=graft versus host disease; DSNCC=diffuse small non-cleaved cell; BMT=bone marrow transplantation; TBI=total body irradiation.

Figure 2.1 A. Survival after allogeneic BMT for lymphoma according to histologic subtype. B. Disease-free survival after allogeneic BMT for lymphoma according to histologic subtype. (—) Diffuse small non-cleaved, (---) Intermediate grade, (.....) Lymphoblastic, (-.-.-) Low grade. BMT= bone marrow transplantation.

Table 2.2 Causes of death after bone marrow transplantation.

	Low Grade	Intermediate Grade	Lymphoblastic	DSNCC ^a
Toxicity				
Hepatic	1	1		
Pulmonary		5 ^a	2 ^b	
Multiorgan		1	2	
Infection		1	3	1
Progression		4	8	8
Graft versus host disease	4	1	6	

^a Four pulmonary hemorrhages, 1 diffuse infiltrates

^b One pulmonary hemorrhage, 1 interstitial pneumonitis

DSNCC= diffuse small non-cleaved cell.

In univariate analysis, the use of double consolidation and a poor performance status at BMT were associated with a decreased survival and disease-free survival ($P < 0.05$). Therefore, the analysis was repeated, excluding patients with a poor performance status and those receiving double consolidation. In this subgroup of 42 patients, those with low-grade lymphoma still had significantly superior survival and disease-free survival compared to any other histologic group ($P = 0.04$, $P = 0.05$, respectively). Their recurrence rate remained significantly lower than that in any other histologic group ($P < 0.03$)

Discussion

The current report summarizes 13 years of experience with allogeneic BMT at our institutions. Because a high mortality was associated with this procedure in the past, it has mainly been offered to patients who did not qualify for autologous BMT. Therefore, the majority of patients in this series had advanced disease, extensive bone marrow involvement, and multiple high risk factors. Our results confirm that some such patients can be cured with allogeneic BMT. Many different subtypes of lymphoma are recognized in the Working Formulation¹⁵ or its recent successors,³⁴ but for practical purposes, patients can be divided into four major subgroups: (1) low-grade lymphoma, (2) intermediate-grade and immunoblastic lymphoma, (3) lymphoblastic lymphoma, and (4) DSNCC lymphoma. Our results indicate the importance of disease histology in determining the outcome of allogeneic BMT for patients with recurrent or refractory lymphoma.

Allogeneic bone marrow transplantation was most effective in patients with low-grade lymphoma. Three of 15 such patients were transplanted in the 1980's without the benefit of cyclosporine and modern infection prophylaxis. They died from infectious complications of severe chronic GVHD. The other 12 underwent

BMT after 1989. Ten of these were included in a previous report.³⁵ At the time of this writing, 10 of the 12 are alive and 8 are in remission, with a median follow-up of 2 years, including 7 of the previously reported patients. In addition, 58 patients who had undergone allogeneic bone marrow transplantation for low-grade lymphoma have been identified in the International Bone Marrow Transplant Registry.³⁶ Kaplan-Meier disease-free survival at 3 years is 44% (range 31% to 58%) for these patients. The probability of recurrence was only 24% despite the inclusion of 49 patients (72%) with stage IV disease. These results, and anecdotal reports in the literature^{6,7,9,12,13} (see also Table 2.3) indicate that allogeneic bone marrow transplantation has a major impact in low-grade lymphoma, regardless of the stage of the disease and its response to prior chemotherapy. Most of the patients in this series had bulky disease and extensive bone marrow involvement at the time of BMT. Responses were often slow to occur. The durability of remission was superior to that reported for autologous BMT, even with marrow purging, consistent with an active graft versus lymphoma effect.³⁷⁻³⁹ The occurrence of a late recurrence in 1 of our patients indicates the need for continued surveillance.

Patients with more aggressive histologies had a less favorable outcome with allogeneic BMT. Our results are similar to those of previously published series that include a majority of patients with intermediate- and high-grade lymphomas.^{10,11,13} There is a high incidence of toxic deaths in patients with advanced disease, and disease-free survival was 10% to 20%, with no significant difference in survival between intermediate grade and high-grade lymphoma. Not surprisingly, a poor performance status at BMT was predictive of a particularly ominous prognosis. There were, however, important differences in response rates and in the causes of treatment failure between those groups.

Table 2.3 Allogeneic bone marrow transplantation for recurrent low grade lymphoma, individually reported cases.

Author	Conditioning regimen	Number of patients	Age (y)	Disease-free survival	Progression	Treatment-related death
van Besien	See Text	15	27-45	8	0	5
Chopra et al. ¹²	NA	1	NA	1	0	0
Appelbaum et al. ⁹	BCNU, Cy, TBI	1	39	0	1	0
Copelan et al. ⁶	Bu, Cy	1	37	1	0	0
Lundberg et al. ⁷	Ara, Cy, TBI	4	27-39	3	0	1 ^a
Total		22		15 (68%)	1 (5%)	6 (27%)

^a Matched unrelated donor. Na=not available; Bu=busulfan; Cy=cyclophosphamide; Ara=cytarabine, TBI=total body irradiation. For exact dosages see indicated references.

Twenty percent to 50% of cases of recurrent intermediate-grade lymphoma can be cured with high dose chemotherapy and autologous peripheral blood or marrow stem cell rescue.⁴⁰⁻⁴⁹ Patients with refractory disease or multiple

recurrences have a poor prognosis with high-dose chemotherapy and autologous BMT.^{41,45,47,48} At our institutions, these patients were considered for allogeneic BMT. They often had bulky disease at the time of BMT and were debilitated by their disease and numerous previous treatments. Most had dramatic responses to treatment, and some obtained prolonged remissions, even though their disease was refractory to conventional-dose chemotherapy. Unfortunately, they tolerated the conditioning regimens poorly: this group, like previously reported cases, had a high rate of mortality from toxicity and infections (Table 2.4). Pulmonary hemorrhage and pulmonary toxicity were especially common and accounted for the majority of the deaths, even among patients who did not receive radiation.

Lymphoblastic lymphoma shares many characteristics with acute lymphoblastic leukemia. The large majority of cases exhibit a T-cell phenotype.^{15,34} Most large series of patients undergoing BMT for recurrent non-Hodgkin's lymphoma include a small number of patients with lymphoblastic lymphoma, but their outcome is not generally specified. Five of the 25 patients who had lymphoblastic lymphoma in our series obtained prolonged disease-free survival after allogeneic BMT, including patients with chemotherapy refractory disease and 1 with central nervous system involvement. This is consistent with previously reported cases (Table 2.5) and with data from the European Bone Marrow Transplant registry, which suggest that allogeneic BMT is superior to autologous BMT for the treatment of this disease.^{12,53}

Table 2.4 Allogeneic bone marrow transplantation for recurrent intermediate grade and immunoblastic lymphoma, individually reported cases.

Author	Conditioning regimen	Number of patients	Age (y)	Disease-free survival	Progression	Treatment-related death
van Besien	See Text	14	22-48	0	5	9
Schmitz ⁵⁰	VP, TBI	1	34	0	0	1
Philips ⁵¹	Cy, TBI	3	35,37,40	1	0	2
Ernst ⁵²	TBI + various chemotherapy	5	10-39	2	2	1
Petersen ¹⁰	Ara, TBI	3	36,38,43	0	0	3
Schouten ⁸	Bu, Cy	1	15	1	0	0
Copelan ⁶	Bu, Cy	1	29	1	0	0
Lundberg ⁷	Ara, Cy, TBI ^a	9	16-44	6 ^b	2 ^c	1
Appelbaum ⁹	Various	9	5-62	2	5	2
Total		46		13 (28%)	14 (30%)	19 (41%)

^a In some cases, additional involved field radiation or chemotherapy was given, for details see indicated references; ^b Includes 2 matched unrelated or mismatched related donors; ^c Includes 1 matched unrelated or mismatched related donor. VP=etoposide; TBI=total body irradiation; Cy=cyclophosphamide; Ara=cytarabine; Bu=busulfan. For exact dosages see indicated references.

Table 2.5 Results of allogeneic BMT in recurrent or refractory lymphoblastic lymphoma, individually reported cases.

Author	Conditioning regimen	Number of patients	Age (y)	Disease-free survival	Progression	Treatment-related death
Lundberg ⁷	Cy-Ara-TBI	2	22, 28		1	1
Ernst ⁵²	Various	8	7-28	2	3	3
Philips ⁵¹	Cy-TBI	7	17-27	1	2	4
Petersen ¹⁰	Ara-TBI	1	23			1
Appelbaum ⁹	Cy-TBI (6) Cy-BCNU-TBI (1)	7	9-32	2	1	4
Copelan ⁶	Bu-Cy	2	18, 36	1	1	
van Besien	see table 2.1	25	see table 2.1	4 ^a	8	13
Total		52		10 (19%)	17 (33%)	25 (48%)

^a One patient died from sepsis 6 years after BMT.

Bu= Busulfan; TBI= Total Body Irradiation; Cy= Cyclophosphamide; Ara= cytarabine. For exact dosages see indicated references.

Although treatment-related mortality accounted for the majority of failures in intermediate-grade and lymphoblastic lymphoma, recurrence was the major problem in patients with DSNCC lymphoma. Most patients had no response, or only transient responses to allogeneic BMT, and tumor regrowth occurred upon hematologic recovery. An overview of individually published cases of BMT for recurrent DSNCC lymphoma in adults and children is presented in Table 2.6, and is consistent with our results. In adults with recurrent or refractory DSNCC, both autologous and allogeneic bone marrow transplantation have yielded poor results, with very high recurrence rates.^{10,54}

Table 2.6 Results of allogeneic BMT in recurrent or refractory DSNCC lymphoma (Burkitt's and non-Burkitt's), individually reported cases.

Author	Conditioning regimen	Number of patients	Age (y)	Disease-free survival	Outcome progression	Treatment-related death
Schouten ^a	BACT	1	29			1
Copelan ⁶	Bu-Cy	3	15-43		3	
Philips ⁵¹	Cy-TBI	3	15-21		2	1
Appelbaum ⁹	Mbu-Cy-TBI	1	24		1	
	Ara-Cy-TBI	1	5			1
Schmitz ⁵⁰	VP-TBI	1	20	1		
van Besien	See table 2.1	10	12-43	1	8	1
Petersen ¹⁰	Ara-TBI	5	7-46		3	2
Total		25		2 (8%)	17 (68%)	6 (24%)

BACT= Carmustine, cytarabine, cyclophosphamide, 6-thioguanine; VP=etoposide; TBI=total body irradiation; Cy=cyclophosphamide; Ara=cytarabine; Bu=busulfan; Mbu = dimethylbusulfan. For exact dosages see indicated references.

The outcome of allogeneic BMT depends on the sensitivity of the disease to chemotherapy and to graft versus lymphoma effects. The results in patients with low-grade lymphoma are very promising and indicate a major impact of allogeneic BMT in this disease.

Sensitivity of low-grade lymphoma to graft versus lymphoma effects is not surprising, given the results of other immunomodulatory approaches such as administration of interferon or anti-idiotypic antibodies.⁵⁵⁻⁵⁷

Graft versus lymphoma effects could explain the slow tumor regression after BMT that was observed in some of these patients. On the other hand, the high recurrence rates in patients with recurrent DSNCC lymphoma may be due in part to a decreased sensitivity to immune effects. This decreased sensitivity may be related to the lack of expression of adhesion molecules by the lymphoma cells.^{58,59} However, graft versus lymphoma effects are not completely absent in this disease. Graft versus lymphoma mediated regression of lymphoma has been reported, followed by relapse upon institution of immunosuppressive treatment.¹⁰ Promising results have also been obtained in high-risk patients in first complete remission.⁶⁰

Selection of patients with less advanced disease may result in decreased toxicity and yield improved results with BMT in all types of lymphoma. Allogeneic BMT should be considered for younger patients with recurrent low-grade lymphoma. Allogeneic BMT for patients with advanced intermediate- and high-grade lymphoma needs further evaluation with attention to measures to reduce toxicity. The use of novel cytokines and/or allogeneic peripheral blood stem cells are currently being explored as a means of reducing the incidence of early complications. In our experience, allogeneic peripheral blood stem cell transplantation has led to a reduction in time to hematopoietic recovery,⁵⁸ and contributed to an improved early survival for such patients.⁵⁹ The presence of mature T-lymphocytes in the graft could enhance the graft versus lymphoma effects and thereby further contribute to improved survival for these patients.

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Chapter 3

Allogeneic bone marrow transplantation for refractory and recurrent low-grade lymphoma: the case for aggressive management

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Abstract

Purpose

To evaluate the role of allogeneic bone marrow transplantation (BMT) in recurrent low-grade lymphoma.

Patients and methods

Between 1989 and 1994, 10 patients with chemotherapy-refractory and recurrent low-grade lymphoma were treated with myeloablative therapy and allogeneic BMT. All patients had poor prognostic features and had been extensively pretreated.

Results

Eight patients achieved a complete remission and none have relapsed at a median follow-up time of 816 days (range, 346 to 1,865). Two patients died of early complications. The actuarial survival and failure-free survival rates are both 80% + 12.6%. For surviving patients, the duration of the current remission exceeds that of any previous remission achieved.

Conclusions

These results compare favorably with those for autologous BMT. Allogeneic BMT offers considerable promise for the treatment of patients with poor prognosis low-grade lymphoma. Its role should be further defined in prospective studies.

Introduction

Low-grade lymphomas are indolent disorders with a high rate of initial response to treatment and a median survival duration of between 7 and 9 years.¹⁻⁴ Radiation therapy or the combination of radiation and chemotherapy can produce durable remissions in some patients with stage I, II, or III disease.⁵⁻⁹ However, patients with advanced, recurrent, or refractory disease have a poor prognosis.^{1,10-12}

Encouraging results have been reported with myeloablative therapy and autologous bone marrow transplantation (BMT) for patients with recurrent low-grade lymphoma.¹³⁻¹⁶ Autologous BMT results in a 4-year disease-free survival rate of approximately 45% in patients with chemosensitive recurrences.^{13,14} For patients with extensive bone marrow involvement and for those with refractory disease, there is no effective therapy.

There have been anecdotal reports on the success of allogeneic BMT in patients with refractory disease, which indicate that prolonged disease-free survival can be obtained.⁷⁻²⁰ Allogeneic BMT has not been widely applied to the treatment of low-grade lymphoma because of concern over transplant-related complications, particularly graft-versus-host disease (GVHD) and infections. However, important advances in supportive care,²¹ graft-versus-host prophylaxis,²² and infection prophylaxis,²³ have reduced the risk of allogeneic BMT in the past decade.

Allogeneic BMT may have advantages over autologous transplantation. Donor marrow cells uninvolved by malignancy are used, avoiding the risk of infusing occult lymphoma cells, which, despite bone marrow purging, may contribute to relapse in many patients who undergo autologous BMT.^{24,25} In addition, donor lymphoid cells can potentially mediate a graft-versus-lymphoma effect.²⁶ In view of the occurrence of spontaneous remissions²⁷ and the sensitivity of the disease to interferon therapy^{28,29} and to anti-idiotypic vaccines,³⁰ low-grade lymphoma may be more susceptible than other subtypes to immune-mediated suppression by a graft-versus-lymphoma effect.

We report the results obtained with allogeneic BMT for low-grade lymphoma in 10 patients treated at our institutions since 1989.

Patients and work-up

Ten patients with low-grade lymphoma underwent allogeneic BMT between December 1989 and February 1994. Eligibility criteria included age ≤ 50 years, performance status ≤ 1 , bilirubin level ≤ 2 mg/dl, creatinine less than 1.5 times normal, adequate pulmonary function (forced expiratory volume in 1 second [FEV₁] and diffusing capacity of carbon monoxide [DLCO] $\geq 50\%$ of predicted)

and adequate cardiac function (left ventricular ejection fraction [LVEF] $\geq 50\%$). Patients with active CNS involvement or human immunodeficiency virus (HIV)-related lymphoma were not eligible. Allogeneic BMT was considered for patients with primary chemotherapyrefractory disease or recurrent disease, whether responsive or unresponsive to chemotherapy. Bone marrow involvement was allowed.

Refractory disease was defined as a less than 25% reduction in the sum of the products of the two greatest perpendicular diameters of measurable lesions, despite treatment with combination chemotherapy regimens that contained an anthracycline, platinum, fludarabine, or combinations of these agents.³¹

All patients provided written, informed consent and were treated on protocols approved by the institutional review board. Pretransplant work-up included history and physical examination; blood counts; 12-element sequential multiplier analyzer (SMA-12); electrolytes; urinalysis; bilateral bone marrow aspirate and biopsy with immunophenotyping; chest x-ray and computed tomography of the chest, abdomen, and pelvis; radionuclide cardiac scan, ECG, and pulmonary function tests; hepatitis, cytomegalovirus (CMV), and HIV serology; and pathology review. Additional tissue biopsies were obtained at relapse, whenever possible, to rule out transformation. Patients with tumor transformation to a higher histologic grade were not included in this analysis. One patient with a mantle-cell lymphoma was included; this disease has clinical features similar to those of low-grade lymphoma, but has a more aggressive course and a poor prognosis.³² Two patients were previously included in a report on conditioning for allogeneic BMT with cyclophosphamide, etoposide, and total-body irradiation (TBI).³³

Conditioning regimens, GVHD prophylaxis, and supportive care

Eight patients underwent conditioning with TBI-containing regimens. Five received cyclophosphamide (120 mg/kg) and TBI, and three received etoposide (1,500 mg/m²), cyclophosphamide (120 mg/kg), and TBI. TBI was administered twice daily using an 18-MeV linear accelerator at a dose rate of .25 Gy/min in six fractions of 1.7 Gy for seven patients and in six fractions of 2.0 Gy for one patient.

Two patients were treated with two courses of high-dose chemotherapy. Course one consisted of cyclophosphamide (5.25 g/m²), etoposide (1,200 mg/m²), and cisplatin (135 mg/m²) (CVP). It was followed, after hematologic recovery, by course 2, which consisted of thiotepa (750 mg/m²), busulfan (10 mg/kg), and cyclophosphamide (120 mg/kg) (TBC) plus bone marrow infusion.³⁴

Donors were human leukocyte antigen (HLA)-identical siblings or, in one case, a one-antigen-mismatched relative. All patients received unmanipulated

marrow. GVHD prophylaxis consisted of cyclosporine and a short course of methotrexate in nine patients²² and cyclosporine and corticosteroids in one patient.³⁵

All patients were treated in laminar-air flow rooms or in high-efficiency particulate-free air rooms with strict reverse isolation. Infection prophylaxis consisted of acyclovir and fluconazole plus oral quinolones or nonabsorbable antibiotics during neutropenia. After granulocyte recovery, patients who were seropositive for CMV or who received bone marrow from a seropositive donor received prophylactic ganciclovir until day 100.³⁶ All patients received prophylaxis against *Pneumocystis carinii* with trimethoprim/sulfamethoxazole or aerosolized pentamidine for 1 year after BMT. Intravenous immunoglobulin (0.5 g/kg) was administered weekly for 100 days after transplant and then monthly for 1 year. Those with chronic GVHD continued to receive antibiotic prophylaxis indefinitely.^{23,37-39} Irradiated blood products were administered to maintain a haemoglobin level more than 8 g/dl and platelet count more than $20 \times 10^9/l$. Six patients received growth factor support with recombinant human granulocyte colony-stimulating factor (5 µg/kg/d subcutaneously) beginning on day 0 until recovery of granulopoiesis.

Posttransplant evaluation and response criteria

Toxicity was assessed according to the criteria reported by Bearman et al.⁴⁰ Hematopoietic chimerism was evaluated by conventional cytogenetic analysis for sex-mismatched patient-donor pairs or by restriction fragment-length polymorphisms at the AY-29 or YNH24 loci.⁴¹ Patients were evaluated for acute and chronic GVHD 28 days and 100 days, respectively, after marrow infusion, and GVHD was scored and treated according to standard criteria.^{42,43}

Response to therapy was evaluated at 6 weeks, 3 months, 6 months, and 1 year after transplant, and annually thereafter. Evaluation consisted of physical examination; blood counts; chest x-ray and computed tomography of the chest, abdomen, and pelvis; and bilateral marrow aspirate and biopsy. Additional tests, such as immunophenotyping of the blood and bone marrow, lymph node aspiration, or biopsy, were performed when clinically indicated.

Complete remission was defined as the disappearance of all disease and symptoms related to lymphoma for more than 1 month. Partial remission was defined as more than 50% reduction in the sum of the products of the two greatest perpendicular diameters of measurable lesions for more than 1 month. All other outcomes were considered treatment failures.

In keeping with published eligibility criteria for autologous BMT, bulky lymphadenopathy was defined as any lymph node mass more than 2 cm in its greatest diameter.^{13,24} Anemia was defined as a hemoglobin level ≤ 12 g/dl.³¹

Statistical considerations

The end points included the following: (1) response, (2) survival (interval from the day of BMT until death or end of follow-up period), and (3) time to treatment failure (interval from the day of BMT until relapse, disease progression, death due to disease or its treatment, or end of follow-up). Survival curves were estimated using the Kaplan-Meier product-limit method.⁴⁴

Results

Patient characteristics

The median age at transplant was 36 years (range, 23 to 45). There were eight men and two women. Characteristics for each patient are listed in Table 3.1. All patients had poor prognostic features and had been extensively pretreated. Eight patients had refractory disease, five had primary refractory disease, and three had refractory relapses (one had experienced disease relapse after a previous autologous BMT). Six patients had extensive (>20%) bone marrow involvement at the time of transplantation. Eight patients had bulky disease, four had increased lactate dehydrogenase levels, four had constitutional symptoms, and six had anemia.

Early deaths, toxicity, and infections

Data on early deaths, toxicity and infections are listed in Table 3.2. Two patients died early, one on day 16 of venoocclusive disease after receiving the CVP/TBC regimen, and one on day 26 of multiorgan failure and grade IV acute GVHD.

The second patient, who received the CVP/TBC regimen, had experienced a relapse after a previous autologous BMT with a conditioning regimen of etoposide, cyclophosphamide, and TBI. She received a one-antigen-mismatched bone marrow transplant from her son and developed grade III hemorrhagic cystitis, and grade II cardiac, renal, and CNS toxicity, but eventually recovered.

Toxicity was generally mild among patients who received TBI-containing conditioning regimens. There was one case of transient renal failure, and all patients who received methotrexate developed grade II mucositis. One patient developed a small subarachnoid hemorrhage, which was successfully managed with platelet transfusions and tranexamic acid.

Viral, fungal, and bacterial infections occurred, but all were successfully treated. No infection-related deaths occurred.

Table 3.1 Patient characteristics.

Patient No	Age yrs / sex	Histology	Stage at diagnosis ^a	Duration (months)	Response status ^a	Prior chemotherapy ^b	Time from diagnosis to BMT (months)	Hemoglobin at BMT (g/dl)	LDH of BMT (nl<618)	Size of largest mass of BMT (cm)	Performance status at BMT	Stage at BMT	% Bone marrow involvement at BMT ¹²
1	28 / F	FSCCL	III	NR	Refractory	COPP, CHLOR, CHOPB, COP, IFN, MITO, FLUD	72	7.4	810	9 x 6	50	IVB	100
2	36 / M	DWDL	IV	18	Refractory	CHOPB-ESAP-NOPP, IFN, FND	41	13.1	498	2 x 3	100	IVB	90
2	36 / M	DWDL	IV	NR	Refractory	COP, CHOP, MACOPB, DHAP, ESAP	21	12.2	642	4 x 5	100	IVA	100
4	23 / M	FSCCL	IV	NR	Refractory	COP, CHOP, DHAP	9	13.4	581	3 x 2	100	IVA	20
5	38 / M	FSCCL	IV	8	Response	CHOPB, IFN, ESAP, NOPP, FND	88	13.6	509	2 x 2	100	IIIA	0
6	38 / M	FSCCL	IV	NR	Refractory	CHOP, MINE, ESAP	14	11.6	664	8 x 4	70	IVA	5
7	45 / F	FSCCL	IV	7	Refractory	CHOP, COP, ESAP, AMBT, FND, ESAP	38	8.1	437	2 x 2	100	IVA	50
8	42 / M	FMCL	IV	NR	Refractory	PROMACE-CYTABOM, CHOP, FND, MINE, ESAP	26	10.9	783	3 x 4	100	IVA	10
9	31 / M	MCL	IV	NR	Response	COP, CHOP, FLUD	11	10	291	8 x 7	100	IVB	80
10	43 / M	FMCL	IV	12	Refractory	PROMACE-CYTABOM, ASHAP, MBACOS-MINE, ASHAP, ESAP, ADR-VCR-VO-CSA	12	9.4	503	9 x 5	100	IVB	25

F=female; M=male; FSCCL=follicular small cleaved-cell lymphoma; DWDL=diffuse well-differentiated lymphocytic lymphoma; FMCL=follicular mixed-cell lymphoma; MCL=mantle-cell lymphoma; CR1=first complete remission; NR=not reached; COPP=cyclophosphamide, vincristine, prednisone, and procarbazine; CHLOR=chlorambucil; CHOPB=cyclophosphamide, doxorubicin, vincristine, prednisone, and bleomycin; COP= cyclophosphamide, vincristine, and prednisone; IFN=alpha interferon; MITO=mitoxantrone; FLUD=fludarabine; CHOPB-ESAP-NOPP=alternating CHOPB, ESAP, and NOPP; MACOPB=methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; DHAP=dexamethasone, high-dose cytarabine, cisplatin, and prednisone; ESAP=etoposide, methylprednisolone, high-dose cytarabine, and cisplatin; NOPP=mitoxantrone, vincristine, prednisone, and procarbazine; MINE=mitoxantrone, ifosfamide, etoposide, and mesna; ABMT=autologous BMT; FND=fludarabine, mitoxantrone, and dexamethasone; PROMACE-CYTABOM=prednisone, vincristin, methotrexate, cytarabine, etoposide, cyclophosphamide, doxorubicin, and bleomycin; ASHAP-MBACOS-MINE= alternating ASHAP, MBACOS, and MINE; ASHAP= doxorubicin, methylprednisone, high-dose cytarabine, and cisplatin; MBACOS=methotrexate, doxorubicin, bleomycin, cyclophosphamide, vincristin, and methylprednisolone; ADR-VCR-VP-CSA=doxorubicin, vincristin, etoposide, and cyclosporine; LDH=lactate dehydrogenase; nl=normal.

^a Response to last chemotherapy before transplant. Response is >25% reduction in the sum of the products of the 2 greatest perpendicular diameters of measurable lesions. ^b prior regimens in sequence they were given.

Table 3.2 Clinical toxicity

Toxicity	No. of patients
Treatment-related deaths	
Venoocclusive disease	1
GVHD	1
Grade II-IV toxicity	
Cardiac	1
Renal	3
Hepatic	1
Bladder	1
Mucositis	9
Infections	
Bacterial sepsis	2
Fungal sepsis	2
CMV pneumonia	1
Respiratory syncytial virus infection	1
Herpes simplex II	1

Engraftment and GVHD

Seven of eight assessable patients achieved complete hematopoietic engraftment. One patient continues to require platelet transfusions, 11 months after transplantation. The median time to reach an absolute granulocyte count more than $0.5 \times 10^9/l$ was 16 days (range, 14 to 21). The median time to reach a platelet count more than $20 \times 10^9/l$ was 25 days (range, 15 to >346). Acute GVHD (grade II to IV) developed in five patients. One patient had fatal grade IV acute GVHD. Four patients developed chronic GVHD. Two of them continue to require treatment for lichenoid skin lesions. Six patients have a Karnofsky performance status of 100%.⁴⁵ One patient with chronic GVHD of the skin and one patient who underwent BMT recently have a performance status of 90%.

Response

Antitumor responses after BMT are listed in Table 3.3. Eight patients achieved a complete remission. Maximal cytorreduction may take several months to occur. In one patient, bone marrow biopsy still showed involvement on day 75, but was persistently negative thereafter. One patient with chronic GVHD had polyclonal lymphoid nodules in the bone marrow up to 820 days after BMT. No rearrangement of the immunoglobulin heavy-chain gene could be demonstrated in bone marrow samples from this patient. One patient has residual splenomegaly.

Table 3.3 Conditioning outcome.

Patient no.	D/R Sex	Donor type	Conditioning	GVHD Prophylaxis	Acute GVHD	Chronic GVHD	Response	KPS (%)	Failure-Free
1	F / F	ID-SIB	CY/VP16/TBI	CYCLOSP MTX	No	Skin & Mouth	CR ¹	90	1,439+
2	F / M	ID-SIB	CY/TBI	CYCLOSP MTX	II	Skin & Mouth	CR	100	6,47+
3	M / M	ID-SIB	CY/VP16/TBI	CYCLOSP MTX	III	Skin	CR	100	1,865+
4	F / M	ID-SIB	CY/TBI	CYCLOSP MTX	No	No	CR ²	100	1,186+
5	F / M	ID-SIB	CY/VP16/TBI	CYCLOSP MTX	No	Skin	CR	100	990+
6	F / M	ID-SIB	CVP/TBC	CYCLOSP MTX	NA	NA	NA	100	Died day 6 VOD
7	M / F	1AGMM	CVP/TBC	CYCLOSP MTX	II	No	CR	100	585+
8	M / M	ID-SIB	CY/TBI	CYCLOSP MTX	No	NA	CR	90	346+
9	M / M	ID-SIB	CY/TBI	CYCLOSP PDN	II	No	CR	100	502+
10	M / M	ID-SIB	CY/TBI	CYCLOSP MTX	IV	NA	NA		Died day 26 AGVHD

1AGMM=1 -antigen-mismatched family donor; AGVHD=acute GVHD; CR=complete remission; CY=cyclophosphamide; VP16=etoposide; CYCLOSP=cyclosporine; MTX=methotrexate, PDN=corticosteroids; D/R=donor/recipient; ID-SIB=HLA-identical sibling; KPS, Karnofsky performance score; NA=not assessable; PR=partial remission; VOD=venoocclusive disease.

¹ Lymphoid nodules in bone marrow until day 820.

² Persistent splenomegaly.

Failure-free survival

Eight patients are alive a median of 816 days (range, 346 to 1,865) after BMT. No patients have had relapses. The actuarial survival and failure-free survival rates are both $80\% \pm 12.6\%$ (Figure 3.1). For surviving patients, the duration of the current remission exceeds the duration of any prior remission achieved.

Figure 3.1 Survival and failure-free survival curves. The curves are identical.

Discussion

Our results with allogeneic BMT for low-grade lymphoma indicate a high rate of complete responses and a prolonged remission duration in a group of patients with end-stage disease, only one of whom would have qualified for an autologous BMT. With conventional chemotherapy, the median survival duration for a group of patients with similar disease characteristics, treated at the same institution, was only 5 months.³¹ Our data compare favourably with autologous BMT results, despite the inclusion of patients with advanced disease. As in autologous BMT, the high response rate is due to the intensive conditioning, but an immune-mediated graft-versus-lymphoma effect probably contributes as well. The slow regression of residual lymph node and bone marrow involvement is reminiscent of the gradual disappearance of leukemic cells observed after allogeneic BMT for chronic myelogenous leukemia.^{46,47}

Most studies of allogeneic BMT for lymphoma have included primarily intermediate-grade and high-grade subtypes. Although a graft-versus-lymphoma effect has been reported in patients with aggressive disease,^{26,48,49} any benefit of allogeneic BMT has been offset by an increased treatment-related death rate. Overall results are similar to those achieved with autologous BMT.^{20,26,49,50} Low-grade lymphoma patients, on the other hand, have more indolent disease. They are usually in better condition and more likely to survive intensive conditioning therapy, thereby allowing the graft-versus-lymphoma effect to have its full impact.

Consistent with our data, favorable outcomes have been reported with allogeneic BMT for refractory chronic lymphocytic leukemia, another indolent lymphoid malignancy.⁵¹⁻⁵³

Our data were obtained in patients who had experienced multiple relapses or who had refractory disease. Performing allogeneic BMT earlier in the course of the disease might improve the results,^{54,55} and this option could be offered to patients with a poor prognosis. Several features, such as refractory disease, male sex, short duration of remission, and extensive tumor burden, allow the identification of such patients.^{3,11,31,56} In our situation, the median survival duration for males with stage IV disease and a high tumor burden is only 43 months.³ For patients with recurrent follicular lymphoma, the median survival duration ranges from 20 months³¹ to almost 6 years,⁵⁶ but patients with unfavorable characteristics have a median survival time of only 5 months.³¹ This is substantially worse than for patients with chronic myelogenous leukemia, a disease for which allogeneic BMT is routinely recommended.⁵⁷

Considerable attention has focused on autologous BMT for patients with recurrent low-grade lymphoma and chemotherapy-sensitive disease. The early treatment-related mortality rate of autologous BMT is less than 5%, which indicates that it might be a safer treatment.^{13,14} However, with prolonged follow-

up time, there has been a continued pattern of relapse after autologous BMT, and it is not entirely certain whether the survival of transplanted patient is better than that of patients with similar characteristics who do not undergo autologous BMT.^{14,56,58} Another potential problem is the occasional occurrence of posttransplant leukemia or myelodysplastic syndrome following autologous BMT, possibly related to the heavy exposure of the patient and the infused marrow to alkylating agents, epipodophyllotoxins, and other cytotoxic drugs.^{13,24,59,60} Secondary leukemias have been reported only rarely as a complication of allogeneic BMT.^{61,63}

The indications for allogeneic BMT in low-grade lymphoma need to be further defined in prospective studies. Given the encouraging results in patients with advanced and refractory disease, we consider it reasonable to offer allogeneic BMT to all patients younger than 55 years with recurrent disease who have an HLA-compatible sibling, regardless of their response to chemotherapy. The median age at diagnosis for low-grade lymphoma is between 50 and 60 years⁶⁴⁻⁶⁶; hence, many patients should be eligible for the procedure. Recent studies suggest that the use of allogeneic BMT may be extended to older patients as well, further increasing the number of patients who could benefit.⁶⁷ For patients with particularly poor prognostic features, the procedure could be considered as a component of their initial therapy. For younger patients with a poor prognosis who lack an HLA-identical sibling donor and who do not qualify for autologous BMT, the role of unrelated-donor transplantation should be explored.

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Chapter 4

Allogeneic transplantation for low-grade
lymphoma: long-term follow-up

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In 1995 we reported on 10 patients with a history of advanced, refractory low-grade lymphoma who had undergone allogeneic transplantation.¹ Seven patients had follicle-center lymphomas, two had small lymphocytic lymphomas, and one had a mantle cell lymphoma. Two patients had died from transplant-related toxicity and eight had obtained remissions. With a median follow-up of 27 months (range, 11 to 62 months), no recurrences had occurred. Figure 4.1 shows the survival and disease-free survival of this patient cohort as of October 1999. Currently, the median follow-up is 6 years after transplantation (range, 5 to 9 years), and only one patient has developed disease progression. That patient is currently in remission 8 years after the initial transplant and 4 years after a second allogeneic transplantation. That same patient developed extensive chronic graft-versus-host disease after transplantation and developed disease recurrence while receiving chronic immunosuppression. Two additional patients have developed limited chronic graft-versus-host disease, and one patient has developed aseptic hip necrosis. No other posttransplant complications have occurred.

Since our initial publication, several groups have confirmed the ability to induce remissions of low-grade lymphoma with allogeneic transplantation, but the median follow-up in these studies was, at best, 3 years.²⁻⁵ Hence, the possibility remained that, as with autologous transplantation, late recurrences and complications such as secondary MDS would affect long-term outcome.⁶ However, our data, admittedly obtained on a small patient sample, indicate the possibility of durable remissions in the majority of survivors of allogeneic transplantation. Confirmation of these data in larger studies with long follow-up is necessary.

Figure 4.1 Survival and disease-free survival.

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Chapter 5

Allogeneic bone marrow transplantation for low-grade lymphoma

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Abstract

Advanced low-grade lymphomas are usually incurable with conventional-dose chemotherapy. It is uncertain whether cures are possible with high-dose therapy and bone marrow transplant from a human leukocyte antigen (HLA)-identical sibling. We sought to determine the outcome of HLA-identical sibling bone marrow transplants in advanced low-grade lymphoma in an observational study of 113 patients conducted at 50 centers participating in the International Bone Marrow Transplant Registry (IBMTR). The median patient age was 38 years (range, 15 to 61). Eighty percent had stage IV disease at the time of transplantation. The median number of prior chemotherapy regimens was two (range, 0 to 5). Thirty-eight percent had refractory disease and 29% a Karnofsky performance score (KPS) less than 80%. All patients underwent allogeneic bone marrow transplantation from a HLA-identical sibling donor. The conditioning regimen included total-body irradiation (TBI) in 82% of patients; cyclosporine was used for graft-versus-host disease prophylaxis in 74%. Survival, disease-free survival, recurrence rate, treatment-related mortality, and causes of death were determined. Three-year probabilities of recurrence, survival, and disease-free survival were 16% (95% confidence interval [CI], 9% to 27%), 49% (95% CI, 39% to 60%), and 49% (95% CI, 39% to 59%), respectively. Higher survival was associated with pretransplant KPS $\geq 90\%$, chemotherapy-sensitive disease, use of a TBI-containing conditioning regimen, and age less than 40 years. We conclude that high-dose therapy followed by transplantation from a HLA-identical sibling leads to prolonged survival in some patients with advanced low-grade lymphoma. Most mortality is treatment-related, and recurrences are rare.

Introduction

Advanced-grade lymphomas are relatively indolent, but are incurable with conventional treatments.¹⁻⁴ The median survival duration from diagnosis is 7 to 9 years. High-dose therapy and a blood cell or bone marrow autotransplant reportedly results in sustained remission in some patients.⁵⁻⁹ Recurrences are common and there is concern about posttransplant myelodysplastic syndromes.^{5,10-12} Prolonged remissions have been reported in small numbers of patients treated with allogeneic bone marrow transplantation.¹³⁻¹⁹ We studied 113 patients with advanced low-grade lymphoma who received a bone marrow transplant from a human leukocyte antigen (HLA)-identical sibling.

Patients and methods

Patients

We reviewed all HLA-identical sibling transplants for low-grade lymphoma performed between 1984 and 1995 and reported to the International Bone Marrow Transplant Registry (IBMTR) by 50 centers worldwide. The study included 113 patients with a diagnosis of low-grade lymphoma at diagnosis and at the time of transplant. This included patients with diffuse well-differentiated lymphocytic lymphoma (Working Formulation group A), follicular small cleaved-cell lymphoma (Working Formulation group B), and follicular mixed-cell lymphoma (Working Formulation group C).²⁰ Patients initially diagnosed with low-grade lymphoma, but whose disease transformed to intermediate-grade or high-grade lymphoma before transplantation, were excluded.

Pathology reports confirming the diagnosis of low-grade lymphoma were reviewed by Koen van Besien. Discrepancies in nomenclature among centers were resolved using the recent publication on the Revised European-American Lymphoma (REAL) classification.²¹

IBMTR.

The IBMTR is a voluntary working group of more than 300 transplant teams worldwide that contribute detailed data on their allogeneic bone marrow transplants to the Statistical Center at the Medical College of Wisconsin. Participants are required to report all consecutive transplants; compliance is monitored by on-site audits. Approximately two thirds of all active transplant centers report their data to the IBMTR. The IBMTR database includes 40% to 45% of all allogeneic transplant recipients since 1970. Patients are monitored

longitudinally. Computerized error checks, physician review of submitted data, and on-site audits of participating centers ensure data quality.

Statistical methods

Primary outcomes were survival, disease-free survival (survival without lymphoma posttransplant), recurrence, and treatment-related mortality (nonrelapse death). For treatment-related mortality, patients were considered treatment failures at the time of death from any cause in the first 28 days posttransplant or at time of death in continuous remission for those surviving more than 28 days posttransplant; patients with recurrent lymphoma were censored at the time of relapse and those alive in remission were censored at the last follow-up evaluation. For disease-free survival, patients were considered treatment failures at the time of relapse or death from any cause; patients alive in continuous remission were censored at the last follow-up evaluation. Patients who never achieved remission were analyzed as having recurrent lymphoma on day 28.

Other outcomes examined were acute graft-versus-host disease (GVHD), chronic GVHD, and survival. Acute GVHD was defined as moderate to severe (grade II to IV) disease using established criteria; patients surviving more than 21 days with evidence of engraftment were considered at risk.²² Chronic GVHD was determined by clinical criteria in patients surviving more than 90 days with evidence of engraftment.²³

Probabilities of outcomes were calculated using the Kaplan-Meier product-limit estimate and expressed as probabilities with a 95% confidence interval (CI) computed using the arcsine-square root transformation. Patient-, disease-, and transplant-related variables were studied for associations with survival. Univariate comparisons used the log-rank test. Multivariate analyses used Cox proportional hazards regression with stepwise forward variable selection. As disease-free survival was nearly identical to survival, multivariate analyses were performed only for survival. The incidence of lymphoma relapse was too low to allow a multivariate analysis of this parameter.

Results

Patient characteristics

Patient-, disease-, and transplant-related characteristics are listed in Table 5.1. Fifty-eight percent of patients were male. The median age was 38 years (range, 15 to 61). Twenty-nine percent had a Karnofsky performance score (KPS) less than 90%.

Table 5.1 Patient-, disease-, and transplant-related characteristics of 113 recipients of HLA-identical sibling bone marrow transplants for low-grade non-Hodgkin's lymphoma reported to the IBMTR by 50 centers worldwide.

Variable	No. assessable	Patients No. %	
Patient characteristics			
Male gender	113	66	58
Age at transplant (yr)	113		
Median		38	
Range		15-61	
<40		63	56
≥40		50	44
KPS ≤80%	113	33	29
Disease characteristics at diagnosis			
Histology	113		
Small lymphocytic		20	18
Follicular small cleaved		52	46
Follicular mixed		41	36
Disease stage	113		
I		2	2
II		9	8
III		10	9
IV		92	81
Extranodal involvement	110		
None		19	17
Bone marrow		66	60
Bone marrow + other ^a		13	12
Other ^a		12	11
Disease characteristics at transplant			
Disease stage	113		
Complete remission		16	14
I		2	2
II		7	6
III		7	6
IV		80	71
Unknown		1	1
Extranodal involvement	110		
None		30	27
Bone marrow		64	58
Bone marrow + other ^b		11	10
Other ^b		5	5
Response to chemotherapy	105		
Sensitive		66	63
Resistant		39	37
No. of prior chemotherapy regimens	110		
Median		2	
Range		1-5	
Prior complete remission	112	46	41

Variable	No. assessable	Patients No. %	
Disease duration (mo)	113		
Median		24	
Range		5-130	
Transplant characteristics			
Year of transplant	113		
1984-1987		3	3
1988-1989		15	13
1990-1991		23	20
1992-1993		35	31
1994-1995		37	33
Donor-recipient sex match	113		
Male-male		35	31
Male-female		29	26
Female-male		30	27
Female-female		19	16
Donor-recipient CMV status	109		
+ / +		36	33
- / +		19	17
Donor-recipient CMV status (Cont'd)			
+ / -		21	19
- / -		33	30
Conditioning regimen	113		
TBI + Cy		32	28
TBI + Cy + VP16 ± other		43	38
TBI + Cy + other (not VP16)		11	10
TBI + other		7	6
LFR + Cy + Bu		1	1
Cy + BCNU + VP16		1	1
Cy + Bu		15	13
Other		3	3
GVHD prophylaxis	113		
MTX + CsA ± other		68	60
MTX ± other		2	2
CsA ± other		17	15
T-cell depletion ± other		25	22
FK506 + corticosteroids		1	1

KPS=Karnovsky performance score; CMV=cytomegalovirus; TBI=total-body irradiation; Cy=cyclophosphamide; VP16=etoposide; LFR=limited-field radiation; Bu=busulfan; BCNU=nitrosurea; MTX=methotrexate; CsA=cyclosporine.

^a Other 5 pleura, liver, bone, skin, lung, kidney, epidural space; ^b Other 5 pleura, liver, kidney, bone, lung, brain.

Eighteen percent of patients had small lymphocytic lymphoma, 46% had follicular small cleaved-cell lymphoma, and 36% had follicular mixed-cell lymphoma. Eighty-one percent were diagnosed with stage IV disease, most commonly due to bone marrow involvement. Only 14% were in complete remission at transplant. Seventy-one percent had stage IV disease at transplant, despite a median of two prior chemotherapy regimens. Diverse

chemotherapy regimens were used pretransplant; 37% of patients were felt to have chemotherapy-resistant lymphoma (i.e., they had achieved less than a partial remission to the last chemotherapy regimen administered before transplant).

Eighty-four percent of the transplants were performed after 1990. The median interval from diagnosis to transplant was 24 months (range, 5 to 130). The pretransplant conditioning regimen included total-body irradiation (TBI) in 82% of cases. Among the 20 patients (18%) not receiving TBI for conditioning regimens, only three had received prior radiation. Twenty-two percent of patients received T-cell-depleted transplants.

Outcomes

Outcomes are summarized in Table 5.2. The median follow-up duration of surviving patients was 25 months (range, 4 to 95). Three-year probabilities of recurrence and treatment-related mortality were 16% (95% CI, 9% to 27%) and 40% (95% CI, 30% to 50%), respectively (Figure 5.1). Three-year probabilities of survival and disease-free survival were both 49% (95% CI, 39% to 59%) (Figure 5.2). Among 33 patients monitored for more than 2 years after transplantation, only one relapse was documented.

Table 5.2 Probabilities ($\pm$ 95% CI) of transplant outcomes (at 3 years unless otherwise stated).

	3-Year probability (%)	No. assessable
Graft failure	1 (0-5)	101
Relapse ^a	16 (9-27)	93
Treatment-related mortality	40 (30-50)	113
Acute GVHD (at 100 days) ^b	27 (19-37)	99
Chronic GVHD ^c	66 (53-77)	67
Survival	49 (39-60)	113
Disease-free survival	49 (39-59)	113

^a Among patients surviving $\geq$ 28 days posttransplant; ^b Among patients surviving $\geq$ 21 days with evidence of engraftment; ^c Among patients surviving $\geq$ 90 days with evidence of engraftment.

In multivariate analysis, KPS, chemotherapy-resistance, conditioning regimen, and age significantly predicted survival (Table 5.3).

Fifty-one patients died; causes of death are summarized in Table 5.4. Pulmonary complications were most common, including interstitial pneumonitis (n=7), acute respiratory distress syndrome (n=5), and pulmonary hemorrhage (n=1). Two patients died of acute GVHD and three of chronic GVHD.

Figure 5.1 Probability of relapse and treatment-related mortality after HLA-identical sibling bone marrow transplant for low-grade non-Hodgkin's lymphoma.

Figure 5.2 Probability of survival and disease-free survival after HLA-identical sibling bone marrow transplant for low-grade non-Hodgkin's lymphoma.

Table 5.3 Factors significantly associated with survival in multivariate analysis of 113 recipients of HLA-identical sibling bone marrow transplants for low-grade non-Hodgkin's lymphoma reported to the IBMTR by 50 centers worldwide.

Covariate	No.	RR of death	95% CI	P value ^a
KPS pretransplant				
<90%	33	1.00		-
≥90%	80	0.42	(0.23-0.77)	0.005
Conditioning regimen				
Chemotherapy alone	20	1.00		-
TBI 1 chemotherapy	93	0.47	(0.24-0.93)	0.03
Sensitivity to chemotherapy				
Resistant	66	1.00		-
Sensitive	39	0.50	(0.27-0.91)	0.02*
Unknown	8	1.02	(0.35-2.99)	0.97*
Age at transplant (yr)				
<40	63	1.00		-
≥40	50	1.85	(1.05-3.24)	0.03*

RR=relative risk.

^a P value for pairwise comparison of specific category with the reference (baseline) group.

Table 5.4 Causes of death of 51 recipients of HLA-identical sibling bone marrow transplants for low-grade non-Hodgkin's lymphoma.

Cause of Death	Patients	
	No.	%
Persistent or recurrent lymphoma	11	22
Interstitial pneumonia	10	20
VOD	7	14
GVHD (chronic or acute)	6	12
Adult respiratory distress syndrome	5	10
Sepsis	4	8
Organ failure	2	4
Hemorrhage	2	4
Unknown	2	4
Pulmonary embolism	1	2
Stroke	1	2

VOD=veno-occlusive disease.

Discussion

This report evaluates the outcome of HLA-identical sibling bone marrow transplants for advanced low-grade lymphomas among centers reporting consecutive patients to the IBMTR. Not surprisingly, the data indicate that transplants are mainly offered to younger patients with advanced disease. Most patients in this study received extensive prior therapy. Many had chemotherapy-resistant disease and low performance scores. Most were not candidates for autotransplants because of extensive bone marrow involvement. Characteristics of these patients and their outcomes are consistent with those reported in three smaller single-institution series.^{13,18,19} Only 22 of the patients in this study were included in those series. Given the unfavorable characteristics of this population, the observed lymphoma-free and overall survival rates of 49% and the recurrence rate of only 16% are encouraging. Interestingly, there was only one recurrence among 33 patients monitored for more than 2 years. This seems lower than has been reported for autotransplants and is consistent with other recent reports.^{24,25} The low recurrence rate, if true, may be due to graft-versus-lymphoma effects as suggested by some,²⁶⁻²⁸ or, alternatively, to lack of tumor contamination of the allogeneic graft.^{29,30} Our results should be interpreted cautiously. Although we tried to obtain current information on all patients, follow-up methods and accuracy of restaging varies considerably among reporting centers; failure to detect early recurrences may at least partially explain the results. Multivariate analyses identified poor KPS and chemotherapy-resistance as adverse prognostic factors. Better patient selection and earlier transplants

could improve outcome. Use of TBI for pretransplant conditioning was also associated with better survival. Radiation is effective in low-grade lymphoma and is frequently used in autotransplant conditioning regimens. However, in a recent analysis of autotransplants for low-grade lymphoma, there was a trend ($P=0.09$ in multivariate analysis) for poorer survival among patients receiving TBI.³¹ Only 18% of the patients in this series received non-TBI regimens and it is possible that such patients differed for unknown but important (latent) covariates.

The 3-year probability of treatment-related mortality was 40% (95% CI, 30% to 50%). Most treatment-related deaths were from pulmonary complications, similar to observations in allogeneic transplants for Hodgkin's disease.³² This high incidence of pulmonary complications may be related to the use of busulfan or TBI. Chronic GVHD, though common, was a rare cause of death.

In conclusion, this analysis establishes the potential of allogeneic transplantation to achieve survival in patients with advanced low-grade lymphoma. Our data provide a rationale for prospective studies of allogeneic transplants earlier in the course of the disease.

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Chapter 6

Comparison of autologous and allogeneic hematopoietic stem cell transplantation for follicular lymphoma

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Abstract

In this article, we report on 904 patients undergoing transplantation for follicular lymphoma. A total of 176 (19%) received allogeneic, 131 (14%) received purged autologous, and 597 (67%) received unpurged autologous transplants. Five-year treatment-related mortality (TRM) rates were 30%, 14%, and 8% and 5-year recurrence rates were 21%, 43%, and 58% after allotransplantation, purged autotransplantation, and unpurged autotransplantation, respectively. In multivariate analyses, allotransplantation had higher TRM and lower disease recurrence. Purged autotransplantation had a 26% lower recurrence risk than unpurged autotransplantation. Five-year probabilities of survival were 51%, 62%, and 55% after allogeneic, purged autotransplantation, and unpurged autotransplantation, respectively. Advanced age, prolonged interval from diagnosis to transplantation, high lactate dehydrogenase (LDH), refractory disease, bone marrow involvement, low performance scores, and transplantation between 1990 and 1993 were associated with adverse outcomes. Total body irradiation was associated with higher TRM but lower recurrence. There was no association between acute or chronic graft-versus-host disease and recurrence after allotransplantation. We conclude that both allogeneic and autologous transplantation can induce durable remissions. There may be a benefit to graft purging in autologous transplantation. The decreased recurrence after allotransplantation is offset by increased TRM. We did not detect a correlation between graft-versus-host disease (GVHD) and recurrence. Finally, outcomes of transplantation for follicular lymphoma show improvement over the past decade.

Introduction

Follicular lymphoma is considered an indolent disorder but can have an unpredictable and often relentless course.¹⁻⁵ Treatments such as chemotherapy, biologic response modifiers, and monoclonal antibodies are not considered curative and, with the possible exception of interferon, do not prolong survival.^{6,7} In contrast, autologous hematopoietic stem cell transplantation is shown in several phase 2 studies to induce remissions in patients with recurrent or newly diagnosed disease.⁸⁻²¹ Although recurrence rates are high in some of these studies, some patients have very durable remissions and may be cured.²² Allogeneic hematopoietic stem cell transplantation is also a potentially curative approach. Recurrence rates after allogeneic transplantation are low, but treatment-related mortality (TRM) is high, related, in part, to a tendency to use this therapy in patients with very advanced disease.²³⁻³² To evaluate the roles of allogeneic versus autologous transplantation, as well as to gather additional insights into mechanisms of disease control, we studied 904 patients undergoing allogeneic or autologous transplantation for follicular lymphoma between 1990 and 1999 who were reported to the International Bone Marrow Transplant Registry (IBMTR) or the Autologous Blood and Marrow Transplant Registry (ABMTR).

Patients and methods

Data sources

The IBMTR is a voluntary working group of more than 350 transplantation centers worldwide that contribute detailed data on consecutive allogeneic hematopoietic stem cell transplantations to a statistical center at the Health Policy Institute of the Medical College of Wisconsin in Milwaukee. The ABMTR is a voluntary organization of more than 250 transplantation centers primarily in North and South America that report data on consecutive autotransplantations to the same statistical center. On the basis of data collected in the Centers for Disease Control Hospital Surveys and the U.S. Government Accounting Office and worldwide surveys of transplantation activity, approximately 35% of allogeneic transplantations worldwide and more than 50% of autotransplantations in North and South America are registered with the IBMTR/ABMTR. Participating centers are required to register all transplants consecutively; compliance is monitored by on-site audits. Patients are followed longitudinally, with yearly follow-up. Computerized checks for errors, physician

reviews of submitted data, and on-site audits of participating centers ensure data quality. The IBMTR/ABMTR collects data at 2 levels: registration and research. Registration data include disease type, age, sex, pretransplantation performance status, disease stage and chemotherapy responsiveness, date of diagnosis, donor and graft type (bone marrow- and/or blood-derived stem cells), high-dose conditioning regimen, posttransplantation engraftment, graft-versus-host disease, disease recurrence and survival, development of a new malignancy, and cause of death. Requests for data on disease or death for registered patients are at 6-month intervals. All IBMTR/ABMTR teams contribute registration data on all patients. Research data are collected on subsets of registered patients selected by using a weighted randomization scheme, including comprehensive pretransplantation and posttransplantation clinical information.

Patients

We reviewed all HLA-identical sibling transplantations and autologous transplantations for follicular lymphoma performed between 1990 and 1999 and reported to the IBMTR/ABMTR. A total of 2459 registered cases were identified. Of these cases, 904 patients with follicular lymphoma both at diagnosis and at the time of transplantation had full research data and were included in the analysis. This analysis included patients with follicular small cleaved-cell lymphoma (Working Formulation group B), follicular mixed-cell lymphoma (Working Formulation group C), and follicular large cell lymphoma (Working Formulation group D). Patients initially diagnosed with follicular lymphoma, but whose disease transformed to intermediate-grade or high-grade lymphoma before transplantation, were excluded. Patients receiving nonmyeloablative conditioning regimens for allogeneic transplantation were excluded. To ensure that the research patients were representative of all registered patients, demographics, relapse rates, and survival rates between research and registered patients were compared; no differences were noted. Patients were considered to have "early" disease if they received their transplant in first or second complete remission or at the time of first relapse. All other patients were considered to have advanced disease.

Endpoints

Primary outcomes were survival, disease-free survival (DFS; survival without lymphoma after transplantation), recurrence, and TRM (treatment-related or nonrelapse mortality). Any death occurring within 28 days after transplantation was considered a TRM. Additionally, any death occurring 28 days or more after transplantation in a patient in continuous remission was considered treatment related. Patients with recurrent lymphoma were censored at the time of

relapse, and those patients alive in remission were censored at the last follow-up evaluation. For DFS, patients were considered treatment failures at the time of relapse or death from any cause; patients alive in continuous complete remission were censored at the last follow-up evaluation. Patients who never achieved complete remission were analyzed as having recurrent lymphoma on day 28. Other outcomes examined were acute graft-versus-host disease (GVHD) and chronic GVHD. Acute GVHD was defined as moderate to severe (grades II to IV) disease using established criteria; patients surviving more than 21 days with evidence of engraftment were considered at risk. Chronic GVHD was determined by clinical criteria in patients surviving more than 90 days with evidence of engraftment.

Statistical analysis

Univariate comparisons were done by using the Kruskal-Wallis test for continuous data and the chi-square test for categorical variables. Probabilities of survival and DFS were calculated by using the Kaplan-Meier product-limit estimate. Probabilities of relapse and TRM were calculated by using cumulative incidences to allow for competing risks. The 95% confidence intervals (CIs) were computed by using the arc sine-square root transformation. TRM, relapse, DFS, and survival after autologous (purged/unpurged) versus HLA-identical sibling transplantation were evaluated in multivariate analyses by using Cox proportional hazards regression to adjust for other potentially confounding differences between the cohorts. Variables considered in multivariate analysis are as follows: type of transplant, age, sex, Karnofsky performance score at transplantation, disease stage at transplantation, chemosensitivity, bone marrow involvement at diagnosis and transplantation, histology type, presence of B symptoms at diagnosis, serum lactate dehydrogenase (LDH) at transplantation, initial chemotherapy given, interval from diagnosis to transplantation, use of total body irradiation (TBI) or other field radiation, use of growth factors, graft source, and year of transplantation. Each model contained the main effect (type of transplant: unpurged autologous transplant versus purged autologous transplant versus HLA-identical sibling transplant). We tested the proportional hazards assumption for each factor in the Cox model by using time-dependent covariates. When this statistic indicated differential effects over time (nonproportional hazards), models were constructed to break the posttransplantation time course into 2 periods, using the maximized partial likelihood method to find the most appropriate breakpoint. Interactions between the type of transplant and all covariates were tested prior to stepwise modeling. After modeling time-varying effects and interactions, the final multivariate model was built by using a forward stepwise model selection approach. Factors significantly associated with the outcome

variable at a 5% α level were kept in the final model. First-order interactions were again examined between the type of transplant and all significant prognostic factors. Examination for center effects used a random effects or frailty model. No statistically significant center effect was noted. All P values are 2-sided.

Results

Patient and transplant characteristics

Patient-, disease-, and transplant-related characteristics are listed in Table 6.1 and compared across the 3 treatment groups. A total of 176 patients underwent allogeneic transplantation and 728 underwent autologous transplantation; 131 of the autologous grafts were treated in vitro to remove residual lymphoma cells (purged). There was a slight majority of men in each of the groups, reflective of the slightly higher incidence of follicular lymphoma in men.

Table 6.1 Patient-, disease-, and transplantation-related characteristics

Variables	Type of transplant		
	HLA-identical sibling	Autologous purged	Autologous unpurged
N	176	131	597
Median age, y (range)	42 (22-64)	49 (29-64)	49 (18-71)
Men (%)	95 (54)	83 (63)	320 (54)
Karnofsky performance score at transplantation (%) ^a			
No more than 80%	60 (34)	17 (13)	183 (31)
90%-100%	116 (66)	114 (87)	414 (69)
CMV status at transplantation (%) ^a			
Negative	85 (48)	16 (12)	153 (26)
Positive	88 (50)	32 (25)	205 (34)
Unknown	3 (2)	83 (63)	239 (40)
Disease status at transplantation (%) ^{ab}			
Early	85 (48)	69 (53)	350 (59)
Advanced	91 (52)	62 (47)	247 (41)
Bone marrow involvement at diagnosis (%)			
Absent	102 (58)	71 (54)	355 (59)
Present	74 (42)	60 (46)	242 (41)
Bone marrow involvement at transplantation (%) ^a			
Absent	119 (68)	103 (79)	486 (81)
Present	57 (32)	28 (21)	111 (19)
Histology (%) ^a			
Follicular, small cleaved	91 (52)	67 (51)	218 (36)
Follicular, mixed small and large	72 (41)	52 (40)	242 (41)
Follicular, large cell	13 (7)	12 (9)	137 (23)

Variables	Type of transplant		
	HLA-identical sibling	Autologous purged	Autologous unpurged
Disease stage at diagnosis (%)			
I-II	22 (13)	23 (17)	113 (19)
III-IV	152 (86)	107 (82)	476 (80)
Unknown	2 (1)	1 (1)	8 (1)
B symptoms at diagnosis (%)			
Absent	116 (66)	94 (72)	367 (62)
Present	48 (27)	33 (25)	182 (30)
Unknown	12 (7)	4 (3)	48 (8)
Chemosensitivity (%) ^a			
Sensitive	118 (67)	111 (85)	488 (82)
Resistant	31 (18)	14 (11)	66 (11)
Untreated/unknown	27 (15)	6 (4)	43 (7)
Serum LDH at diagnosis (%) ^a			
Normal	117 (67)	55 (42)	389 (65)
Abnormal	44 (25)	27 (21)	174 (29)
Unknown	15 (8)	49 (37)	34 (6)
Initial chemotherapy (%) ^a			
CHOP ± other	44 (25)	57 (44)	206 (34)
Fludarabine ± other	29 (16)	7 (5)	63 (11)
Other	44 (25)	32 (24)	221 (37)
Unknown	59 (34)	35 (27)	107 (18)
Interval from diagnosis to transplantation (%)			
Less than 1 y	26 (15)	27 (21)	115 (19)
1-2 y	56 (32)	32 (24)	156 (26)
More than 2 y	94 (53)	72 (55)	326 (55)
Graft type (%) ^a			
Bone marrow	135 (77)	100 (76)	89 (15)
Peripheral blood/both	41 (23)	31 (24)	508 (85)
Year of transplantation (%) ^a			
1990-1993	50 (28)	70 (54)	181 (30)
1994-1996	64 (37)	41 (31)	269 (45)
1997-1999	62 (35)	20 (15)	147 (25)
Conditioning regimen (%) ^a			
TBI	120 (68)	44 (34)	184 (31)
Non-TBI	56 (32)	87 (66)	413 (69)
Use of involved field radiation (%)			
No	169 (96)	128 (98)	576 (96)
Yes	7 (4)	3 (2)	21 (4)
GVHD prophylaxis (%)			
T-cell depletion	28 (16)	—	—
MTX ± other	113 (64)	—	—
CSA ± other/other or none	35 (20)	—	—
AGVHD (%)			
None-mild	108 (61)	—	—
Moderate-severe	65 (37)	—	—
Unknown	3 (2)	—	—

Variables	Type of transplant		
	HLA-identical sibling	Autologous purged	Autologous unpurged
Chronic GVHD (%)			
None	131 (74)	—	—
Mild-severe	42 (24)	—	—
Unknown	3 (2)	—	—
Number of centers	56	21	98

CMV=cytomegalovirus; CHOP=Cyclophosphamide Hydroxydaunomycin Oncovin Prednisone; MTX=methotrexate; CSA=cyclosporin A; —, not applicable; and AGVHD, acute graft-versus-host disease.

^a $P < 0.01$ for difference between transplant groups; ^b Early disease indicates patients whose disease status at transplantation is in first or second complete remission, or in first relapse; advanced disease, patients whose disease status at transplantation is in second or greater relapse, in third complete remission, or with primary induction failure.

The median age of those patients receiving allogeneic transplants was 42 versus 49 years for those patients receiving autologous transplants. This difference was not statistically significant. There were statistically significant imbalances among the 3 treatment groups in several other characteristics. Allograft recipients were more likely to have poor performance status, advanced disease, increased LDH, and bone marrow involvement at transplantation and to have chemotherapy-resistant disease. Autograft recipients were more likely to have follicular large cell lymphoma.

Transplantation regimens also varied significantly. Bone marrow grafts and TBI conditioning were most commonly used for allogeneic transplantation. Chemotherapy conditioning was more commonly used for autologous transplantation. Bone marrow was more commonly used for purged autologous grafts, whereas peripheral blood was the preferred stem cell source for unpurged autologous transplantations. Purged autologous transplantation was performed more commonly at the beginning of the decade, whereas allogeneic transplantation was increasingly used toward the late 1990s.

The median follow-up of survivors was 36 months for allograft recipients, 49 months for purged autograft recipients, and 41 months for unpurged autograft recipients.

The types of purging used are summarized in Table 6.2. A variety of methodologies were reported, but purging by in vitro exposure to 4-hydroperoxycyclophosphamide was the most common, accounting for 50% of purged grafts.

Table 6.2 Purging methods used for autologous transplantation (N=131).

n (%)	
Monoclonal antibody	14 (11)
4-hydroperoxycyclophosphamide	65 (50)
Positive stem cell selection	28 (21)
Drugs	24 (18)
4-hydroperoxy cyclophosphamide	65
Etoposide + methylprednisolone	18
Vincristine + methylprednisolone	6

Outcomes

Outcomes are summarized in Table 6.3. TRM after allogeneic transplantation was 24% at 1 year and 30% at 5 years. TRM after autologous transplantation was 4% to 8% at 1 year and 8% to 14% at 5 years. The recurrence rate after allogeneic transplantation was 19% at 1 year with very few relapses thereafter. The recurrence rate after unpurged autologous transplantation was 36% at 1 year and 58% at 5 years. The recurrence rate after purged autologous transplantation was 25% at 1 year and 43% at 5 years.

These marked differences in recurrence rates and TRM resulted in a higher treatment failure (relapse or death) among patients who received allogeneic transplants in the first year after transplantation. But the results were almost identical for disease-free and overall survival after autologous or allogeneic transplantation by 5 years after transplantation.

Table 6.3 Univariate outcome probabilities.

Outcomes		Type of transplant, probability, % (95% CI)		
		HLA-identical sibling	Autologous purged	Autologous unpurged
Treatment-related mortality ^a	1 y	24 (18-32)	8 (5-15)	4 (3-6)
	3 y	28 (21-36)	10 (6-17)	6 (4-8)
	5 y	30 (23-40)	14 (8-22)	8 (6-11)
Relapse ¹	1 y	19 (14-26)	25 (18-34)	36 (32-40)
	3 y	21 (15-28)	40 (32-50)	52 (48-57)
	5 y	21 (15-28)	43 (35-54)	58 (53-63)
Disease-free survival ^b	1 y	55 (48-62)	66 (58-74)	59 (55-63)
	3 y	48 (40-55)	48 (39-57)	41 (37-45)
	5 y	45 (36-53)	39 (30-48)	31 (27-36)
Overall survival ^b	1 y	61 (54-68)	82 (76-89)	81 (78-84)
	3 y	54 (47-62)	71 (63-79)	65 (61-69)
	5 y	51 (43-60)	62 (53-72)	55 (50-60)

^a Cumulative incidence; ^b Kaplan-Meier estimate.

Multivariate analysis

Multivariate analyses allowed comparisons among the 3 main groups, taking into account the potentially confounding effects of other important patient, disease, and treatment-related variables. Results are summarized in Tables 6.4-7.

Table 6.4 Multivariate analysis of treatment-related mortality.

Variables	Relative risk of treatment-related mortality (95% CI)	P
Type of transplant ¹		<0.001 ^b
Autologous unpurged, n=596	1.00	—
Autologous purged, n=130	0.98 (0.52 – 1.87)	0.96
Allogeneic, n=175	4.44 (2.81 – 7.02)	<0.001
Chemosensitivity		<0.001 ^b
Sensitive, n=714	1.00	—
Resistant, n=111	2.71 (1.69 – 4.36)	<0.001
Untreated/unknown, n=76	1.78 (0.99 – 3.19)	0.06
Serum LDH at transplantation		<0.001 ^b
Normal, n=561	1.00	—
Abnormal, n=243	2.03 (1.32 – 3.14)	0.001
Unknown, n=97	2.69 (1.43 – 5.04)	0.002
Age at transplantation		—
No older than 40 y, n=198	1.00	—
Older than 40 y, n=703	1.98 (1.21 – 3.26)	0.007
Conditioning regimen		—
Non-TBI, n=553	1.00	—
TBI, N=348	1.80 (1.16 – 2.77)	0.008
Year of transplantation		0.03 ^b
1990-1993, n=300	1.00	—
1994-1996, n=373	0.67 (0.42 – 1.06)	0.09
1997-1998, n=228	0.49 (0.28 – 0.87)	0.01

— Indicates reference group; LDH=lactate dehydrogenase; TBI=total body irradiation.

^a Allogeneic versus autologous-purged (relative risk (RR), 4.52; 95% CI, 2.29-8.92; $P<0.001$

^b Determined by 2-degree of freedom test.

After adjustment for other covariates, the risk of TRM (Table 6.4) was 4.4 times higher after allogeneic than after autologous transplantation ($P<0.001$). There was no statistically significant difference in TRM after purged versus unpurged autotransplantation. Other factors significantly associated with higher TRM were age older than 40 years, chemotherapy-resistant disease, high serum LDH at transplantation, TBI for conditioning, and transplantation between 1990 and 1993. Figure 6.1 shows the cumulative incidence of TRM by type of transplant.

Table 6.5 Multivariate analysis of relapse.

Variables	Relative risk of relapse (95% CI)	P
Type of transplant ^a		<0.001 ^c
Autologous unpurged, n=596	1.00	—
Autologous purged, n=130	0.74 (0.55-0.99)	0.04
Allogeneic, n=175	0.46 (0.33-0.66)	<0.001
Disease stage at transplantation ^b		—
Early, n=501	1.00	—
Advanced, n=400	1.29 (1.06-1.58)	0.01
Chemosensitivity		0.001 ^c
Sensitive, n=714	1.00	—
Resistant, n=111	1.69 (1.27-2.23)	<0.001
Untreated/unknown, n=76	0.98 (0.68-1.42)	0.93
Serum LDH at transplantation		<0.001 ^c
Normal, n=561	1.00	—
Abnormal, n=243	1.51 (1.21-1.87)	<0.001
Unknown, n=97	1.00 (0.69-1.43)	0.98
Karnofsky performance score at transplantation		—
90%-100%, n=641	1.00	—
No more than 80%, n=260	1.31 (1.07-1.61)	0.01
Conditioning regimen		—
Non-TBI, n=553	1.00	—
TBI, n=348	0.77 (0.62-0.95)	0.02
Interval from diagnosis to transplantation		0.05 ^c
Less than 1 y, n=168	1.00	—
1-2 y, n=244	1.37 (1.01-1.87)	0.05
More than 2 y, n=489	1.40 (1.06-1.84)	0.01
Bone marrow involvement at transplantation		—
No, n=705	1.00	—
Yes, n=196	1.31 (1.04-1.65)	0.02

— Indicates reference group; LDH=lactate dehydrogenase; TBI=total body irradiation.

^a Allogeneic versus autologous purged transplantation (RR, 0.63; 95% CI, 0.41-0.97; $P<0.03$);

^b Early disease indicates complete remission (1st or 2nd) or relapse (1st); advanced disease, complete remission (3rd) or relapse (>2nd) or primary induction failure.

^c Determined by 2-degree of freedom test.

Figure 6.1 Cumulative incidences of treatment-related mortality by type of transplant.

The risk for disease recurrence (Table 6.5) was 54% lower in recipients of allogeneic transplants ($P<0.001$) and 26% lower in recipients of purged autotransplants ($P=0.04$) than in recipients of unpurged autotransplants. Other factors associated with higher risk of relapse were advanced disease, high serum LDH at transplantation, chemotherapy-resistant disease, poor Karnofsky performance score, bone marrow involvement, and an interval greater than 1 year between diagnosis and transplantation. The use of TBI was associated with a lower risk of disease recurrence. Figure 6.2 shows the cumulative incidence of relapse by type of transplant.

Figure 6.2 Cumulative incidences of relapse by type of transplant.

The risk of treatment failure (relapse or death) (Table 6.6) was higher after purged autologous than unpurged autologous transplantation, although this difference was not statistically different ($P=0.14$). In the first 6 months after transplantation, the risk of treatment failure was higher among patients who received allotransplants than autotransplants ($P<0.001$). Among patients surviving 6 months in remission, the subsequent risk of treatment failure was significantly lower among patients who received allotransplants than autotransplants ($P<0.001$). Again, advanced disease stage, chemotherapy-resistant disease, high LDH at transplantation, age older than 40 years, poor performance status, and prolonged delay between diagnosis and transplantation were associated with lower DFS. We failed to detect statistical difference in DFS by year of transplantation; however, this could be due to lack of statistical power. Figure 6.3 shows the probability of DFS by type of transplant adjusted for other significant covariates.

Figure 6.3 Probabilities of disease-free survival by type of transplant, adjusted for other significant covariates listed in Table 6.6.

Table 6.6 Multivariate analysis of disease-free-survival.

Variables	Relative risk of treatment failure (95% CI)	P
Type of transplant ^a		<0.001 ^d
Autologous unpurged, n=596	1.00	—
Autologous purged, n=130	0.82 (0.63-1.07)	0.14
Allogeneic, n=175 ^b		—
First 6 mo after transplantation	1.77 (1.34-2.34)	<0.001
6 mo after transplantation	0.35 (0.22-0.57)	<0.001
Disease stage at transplantation ^c		—
Early (n=501)	1.00	—
Advanced (n=400)	1.27 (1.07-1.52)	0.007
Chemosensitivity		<0.001□
Sensitive, n=714	1.00	—
Resistant, n=111	1.92 (1.52-2.44)	<0.001
Untreated/unknown, n=76	1.12 (0.83-1.53)	0.45
Serum LDH at transplantation		<0.001□
Normal, n=561	1.00	—
Abnormal, n=243	1.58 (1.30-1.93)	<0.0001
Unknown, n=97	0.95 (0.70-1.30)	0.76
Karnofsky performance score at transplantation		—
90%-100%, n=641	1.00	—
No more than 80%, n=260	1.31 (1.09-1.57)	0.004
Interval from diagnosis to transplantation		0.05 ^e
Less than 1 y, n=168	1.00	—
1-2 y, n=244	1.37 (1.04-1.80)	0.03
More than 2 y, n=489	1.35 (1.06-1.72)	0.02
Age at transplantation		—
No older than 40 y, n=198	1.00	—
Older than 40 y, n=703	1.31 (1.04-1.64)	0.02

— Indicates reference group; LDH=lactate dehydrogenase.

^a Time-dependent covariate; such that risk of death before and after 6 months after transplantation varies; ^b Allogeneic (≤ 6 months) versus autologous-purged transplantation (RR, 2.15; 95% CI, 1.50-3.08; $P<0.001$); allogeneic (>6 months) versus autologous-purged transplantation (RR, 0.43; 95% CI, 0.26-0.73; $P<0.001$); ^c Early disease indicates complete remission (1st or 2nd) or relapse (1st); advanced disease, complete remission (3rd) or relapse (>2 nd) or primary induction failure; ^d Determined by 3-degree of freedom test; ^e Determined by 2-degree of freedom test.

The risk of mortality (Table 6.7) was lower after purged versus unpurged autotransplantation ($P=0.03$). In the first 6 months after transplantation, the risk of death was higher among patients who received allogeneic transplants than autologous transplants ($P<0.001$). Among patients who survived the first 6 months, there was a slightly lower risk of death in the allotransplant group ($P=0.14$). Advanced disease stage, chemotherapy-resistant disease, high serum LDH at transplantation, age older than 40 years, poor performance status, and prolonged delay between diagnosis and transplantation were associated with worse survival as was transplantation in the first 3 years of the decade. Figure 6.4 shows the probability of survival by type of transplant adjusted for other significant covariates. The 5-year adjusted probabilities of survival after allotransplantations, purged autologous transplantations, and unpurged autologous transplantations were 51% (95% confidence interval [CI], 43%-60%), 62% (95% CI, 53%-72%), and 55% (95% CI, 50%-60%), respectively.

In a separate multivariate analysis restricted to recipients of allogeneic transplants, we evaluated the effect of acute and chronic GVHD on the probability of disease recurrence by using a time-dependent covariate. The risk of relapse for patients with acute GVHD was not significantly different from that of patients without acute GVHD. The risk of relapse for patients with chronic GVHD after transplantation was not significantly different from that of patients without chronic GVHD.

Figure 6.4 Probabilities of survival by type of transplant adjusted for other significant covariates listed in Table 6.7.

Table 6.7 Multivariate analysis of overall survival.

Variables	Relative risk of death (95% CI)	P
Type of transplant ^a		<0.001 ^d
Autologous unpurged, n=597	1.00	—
Autologous purged, n=131	0.67 (0.48-0.95)	0.03
Allogeneic, n=176 ^b		—
First 6 mo after transplantation	3.59 (2.52-5.10)	<0.001
6 mo after transplantation	0.71 (0.44-1.13)	0.14
Disease stage at transplantation ^c		—
Early, n=504	1.00	—
Advanced, n=400	1.26 (1.01-1.57)	0.04
Chemosensitivity		<0.001 ^e
Sensitive, n=717	1.00	—
Resistant, n=111	2.63 (2.01-3.44)	<0.001
Untreated/unknown, n=76	1.42 (1.00-2.02)	0.06
Serum LDH at transplantation		<0.001 ^e
Normal, n=561	1.00	—
Abnormal, n=245	2.26 (1.79-2.84)	<0.001
Unknown, n=98	2.11 (1.48-3.01)	<0.001
Karnofsky performance score at transplantation		—
90%-100%, n=644	1.00	—
No more than 80%, n=260	1.51 (1.21-1.88)	<0.001
Interval from diagnosis to transplantation		0.001 ^e
Less than 1 y, n=168	1.00	—
1-2 y, n=244	1.71 (1.20-2.42)	0.003
More than 2 y, n=492	1.38 (1.01-1.90)	0.05
Age at transplantation		—
No older than 40 y, n=199	1.00	—
Older than 40 y, n=705	1.42 (1.07-1.88)	0.01
Year of transplantation		0.007 ^e
1990-1993, n=301	1.00	—
1994-1996, n=374	0.71 (0.55-0.90)	0.006
1997-1998, n=229	0.67 (0.49-0.92)	0.01

— Indicates reference group; LDH=lactate dehydrogenase.

^a Time-dependent covariate; such that risk of death before and after 6 months after transplantation varies; ^b Allogeneic (≤ 6 months) versus autologous-purged transplantation (RR, 5.33; 95% CI, 3.34-8.50; $P<0.001$); allogeneic (≤ 6 months) versus autologous-purged transplantation (RR, 1.05; 95% CI, 0.60-1.83; $P<0.87$); ^c Early disease indicates complete remission (1st or 2nd) or relapse (1st); advanced disease, complete remission (3rd) or relapse (>2 nd) or primary induction failure; ^d Determined by 3-degree of freedom test; ^e Determined by 2-degree of freedom test.

Discussion

Follicular lymphoma, although unpredictable and often associated with a prolonged course, is in most cases a fatal illness.¹ Although numerous treatment modalities are effective, very few are shown to prolong survival, and none are curative, with the possible exception of autologous or allogeneic transplantation.²² A recently reported randomized study of 89 patients with a

median follow-up of 6 years indicates a considerable benefit in disease-free survival ($P=0.0037$) and survival ($P=0.079$) of autologous transplantation compared with conventional chemotherapy for patients with recurrent follicular lymphoma.³³

The identification of patient- or disease-related prognostic variables in a large group of patients undergoing these procedures constituted a major purpose of the current analysis. We hoped to identify patient populations that might specifically benefit from allogeneic versus autologous transplantation and studied the effect of conditioning (TBI versus non-TBI), stem cell source (peripheral blood versus bone marrow), and stem cell manipulation (purged versus unpurged) on outcome. In a separate analysis restricted to recipients of allogeneic transplants, we evaluated the relationship between acute and chronic GVHD and disease recurrence. We excluded patients receiving nonmyeloablative regimens because few of such reported patients have yet achieved sufficient follow-up for meaningful analysis.²²

We confirmed that both autologous and allogeneic transplantation induce long-term disease control in a proportion of patients. Disease-free survival at 5 years is approximately 50% with both procedures, a result consistent with previous studies. As in most previous studies a continuous pattern of treatment failure was observed after autologous transplantation, suggesting that cure may be achieved in only a small minority of patients. Most late failures were due to disease recurrence, but some were also related to the occurrence of secondary hematologic malignancy, a well-known complication following autologous transplantation.³⁴⁻³⁶ (Table 6.8). The pattern of treatment failure after allogeneic transplantation was markedly different from that after autologous transplantation. The recurrence rate was only 20%, with almost all recurrences occurring within the first year after transplantation. This recurrence rate was virtually identical to that observed in our previous report that included many fewer patients with follicular lymphoma and covered, in part, an earlier time period.²⁷ Long-term outcome after allogeneic transplantation was, however, adversely affected by a high early TRM rate.

Table 6.8 Causes of nonrelapse mortality.

Cause of death	Type of transplant, %		
	HLA-identical, sibling, n=50	Autologous purged n=18	Autologous unpurged, n=45
New malignancy	—	5	9
GVHD	10	—	—
Interstitial pneumonitis	28	20	28
Infection	18	24	22
Organ failure	24	22	18
Other causes	16	17	13
Unknown	4	12	10

— Indicates no events.

Patient- and disease-related covariates that adversely affected overall outcome included advanced age, poor performance status, an interval between diagnosis and transplantation of more than 1 year, chemotherapy-refractory disease, and increased serum LDH at transplantation. Patients with any of these features had lower overall survival regardless of the type of transplant they received. Age,¹² serum LDH,¹⁶ chemotherapy refractory disease,^{12,13,16,17} and bone marrow involvement¹⁰ have all been previously correlated with adverse outcome of autologous transplantation. In our prior report on allogeneic transplantation, patient age older than 40 years and chemotherapy refractory disease were associated with a worse outcome.²⁷ Of note, neither disease histology (or lymphoma "grade," by World Health Organization [WHO] classification³⁷), stem cell source (bone marrow versus peripheral blood stem cells), nor use of posttransplantation myeloid growth factors correlated with outcome in multivariate analysis.

The Dana-Farber group initially reported a correlation between outcome of transplantation and optimal purging of the stem cell product.³⁸ In an update of their experience, patients receiving transplants of stem cell products devoid of lymphoma cells had up to 80% DFS at 8 years after transplantation.¹⁰ Those patients receiving cells that were contaminated with lymphoma had a very high recurrence rate. These results are confirmed in some,^{14,39} but not all studies,^{8,12,13,33,40,41} and the clinical benefits of stem cell purging remain a matter of ongoing study. Our analysis is the first controlled comparison between the outcomes of purged versus unpurged transplantation in a large patient group. In multivariate analyses, an effect of stem cell purging on recurrence rates and overall survival was found. As indicated by the relapse curve, there is a decrease in early as well as late recurrences associated with purging. These data suggest that graft purging, even with current technical limitations, might be of clinical benefit in patients with follicular lymphoma undergoing autologous transplantation. This observation is consistent with our observation of a markedly reduced recurrence rate after syngeneic versus autologous transplantation in follicular lymphoma, because syngeneic transplantation may be considered the equivalent of an optimally purged autologous transplantation.⁴²

Allogeneic transplantation was associated with a low early recurrence rate and near absence of documented recurrences beyond 1 year after transplantation. The lack of late recurrences confirms the curative potential of allogeneic transplantation. Whether cure results from graft-versus-lymphoma (GVL) effects^{28,43-48} or from the complete eradication of tumor by high-dose chemotherapy followed by infusion of uncontaminated stem cells (a "purging" effect)^{10,42} or from a combination of both is unclear. In the current study, we were unable to detect a GVL effect of either acute or chronic GVHD. Because

of sample size limitations, it is possible we lacked the power to detect such an effect.

The use of TBI was associated with increased TRM, but with decreased recurrence rates. In our previous analysis of allogeneic transplantation for follicular lymphoma, the use of TBI was associated with an improved outcome.²⁷ By contrast, a European analysis of patients undergoing autologous transplantation indicated a worse overall survival for patients with low-grade lymphoma receiving TBI.⁴¹ Although these data must be interpreted with caution, they may indicate that TBI is a highly effective although toxic treatment for follicular lymphoma. They may also suggest that less toxic methods of administration of radiation, perhaps in the form of radiolabeled antibodies, may improve transplantation outcomes.⁴⁹

Figures 6.5 and 6.6 show survival rates after autologous and allogeneic transplantation during successive 3-year periods. It is reassuring that, independent of other covariates, TRM after transplantation, particularly after allogeneic transplantation, declined over the past decade. This decline is probably related to selection of patients with more favorable characteristics, improvements in supportive care, and improvements in early diagnosis and treatment of opportunistic infections.

This analysis confirms that transplantation has its major benefit when performed early in the course of disease. Transplantation for refractory disease is associated with a dismal course and should probably be avoided. When comparing the patient characteristics of patients in this study with those of our previous report on allogeneic transplantation for low-grade lymphoma, it is apparent that this is the approach increasingly favored by most physicians. Patients in the current study had, on average, far less advanced disease than those in our previous report that included patients receiving transplants between 1985 and 1995.

Whether to recommend autologous or allogeneic transplantation for patients who have an HLA-matched sibling donor remains, at present, a matter of physician and patient preference. We had hoped to identify variables that would have a differential effect on allogeneic versus autologous transplantation but were unable to do so. Adverse prognostic features had similar effects on long-term outcome of both allogeneic and autologous transplantation.

If autologous transplantation is performed, consideration should be given to the use of in vitro or in vivo stem cell purging. Novel in vitro purging methods continue to be explored and are of considerable interest.^{50,51} Data indicating that administration of rituximab results in highly efficient purging of peripheral blood stem cell products require testing in larger cohorts of patients.⁵² Whenever one recommends autologous transplantation, the considerable risk for secondary myelodysplastic syndrome (MDS) should be taken into account.³⁴⁻³⁶ Allogeneic transplantation has an increased risk of early TRM, but,

as shown in Figure 6.5, survival has improved in recent years. In the most recent patient cohorts, 1-year survival after transplantation is approximately 80%. The rapid development of new transplantation technologies may further reduce recurrence rates as well as TRM and, thus, affect the risk-benefit ratios of these procedures. Reduced intensity conditioning, which relies on graft-versus-lymphoma effects, is one of the strategies currently under study. Our analysis failed to identify a beneficial effect of GVHD on the incidence of relapse, thus raising some concerns about the ultimate effect of reduced intensity conditioning. However, with highly effective high-dose conditioning, an otherwise effective GVL reaction may have been difficult to detect. A plethora of novel agents and approaches are now available or are under study for management of follicular lymphoma. These agents include rituximab, its radiolabeled equivalent ibritumomab, and other monoclonal antibodies, as well as vaccine approaches. High-dose chemotherapy and autologous and allogeneic transplantation constitute a different, but possibly complementary, approach. Future studies integrating various approaches might render curative therapy for all patients with follicular lymphoma a realistic goal.

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Chapter 7

Myeloablative allogeneic hematopoietic stem cell transplantation in patients who experience relapse after autologous stem cell transplantation for lymphoma: a report of the international bone marrow transplant registry

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Abstract

Myeloablative allogeneic hematopoietic stem cell transplantation (allo-HSCT) is increasingly used in patients with lymphoma who experience disease relapse after autologous hematopoietic stem cell transplantation (auto-HSCT) because the allograft is tumor free and may induce a graft-versus-tumor effect. We analyzed 114 patients treated with this approach from 1990 to 1999 to assess disease progression, progression-free survival (PFS), and overall survival (OS). Cumulative incidence of disease progression at 3 years was 52%, whereas treatment related mortality was 22%, lower than previously reported. Three-year probabilities of OS and PFS were 33% and 25%, respectively. With prolonged follow-up, however, nearly all patients experienced disease progression, and 5-year probabilities were 24% and 5%, respectively. Complete remission at the time of allo-HSCT and use of total body irradiation (TBI) in patients with non-Hodgkin lymphoma (NHL) were associated with lower rates of disease progression and higher rates of OS. In summary, allo-HSCT is feasible for patients with lymphoma who have relapses after auto-HSCT and can result in prolonged survival for some, but it is usually not curative. Most likely to benefit are patients who have HLA-matched sibling donors, are in remission, and have good performance status.

Introduction

High-dose chemotherapy with autologous hematopoietic stem cell transplantation (auto-HSCT) has an established role in the treatment of patients with lymphoid malignancies.¹⁻³ Unfortunately, relapse or progression of lymphoma is common after auto-HSCT, and the prognosis for patients who experience relapse is poor.⁴⁻⁶ Conventional-dose chemotherapy can induce remission in a small proportion of these patients, but the remissions are usually short.⁴ Second auto-HSCT is sometimes performed, but it is most likely to benefit patients in prolonged remission after the initial auto-HSCT.^{7,8}

Another therapeutic approach for patients who experience relapse after auto-HSCT is to perform myeloablative allogeneic hematopoietic stem cell transplantation (allo-HSCT).⁹ Potential advantages of allo-HSCT include the use of a tumor-free graft and immune-mediated graft-versus-tumor effects.^{10,11} Information is limited regarding the outcome for patients who undergo allo-HSCT after autologous transplantation for lymphoma fails. Published reports include small numbers of patients and show conflicting results.^{8,12-17} To more precisely determine outcomes and to further identify prognostic variables for patients who undergo allo-HSCT after failed auto-HSCT, we undertook an analysis of patients treated between 1990 and 1999 and reported to the International Bone Marrow Transplant Registry (IBMTR) and the Autologous Blood and Marrow Transplant Registry (ABMTR).

Patients and methods

Data sources

The IBMTR/ABMTR is a voluntary working group of more than 400 HSCT centers worldwide that contribute detailed data on consecutive allogeneic or autologous HSCT recipients to a Statistical Center at the Health Policy Institute of the Medical College of Wisconsin in Milwaukee. Approximately 40% of allo-HSCTs worldwide and more than 50% of auto-HSCTs in North and South America are registered with the IBMTR/ABMTR. Participating centers are required to report all transplantations consecutively; compliance is monitored by on-site audits. Patients are followed up longitudinally, with yearly follow-up. Computerized checks for errors, physician reviews of submitted data, and on-site audits of participating centers ensure data quality. Requests for data on disease progression or death for registered patients are at 1-year intervals. IBMTR observational studies are conducted with a waiver of informed consent

and in compliance with HIPAA regulations as determined by the institutional review board and the privacy officer of the Medical College of Wisconsin.

Patients

We reviewed the records of all patients with lymphoma reported to the IBMTR/ABMTR who underwent allo-HSCT after relapse from auto-HSCT. We included patients with Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL), including low-, intermediate-, and high-grade lymphomas according to the Working Formulation for the Classification of Lymphomas.¹⁸ The allo-HSCT had to have been performed between 1990 and 1999. Patients who received nonmyeloablative conditioning regimens were excluded.

Study end points

Primary outcomes studied were disease progression, progression-free survival (PFS), and overall survival (OS). Progression was defined as any increase in size of sites of disease, development of new sites of disease, or recurrence of disease after an initial complete response. OS was defined as the time from transplantation to death from any cause. PFS was defined as time from transplantation to relapse, progressive disease, or death from any cause. Other outcomes examined were transplant-related mortality (TRM), defined as death from any cause in the first 28 days or, thereafter, death without progression, and the incidence and severity of acute and chronic graft-versus-host disease (GVHD). Acute GVHD was defined as moderate to severe (grades II-IV) using established criteria; patients surviving more than 21 days with evidence of engraftment were considered at risk. Chronic GVHD was determined by clinical criteria in patients surviving more than 90 days with evidence of engraftment.

Statistical analysis

Probabilities of OS and PFS were calculated using the Kaplan-Meier product limit estimate, and probabilities of progression, TRM, and acute and chronic GVHD were calculated using cumulative incidence to allow for competing risks. Associations between patient-, disease-, and transplant-related factors and the outcomes of interest were assessed using multivariate Cox proportional hazards regression. Variables included in the model building are listed in Table 7.1. For most patients, we had few data about details of auto-HSCT or treatment before auto-HSCT and, hence, could not examine these factors in model building. HL and NHL are different biologically, and initial treatment for HL commonly involves radiation, limiting the choices for allo-HSCT conditioning in HL. Consequently, we forced the factor HL versus NHL in all the models built and examined interactions between this factor and other significant covariates

identified. If the interaction term was significant, indicating differential effects in HL and NHL, the final model subdivides patients according to this interaction term. For example, Tables 7.4, 7.5, and 7.6 subdivide patients into 4 groups: NHL with or without total body irradiation (TBI) and HL with or without TBI. All computations used the procedure PHREG in the SAS statistical package. Forward stepwise variable selection at a 0.05 significance level was used to identify covariates associated with outcomes. All variables were tested for the assumption of proportional hazards using a time-dependent covariate. All variables satisfied the proportionality assumption. First-order interactions were tested for all significant covariates. Overall covariate effects were tested using the Wald test.

Results

Patient and transplant characteristics

Patient-, disease-, and transplant-related characteristics are listed in Table 7.1. One hundred fourteen patients from 54 different centers underwent allo-HSCT following relapse after auto-HSCT. Their median age at the time of allo-HSCT was 34 years (range, 15-65 years). Sixty-five (57%) patients were male. Fifty (44%) patients had Karnofsky performance scores of 80% or less at the time of allo-HSCT.

Seventy-nine (69%) patients had NHL, and 35 (31%) had HL. Among patients with NHL, 44 (56%) had intermediate-grade, 16 (20%) had low-grade, and 8 (10%) had high-grade lymphomas; 11 (14%) had other types of NHL not defined in the Working Formulation.¹⁸

The median time interval from diagnosis to auto-HSCT was 14 months (range, 3-130 months). Forty-three (38%) patients underwent auto-HSCT less than 1 year after the diagnosis of lymphoma. The median interval between auto-HSCT and allo-HSCT was 16 months (range, 2-66 months). Only 24 (21%) patients were in complete remission at the time of allo-HSCT. Seventy (61%) patients received transplants from an HLA-identical sibling, 17 (14%) from a haploidentical sibling, and 27 (25%) from an unrelated donor. Seventy-seven (68%) patients received bone marrow as the source of allogeneic stem cells; the remaining 37 (32%) patients received peripheral blood. TBI was used as part of the conditioning regimen for allo-HSCT in 45 (39%) patients. Eighty-four (74%) patients received hematopoietic growth factors (HGFs) within 7 days of allo-HSCT. GVHD prophylaxis included methotrexate and cyclosporine in 74 (65%) patients, combinations of cyclosporine with other agents in 24 (21%) patients, and T-cell depletion of the graft in 16 (14%) patients.

Table 7.1 Patient-, disease-, and transplant-related characteristics of patients with HL or NHL who underwent allo-HSCT following relapse after autologous transplantation, 1990 to 1999, reported to IBMTR.

Variables	N(%) ^a
N	114
Age, y, median (range)	34 (15-65) ^b
Male	65 (57)
Karnofsky performance score at allo-HSCT	
90%-100%	64 (56)
80%	29 (25)
70%	16 (14)
60%	2 (2)
50% or lower	3 (3)
Disease type	
NHL	79 (69)
Low grade	16 (20)
Intermediate grade	44 (56)
High grade	8 (10)
Other ^c	11 (14)
HL	35 (31)
Interval from diagnosis to first, autologous, transplantation, mo, median (range)	14 (3-130) ^b
12 or less	43 (38)
More than 12	71 (62)
Interval from auto-HSCT to allo-HSCT, mo, median (range)	16 (2-66) ^b
12 or less	44 (39)
More than 12	70 (61)
Disease status before allo-HSCT	
Complete remission	24 (21)
Relapse or persistent disease, chemosensitive	39 (35)
Relapse or persistent disease, chemoresistant	23 (20)
Relapse or persistent, untreated after auto-HSCT	28 (24)
Donor type for allo-HSCT	
HLA-identical sibling	70 (61)
Haploidentical sibling	17 (14)
Unrelated	27 (25)
Graft type used for allo-HSCT	
Bone marrow	77 (68)
Peripheral blood	37 (32)
TBI for allo-HSCT	45 (39)
Posttransplantation use of growth factors, within 7 d	84 (74)
GVHD prophylaxis	
MTX + CSA ± others	74 (65)
CSA ± others	24 (21)
T-cell depletion ± others	16 (14)
Years of allo-HSCT	
1990-1996	56 (49)
1997-1999	58 (51)
No. centers reporting	54
Follow-up time of survivors, mo, median (range)	43 (3-89) ^b
75th percentile	21
25th percentile	58

MTX=methotrexate; CSA=cyclosporine; ^a Categorical variable; ^b Continuous variable; ^c Includes NHL composite, mantle cell, and peripheral T-cell lymphomas.

Fifty-eight (51%) allo-HSCTs were performed in the 3 years between 1997 and 1999, whereas the remaining procedures were performed in the previous 7 years, 1990 to 1996. Median follow-up of survivors was 43 months.

Outcomes

Estimated outcomes are summarized in Table 7.2. Of the 114 patients studied, 79 (69%) died, 31 (27%) were alive with lymphoma, and 4 (4%) were alive without evidence of lymphoma at last follow-up. The 100-day mortality rate was 21% (95% confidence interval [95% CI], 14%-29%). TRM after allo-HSCT was 22% (95% CI, 16%-31%) at 1 year and 25% (95% CI, 17%-33%) at 5 years. Twenty-four of 90 (27%) patients not in complete remission at the time of allo-HSCT achieved complete remission after allo-HSCT.

Table 7.2 Outcome probabilities.

	100d	1y	3y	5y
Grade II-IV acute GVHD ^a	29 (21-37)	—	—	—
Chronic GVHD ^a	—	11 (6-18)	12 (7-20)	13 (7-20)
TRM ^a	21 (14-29)	22 (16-31)	22 (16-31)	25 (17-33)
Progression ^a	—	45 (36-54)	52 (43-61)	70 (61-76)
Progression-free survival ^b	—	32 (24-41)	25 (18-33)	5 (2-10)
Survival ^b	—	37 (28-46)	33 (24-42)	24 (14-37)

Values in parentheses represent 95% CI.; — indicates not applicable; ^a Cumulative incidence rate;

^b Kaplan-Meier estimate.

Disease-progression rate was 45% (95% CI, 36%-54%) at 1 year and increased to 70% (95% CI, 61%-76%) at 5 years after transplantation. Figure 7.1 illustrates the cumulative incidences of progression and TRM. The probability of OS at 1 year was 37% (95% CI, 28%-46%) and decreased to 33% (95% CI, 24%-42%) at 3 years and 24% (95% CI, 14%-37%) at 5 years after transplantation (Figure 7.2). PFS was 32% (95% CI, 24%-41%), 25% (95% CI, 18%-33%), and 5% (95% CI, 2%-10%) at 1, 3, and 5 years after transplantation, respectively.

The 100-day probability of developing grades II to IV acute GVHD was 29% (95% CI, 21%-37%). The 3-year probability of developing chronic GVHD was 12% (95% CI, 7%-20%). There was no difference in the risk for disease progression between patients who developed grades II to IV acute GVHD and those who did not. For patients who experienced engraftment and survived at least 21 days (n=99), the relative risk (RR) of disease progression for patients with grades II to IV acute GVHD compared with those without acute GVHD using time-dependent Cox models was 0.93 (95% CI, 0.58-1.49; *P*=0.76). Additionally, there was no difference in the risk for progression between patients in whom chronic GVHD developed and those in whom it did not among

patients who experienced engraftment and survived at least 90 days ($n=62$), with an RR of 0.81 (95% CI, 0.40-1.67; $P=0.57$). There were no differences in OS, PFS, or TRM between patients with HL and NHL. In addition, there were no differences in outcome among patients with low-, intermediate-, or high-grade NHL (data not shown).

Figure 7.1 Cumulative incidences of TRM and disease progression after allo-HSCT in patients who experience relapse after auto-HSCT for HL or NHL.

Figure 7.2 Probabilities of PFS and OS after allo-HSCT in patients who experience relapse after auto-HSCT for HL or NHL.

Multivariate analysis

The only factor significantly correlated with TRM risk was donor type. Patients with haploidentical sibling donors had a 3-fold increased risk for TRM (RR, 3.17; 95% CI, 1.04-3.31; $P=0.02$), and those with unrelated donors had a 2-fold increased risk for TRM (RR, 2.15; 95% CI, 0.90-5.12; $P=0.08$) compared with recipients of transplants from HLA-identical siblings.

Table 7.3 shows the multivariate analysis of disease progression. Rate of disease progression was associated with type of conditioning regimen and disease status at allo-HSCT. The effect of conditioning was dependent on the type of lymphoma. Patients with NHL who underwent non-TBI-conditioning HSCT had a 3-fold increased rate of disease progression compared with patients who received TBI. Patients with HL had an increased rate of recurrence compared with the risk in NHL patients receiving TBI. However, among HL patients, we failed to detect any effect of TBI on recurrence. Patients who had active disease before allo-HSCT also had an increased rate of progression compared with patients who underwent transplantation while in remission. Using patients in complete remission as the reference group, the RR for progression ranged from 1.38 for patients with chemosensitive relapse to 2.90 for patients with chemotherapy-refractory relapse and 3.45 for patients with untreated relapse.

Table 7.3 Multivariate analysis of progression.

Variables	RR of progression (95% CI)	P
Disease type and use of TBI		0.002 ^b
NHL with TBI, n=37	1.00	—
NHL no TBI, n=42	3.02 (1.71-5.32)	<0.001
HL with TBI, n=8 ^a	2.18 (0.86-5.52)	0.10
HL no TBI, n=27	2.15 (1.14-4.05)	0.02
Disease status before second transplantation		<0.001 ^b
Complete remission, n=24	1.00	—
Relapse/primary induction failure, chemosensitive, n=39	1.38 (0.77-2.46)	0.28
Relapse/primary induction failure, chemoresistant, n=23	2.90 (1.38-6.08)	0.005
Relapse/primary induction failure, untreated, n=28	3.45 (1.74-6.87)	<0.001

— Indicates not applicable; ^a Pairwise comparison: HL with TBI versus HL with no TBI ($P=0.98$); ^b 3 degrees of freedom test.

Table 7.4 shows the multivariate analysis of PFS (treatment failure, death, or progression). Patients with NHL who received non-TBI conditioning for allo-HSCT had an approximately 2.5-fold increased rate of treatment failure compared with patients who received TBI. Patients with HL had a higher rate of treatment failure than did patients with NHL who received TBI. However, among patients with HL, there was no association between TBI and treatment failure. Patients who had active disease before allo-HSCT also had an increased rate of treatment failure compared with patients who underwent transplantation in remission. Using patients in complete remission as the reference group, the relative risk for treatment failure ranged from 1.74 for patients with chemosensitive relapse to 3.91 for patients with chemotherapy

refractory relapse and to 3.68 for patients with untreated relapse. Patients who received transplants from haploidentical siblings or from unrelated donors had a higher rate of treatment failure than those who received transplants from HLA-identical siblings.

Table 7.4 Multivariate analysis of PFS.

Variables	RR of treatment failure (95% CI)	P
Disease type and use of TBI		0.002 ^b
NHL with TBI, n=37	1.00	—
NHL no TBI, n=42	2.45 (1.49-4.02)	<0.001
HL with TBI, n=8 ^a	1.77 (0.78-4.01)	0.17
HL no TBI, n=27	1.97 (1.14-3.41)	0.01
Disease status before second transplantation		<0.001 ^b
Complete remission, n=24	1.00	—
Relapse/primary induction failure, chemosensitive, n=39	1.74 (0.99-3.03)	0.06
Relapse/primary induction failure, chemoresistant, n=23	3.91 (2.05-7.44)	<0.001
Relapse/primary induction failure, untreated, n=28	3.68 (1.97-6.84)	<0.001
Donor type		0.05 ^c
HLA-identical sibling, n=70	1.00	—
Haploidentical sibling, n=17	1.85 (1.04-3.31)	0.04
Unrelated, n=27	1.47 (0.92-2.34)	0.11

Treatment failure indicates disease progression or death; — indicates not applicable; ^a pairwise comparison: HL with TBI versus HL with no TBI ($P=0.82$); ^b 3 degrees of freedom test; ^c 2 degrees of freedom test.

Table 7.5 shows the multivariate analysis of overall mortality. Patients with NHL who received non-TBI conditioning for allo-HSCT had a 2-fold increased mortality rate compared with patients who received TBI. The mortality rate for patients with HL was similar to that of patients with NHL receiving TBI. Among patients with HL, we failed to detect any association between TBI and mortality rate. Patients with low Karnofsky performance scores (80%) at the time of allo-HSCT died at an approximately 2-fold increased rate. Patients who had active disease before allo-HSCT also had a higher mortality rate than did patients who underwent transplantation while in remission. Finally, the mortality rate was higher in patients who received transplants from haploidentical siblings or from unrelated donors than in patients who received transplants from HLA-identical siblings. Figures 7.3-7.6, and 6 show probabilities of OS according to the identified risk factors.

In summary, multivariate analyses showed that TBI was associated with a decreased rate of disease progression and higher rates of PFS and OS in patients with NHL, but no such effect was shown in a smaller group of patients with HL. Chemotherapy responsiveness was also associated with decreased rate of disease progression and higher PFS and OS rates. Transplants from donors other than HLA-matched siblings were associated with higher TRM and

lower PFS and OS rates, and good performance status was associated with higher OS rate.

Table 7.5 Multivariate analysis of risk for death.

Variables	RR of death (95% CI)	P
Disease type and use of TBI		0.001 ^b
NHL with TBI, n=37	1.00	—
NHL no TBI, n=42	2.11 (1.19-3.77)	0.01
HL with TBI, n=8 ^a	0.98 (0.33-2.85)	0.96
HL no TBI, n=27	1.44 (0.76-2.76)	0.26
Karnofsky performance score at transplantation		—
90%-100%, n=64	1.00	—
80% or less, n=50	1.76 (1.10-2.82)	0.02
Disease status before second transplantation		0.006 ^b
Complete remission, n=24	1.00	—
Relapse/primary induction failure, chemosensitive, n=39	2.76 (1.27-5.96)	0.01
Relapse/primary induction failure, chemoresistant, n=23	3.95 (1.70-9.15)	0.001
Relapse/primary induction failure, untreated, n=28	3.74 (1.67-8.41)	0.001
Donor type		0.004 ^c
HLA-identical sibling, n=70	1.00	—
Haploidentical sibling, n=17	2.40 (1.24-4.66)	0.009
Unrelated, n=27	2.14 (1.24-3.68)	0.006

— Indicates not applicable; ^a pairwise comparison: HL with TBI versus HL with no TBI ($P=0.47$); ^b 3 degrees of freedom test; ^c 2 degrees of freedom test.

Figure 7.3 Probability of survival after allo-HSCT in patients who experience relapse after auto-HSCT for HL or NHL, according to Karnofsky performance score at allo-HSCT.

Figure 7.4 Probability of survival after allo-HSCT in patients who experience relapse after auto-HSCT for HL or NHL according to disease status at allo-HSCT.

Figure 7.5 Probability of survival after allo-HSCT in patients who experience relapse after auto-HSCT for HL or NHL according to type of donor.

Figure 7.6 Probability of survival after allo-HSCT in patients who experience relapse after auto-HSCT for HL or NHL according to disease type and use of TBI as part of conditioning regimen. NHL with TBI versus NHL with no TBI ($P=0.01$). HL with TBI versus HL with no TBI ($P=0.47$).

Discussion

Recurrence occurs relatively frequently after auto-HSCT for lymphoma, and managing patients who experience relapse is difficult. Allo-HSCT is increasingly used because it has the potential advantages of a graft-versus-tumor effect and a tumor-free graft. Despite increasing use, reports describing the results of allo-HSCT are few and include small numbers of patients.^{8,12-17} Identifying patient- or disease-related prognostic variables in a large group of patients undergoing allo-HSCT after failure of auto-HSCT was the major purpose of this analysis. We excluded patients who underwent nonmyeloablative therapy because this technique was introduced recently and the follow-up of patients receiving nonmyeloablative regimens has been short. Diverse lymphoma histology findings were included in this analysis, but most patients had HL or aggressive NHL.

The TRM rate was relatively low (22%) and suggests that with current supportive care, allo-HSCT is feasible for this group of patients. This finding is in apparent contrast to results of several previous studies. Tsai et al.¹² report 85% TRM among 14 patients. Radich et al.¹³ summarize the Seattle experience and report 78% TRM among patients with lymphoma at 2 years after second transplantation. Bierman et al.¹⁵ report 16 patients with a TRM rate of 44% at 100 days. Reports of other small studies also demonstrate high TRM rates.^{14,17} Possible explanations for the low TRM rate in our report compared with previous ones include changes in patient selection over time and improvements in supportive care over the past decade. All patients included in our analysis underwent transplantation after 1990, and half underwent transplantation between 1997 and 1999. The reports by Tsai et al.¹² and by Radich et al.¹³ include considerable numbers of patients who underwent transplantation before 1990, when growth factor support, prevention and management of opportunistic cytomegalovirus (CMV) infections, and donor selection strategies based on high-resolution HLA typing were less optimal. In addition, 15 of 18 patients reported by Radich et al.¹³ had active disease at the time of transplantation, and 7 had HLA-mismatched or unrelated donors, features that in our current study are associated with high risk for TRM. Three of the 14 transplantations in the series by Tsai et al.¹² also involved donors other than HLA-matched siblings. By contrast, in the small series by de Lima et al.,⁸ most patients had chemotherapy-responsive disease and HLA-matched sibling donors. Three of 5 patients in that series obtained durable remissions. Our data are also in agreement with those of Seropian et al.,¹⁹ who recently reported a 55% PFS rate among 11 patients undergoing allo-HSCT after previous auto-HSCT failed. The comparatively low TRM in our report may also be partly explained by methodological differences from other studies, such as the use of cumulative incidence rather than Kaplan-Meier estimates.

Although TRM was within acceptable limits for allo-HSCT, there was a high rate of disease progression in this cohort. The risk for progression was 45% at 1 year after transplantation and 52% at 3 years, with a continued risk for relapse beyond 3 years. At 5 years, almost all survivors experienced lymphoma recurrence or progression, suggesting that allogeneic transplantation is rarely curative in patients for whom autologous transplantation fails. Similarly, in the study by Radich et al.,¹³ the 4 patients who did not die of treatment-related causes experienced relapse. In the report by Tsai et al.,¹² only 2 of 14 patients were alive and in remission 2 years after the second transplantation, and de Lima et al.⁸ report only 3 of 8 patients were alive and disease free at 25, 22, and 7 months after transplantation. In the report by Bierman et al.,¹⁵ the OS and disease-free survival rates were estimated to be 42% at 2 years. In their experience, longer intervals between autologous and allogeneic transplantation were associated with better outcomes, a finding that was not replicated in our analysis.

Although not curative, prolonged survival was observed in a substantial proportion of patients in this study. The study then provided a unique opportunity to determine the effects of donor selection, disease type, performance score, disease stage, conditioning regimen, and potential effect of graft-versus-tumor effects and disease histology on transplantation outcome, specifically on the duration of allotransplantation-induced remissions and survival.

Not surprisingly, recipients of transplants from HLA-identical siblings had better outcomes than those with unrelated donors or related haploidentical donors, and poor performance status was associated with worse outcome. Patients with NHL who received TBI for conditioning had only one third the rate of disease progression of patients who did not receive TBI. This unexpected role of TBI in prolonging remission is consistent with our previous observations in follicular lymphoma²⁰ and with recent data in autologous transplantation.^{21,22} On the other hand, it remains possible that TBI conditioning represents a surrogate for other undetected prognostic variables. No effect of TBI on recurrence rates was observed among patients with HL. The latter data should be interpreted with caution because the number of HL patients receiving TBI was small. Undergoing allo-HSCT while in remission was also associated with a decreased rate of disease progression. Among patients who underwent transplantation with active disease, the rate of disease progression was lower if the disease was chemosensitive. This is consistent with multiple previous observations in studies of allogeneic or autologous transplantation.^{2,23}

Clinical observations of patients undergoing myeloablative and nonmyeloablative allo-HSCT suggest that the graft-versus-tumor effects may be important in inducing prolonged remission in patients with lymphoma²⁴⁻²⁷ and that it constitutes one of the rationales for considering allogeneic

transplantation. Nevertheless, we were unable to clearly demonstrate a graft-versus-lymphoma effect of GVHD in this study. The rate of progression in patients with acute or chronic GVHD was similar to that in patients without GVHD. Several previous registry analyses, including a recent study of first transplantation for follicular lymphoma²⁰ and an analysis of syngeneic transplantation,²⁸ have similarly failed to demonstrate such an effect. However, given that only 30% of patients acquired GVHD, even our relatively large study (and other registry analyses) might not have been large enough to detect a significant graft-versus-lymphoma effect. Additionally, the lack of benefit from graft-versus-tumor effect in this group of patients at very high risk does not rule out that such effects might be operative in patients at standard risk.

We also did not observe any differences in overall outcomes among patients with low-, intermediate-, and high-grade NHL. The outcome for patients with HL was worse than that for patients with NHL receiving TBI for most outcome variables, but it was similar to that for patients with NHL receiving chemotherapy conditioning. It was previously reported that the outcome of allogeneic transplantation depends on disease histology,²⁹ and we have shown that relapse rates after transplantation for low-grade lymphoma in particular are low.²³ The failure to observe an effect of disease histology in the current study is likely attributable to the fact that study patients had disease that was resistant to numerous previous therapies, including high-dose chemotherapy, and, therefore, regardless of histology, was high risk. The small sample sizes of the subgroups of patients whose disease was of indolent histology might also have contributed to the lack of discernible histology related effects.

The OS rate of patients included in this study appears to be superior to the reported OS rate of patients treated with conventional therapy after failed autologous transplantation. Vose et al.⁴ reviewed the outcomes of 169 patients at the University of Nebraska who had malignant lymphoma and experienced relapse after auto-HSCT. With a median follow-up of only 1 year, 18 (11%) of these 169 patients remained alive, off therapy, and without evidence of disease progression. By contrast, in our study, 33% of patients were projected to be alive at 3 years after allo-HSCT, and 25% were projected to be alive and free of disease. This is impressive given the fact that only one fifth of the patients in our study were in remission at the time of allo-HSCT and that almost half had Karnofsky scores lower than 90%. Additionally, nearly 40% of patients received grafts from unrelated or HLA mismatched sibling donors.

In summary, it is apparent from this study that with modern supportive care, selected young patients with lymphoma who experience relapse after autologous transplantation may benefit from allogeneic transplantation, though few will ultimately be cured. Patients who continue to exhibit disease responsiveness and who have HLA identical siblings have relatively good 3-year survival. Conditioning with TBI should be considered for patients with

NHL because it seems to be associated with prolonged duration of remission. In contrast, patients with refractory disease and poor performance status scores and who lack HLA-identical sibling donors have poorer outcomes. Our observations of the impact of TBI in NHL patients and the lack of detectable GVL effects suggest that nonmyeloablative transplantation, with its emphasis on dose reduction, may not constitute an optimal long-term strategy for these patients. Recent reports using nonmyeloablative allo-HSCT after auto-HSCT demonstrate the feasibility of this approach,³⁰⁻³³ but longer follow-up is necessary to demonstrate its effectiveness in achieving long-term disease control.

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Chapter 8

Management of lymphoma recurrence after
allogeneic transplantation: the relevance of graft-
versus-lymphoma effect

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Abstract

Donor lymphocyte infusions, by virtue of a graft-versus tumor effect, have been shown to induce remissions in leukemia that recurs after allogeneic bone marrow transplantation. Similar effects have been postulated to contribute to the decreased recurrence rate observed after allogeneic transplantation in non-Hodgkin's lymphoma. This lower recurrence rate may be due to a variety of other mechanisms. We aimed to evaluate the role of graft-versus-lymphoma effects in patients in whom lymphomas recur after allogeneic transplantation. At the time of recurrence, immunosuppressive therapy was withheld. Patients with non-responding disease received an infusion of donor lymphocytes. Patients were observed for response and graft-versus-host disease. Disease in four of nine patients responded to withdrawal of immunosuppressive therapy. A minor response was observed in one of three recipients of donor lymphocyte infusions. Responses were observed among two patients with follicular lymphoma, one with large cell lymphoma and one with lymphoblastic lymphoma. A minor response was observed in a patient with prolymphocytic leukemia/lymphoma. We conclude that withdrawal of immunosuppressive therapy and donor lymphocyte infusion can induce durable remissions in patients with recurrent lymphoma after allogeneic transplantation.

Introduction

Bone marrow transplantation has been commonly used in treatment of hematologic malignancies. Considerable data indicate that a graft-versus-leukemia effect occurs after allogeneic transplantation and that it contributes to the achievement of durable remissions in leukemia.^{1,2} Syngeneic transplants and T cell-depleted allografts are associated with an increased relapse rate, indicating that T cells participate in the graft-versus-leukemia effect.³ Allogeneic transplantation has also been used to treat non-Hodgkin's lymphoma, and several studies report lower relapse rates than those achieved with autologous transplants.^{4,5} The concept of a graft-versus-lymphoma effect, however, remains unproven, because of the inclusion of heterogeneous patient populations in lymphoma studies and a high treatment-related mortality rate. Discontinuation of immunosuppressive therapy or donor lymphocyte infusions have been successfully used to induce remissions in patients in whom disease has recurred after allogeneic transplantation for chronic or acute myelogenous leukemia.⁶ Similar observations have been reported for patients with multiple myeloma.⁷ We have used immunologic manipulations in several patients with non-Hodgkin's lymphoma in whom disease recurred after allogeneic transplantation; complete or partial responses have been observed in four of nine patients.

Patients and methods

Patients

Between April 1991 and July 1996, 77 patients with lymphoma underwent allogeneic bone marrow or stem cell transplantation at the MD Anderson Cancer Center. Two had diffuse small non-cleaved cell lymphoma, 10 lymphoblastic lymphoma, 26 low-grade lymphoma, 32 had de novo intermediate grade lymphoma and seven transformed lymphoma. Fifteen patients developed disease recurrence.

One, with Burkitt's disease, died within a day of the diagnosis of disease recurrence. Two patients had graft failure prior to disease recurrence. They were treated with conventional chemotherapy and radiation. Three patients were cared for by their local physician at the time of recurrence. Nine fully engrafted patients were cared for at the MD Anderson Cancer Center at the time of disease recurrence. They form the subject of this report.

Details on conditioning, stem cell procurement and prophylaxis for graft-versus-host disease and infections have been previously reported.⁸⁻¹¹ Two patients received conditioning consisting of cyclophosphamide, etoposide (VP-16) and total body irradiation,⁸ six patients received high-dose thiotepea, busulfan and cyclophosphamide,¹⁰ and one received BCNU, etoposide, cytarabine and melphalan.¹² Prophylaxis for graft-versus-host disease consisted of cyclosporine and short-course methotrexate (n=3), cyclosporine and methylprednisolone (n=5) or tacrolimus and methotrexate (n=1). T cell depletion was not used.

Immunologic manipulations at recurrence

Upon diagnosis of recurrence, several immunologic manipulations were attempted. If the patient was receiving cyclosporine or tacrolimus, it was discontinued. If the disease continued to progress after discontinuation of immunosuppression, and the patient remained in good condition, lymphocytes were collected from the allogeneic donor and infused into the patient without further prophylaxis for graft-versus-host disease. If a partial or complete response was obtained, this procedure could be repeated.

Case report

Patient characteristics and details on treatment and outcome are provided in Table 8.1. Response to withdrawal of cyclosporine or tacrolimus was observed in four patients: three patients who failed to respond to cyclosporine withdrawal, then received an infusion of donor lymphocytes; a minor response was observed in one patient. The case histories of patients with a response to immunologic manipulations are detailed below. Patient numbers in the case report refer to numbers assigned in Table 8.1.

Patient 1

A 33-year-old man, presented in January 1991 with T cell lymphoblastic lymphoma. After an initial response to combination chemotherapy, the patient developed leptomeningeal disease. He received combined systemic and intrathecal treatment and obtained a partial response.

He underwent allogeneic BMT from his HLA-identical sister, after conditioning with thiotepea, busulfan, and cyclophosphamide. Prophylaxis for graft-versus-host disease consisted of cyclosporine and methylprednisolone. A complete response was achieved. Acute and chronic graft-versus-host disease of the skin developed and required treatment with steroids and cyclosporine.

Table 8.1 Patient characteristics and results of immunologic manifestations.

UPN	TTP (days)	Histology	Site of relapse	Response to CsA withdrawal	Response to DLI	No. of mononuclear cells/kg infused	Side-effects	Duration of response	Comments
1	1160	LBL	skin	CR			GVHD skin, resolved	600+ days	alive in CR
2	88	DLC	liver, nodes	PR ^b	NA		GVHD skin, resolved with steroids	65+ days	alive with minimal residual disease (Figure 8.1)
3	210	DLCa	liver	CR	NA		GVHD lungs, resolved with steroids	600+ days	day 540, small cleaved cell lymphoma in marrow and blood (see text)
4	1220	SCCL	nodes	PR	NA		none	180 days	alive with disease, no DLI because of history of chronic GVHD
5	75	Polymphocytic	blood, bone marrow, nodes	NRC	NRC	day 99: 6.4 × 10 ⁹	GVHD skin, pancytopenia		death day 156, progressive disease and fungal sepsis
6	180	DLC	pericardium, nodes	NR	NR	day 180: 23.9 × 10 ⁹	none		death day 270, progressive disease
7	90	DLC	pelvic mass	NR	NR	day 90: 14.5 × 10 ⁹	none		death, day 123, progressive disease
8	76	LBL	CNS and BM	NR	NA		none		death day 118, progressive disease
9	35	DLC	stomach, nodes	NR	NA		none		death day 80, progressive disease

^a Histology before BMT: follicular large cell lymphoma with one focus of transformation; ^b Patient receiving tacrolimus as GVHD prophylaxis; ^c Clearance of circulating lymphoma cells from peripheral blood. UPN=unique patient number; TTP=time to progression; CsA=cyclosporin A; DLC=diffuse large cell lymphoma; SCCL=small cleaved cell lymphoma; LBL=lymphoblastic lymphoma; CR=complete remission; PR=partial remission; NR=no response.

Thirty-eight months after BMT, he presented with a biopsy-confirmed, isolated recurrence of lymphoblastic lymphoma in the skin. Cyclosporine was stopped and steroids were tapered. This resulted in a transient flare-up of graft-versus-host disease of the skin and complete resolution of the skin lesions. Twenty-four months after cessation of cyclosporine therapy, the patient's disease continues to be in remission.

Patient 2

A 41-year-old male was diagnosed with T cell-rich B cell large cell lymphoma in May 1995. He failed treatment with two consecutive chemotherapy regimens. He underwent allogeneic stem cell transplantation from his HLA-identical brother after conditioning with BCNU, etoposide, cytarabine and melphalan (BEAM). Prophylaxis for graft-versus-host disease consisted of tacrolimus and methotrexate. After a transient response, the patient's disease progressed in the liver, mediastinal and retroperitoneal lymph nodes on day 88 after transplant. Fine-needle aspiration demonstrated the original disease histology. Tacrolimus was stopped after which disease regression occurred in all sites of involvement (Figure 8.1). The patient has developed GVHD of the gut and liver which is controlled with steroids. His disease continues to be in remission 140 days after withdrawal of tacrolimus.

Patient 3

A 35-year-old man with common variable immunodeficiency and autoimmune hemolytic anemia, was diagnosed with stage IV follicular large cell lymphoma in October 1992. Only transient disease responses were obtained with the administration of several chemotherapeutic regimens. He underwent allogeneic BMT from his HLA-identical brother after conditioning with cyclophosphamide, etoposide and total body irradiation. Prophylaxis for graft-versus-host disease consisted of cyclosporine and methotrexate. The patient's disease entered complete remission. Seven months after BMT, he presented with increasing liver function tests and paratracheal and retroperitoneal adenopathy; a liver biopsy showed B cell large-cell lymphoma. Cyclosporine was stopped.

Figure 8.1 Patient 2 (a) mediastinal adenopathy 88 days after transplantation; (b) mediastinal adenopathy 143 days after transplantation and 55 days after withdrawal of tacrolimus; (c) retroperitoneal adenopathy 88 days after transplantation. Active disease was demonstrated by fine needle aspiration. (d) Retroperitoneal adenopathy 143 days after transplantation and 55 days after withdrawal of tacrolimus.

The patient's bilirubin level decreased from 4.3 to 1.1 mg/dl, but serum SGPT remained elevated. A repeat liver biopsy showed acute hepatitis with polyclonal lymphoid aggregates in the parenchyma. Oligonucleotide *in situ* hybridization did not reveal the presence of Epstein-Barr virus RNA (EBER). An assay for hepatitis C RNA in the serum was positive, and interferon was started at 3 million units subcutaneously three times a week; all liver function tests normalized. Interferon was stopped after 6 months of therapy, but a relapse of hepatitis occurred that was documented by a liver biopsy. There was no evidence of lymphoma. His liver function tests normalized after the reinstitution of interferon. One year after cyclosporine withdrawal, atypical lymphocytes were detected in the bloodstream, and a bone marrow biopsy revealed an interstitial lymphoid infiltrate that was suspicious for lymphoma. Flow cytometry was non-diagnostic, but cytogenetic analysis of the marrow revealed the following karyotype in 25% of the analyzed cells: 45,XY, del(2)(p21), -2, l(7)(q11.1), -7, -9, -11, +del(14)(q21), +mar1. The remainder of the cells had a normal karyotype. Oligonucleotide *in situ* hybridization on sections of the marrow did not show Epstein-Barr virus RNA, rendering the diagnosis of an EBV-related lymphoproliferation unlikely. Twenty months after cyclosporine withdrawal, the patient remains asymptomatic and has not undergone further treatment.

Patient 4

A 31-year-old woman was diagnosed with stage IV follicular small cleaved-cell lymphoma in May 1985. Only transient disease responses were obtained with the administration of several chemotherapeutic regimens.

She then underwent allogeneic BMT from her HLA-identical brother after conditioning with cyclophosphamide, etoposide, and total body irradiation. Prophylaxis for graft-versus-host disease consisted of cyclosporine and methotrexate. Acute grade 1 graft-versus-host disease of the skin developed and required treatment with steroids.

Three months after allogeneic BMT, her bone marrow showed persistent lymphoma, but subsequent biopsies revealed decreasing involvement. One year after BMT she presented with extensive chronic graft-versus-host disease of the skin and esophagus, which was controlled with cyclosporine and methylprednisolone. Several attempts at tapering the medications resulted in flare-ups of graft-versus-host disease.

Four years after BMT, a fine-needle aspiration of an enlarged lymph node in the left crus of the diaphragm showed recurrent small cleaved-cell lymphoma. Cyclosporine was stopped, resulting in a decrease in the lymphadenopathy without recurrence of graft-versus-host disease in the skin. Although a spontaneous remission of low-grade lymphoma could explain the decrease in adenopathy,¹³ the temporal association with withdrawal of cyclosporine

indicates a graft-versus-lymphoma effect. Nine months later, progression of adenopathy was documented. The patient did not respond to treatment with interferon. Donor lymphocyte infusion was not considered for fear of provoking recurrent graft-versus host disease. Currently the patient is receiving monoclonal antibody treatment.

Patient 5

A 53-year-old man was diagnosed in August 1994 with polymorphocytic leukemia. He presented with massive adenopathy, blood and bone marrow involvement and failed treatment with two consecutive chemotherapy regimens.

He underwent allogeneic peripheral blood stem cell transplant from his HLA-identical sister after conditioning with thiopeta, busulfan and cyclophosphamide. Prophylaxis for graft-versus-host disease consisted of cyclosporine and methylprednisolone. After initial tumor reduction, disease progression was documented in the bone marrow, lymph nodes and peripheral blood on day 75.

Cyclosporine was stopped, resulting in a transient clearing of circulating lymphoma cells. No effect on the bone marrow or lymph nodes was observed. On days +99 and +100 after allogeneic BMT, he received a donor lymphocyte infusion, after which clearance of lymphoma cells from the blood was documented. Graft-versus-host disease of the skin and profound pancytopenia developed. The patient received a boost of G-CSF-mobilized donor stem cells on day +139. Despite the response in the peripheral blood, no response was documented in the bone marrow or other disease sites, and the patient died at day +156 after allogeneic BMT as a result of disease progression and *Candida krusei* sepsis.

Discussion

The high incidence of aggressive lymphoid malignancy in AIDS patients¹⁴ and among organ transplantation recipients¹⁵ indicates that immune deficiency plays a pivotal role in the pathogenesis of these malignancies. The susceptibility of lymphoma to host defense mechanisms is further illustrated by the observation of spontaneous remissions¹³ and response to interferon¹⁶ or anti-idiotypic antibodies.¹⁷ Presumably, lymphoid cells are also targets of graft-versus-host disease, and an associated graft-versus-lymphoma effect may occur after allogeneic BMT. In accordance with this hypothesis, favorable outcomes have been reported after allogeneic BMT in patients with low-grade lymphoma,^{9,18-21} and several studies indicate a lower incidence of recurrence

after allogeneic BMT compared with autologous BMT.^{5,22} There have also been reports of successful BMT after failure of autologous BMT in patients with non-Hodgkin's lymphoma.^{23,24}

While such findings are suggestive of graft-versus-lymphoma effects, they could conceivably be due to the lack of bone marrow contamination in recipients of allogeneic bone marrow or potentially to the antitumoral effects of drugs utilized as prophylaxis for graft-versus-host disease. More convincing evidence for graft-versus-lymphoma effects can be obtained by the correlation of graft-versus-host disease with recurrence rates¹ or by the observation of lymphoma regression after immunomodulatory treatments. There are only two previous reports of tumor regression induced by immunologic manipulations in patients with recurrent non-Hodgkin's lymphoma after allogeneic BMT. Petersen et al.²⁵ reported on a patient with Burkitt's disease that recurred after allogeneic BMT, but went into complete remission after cyclosporine was discontinued. Graft-versus-host disease then developed in this patient, which necessitated the reinstitution of immunosuppressive therapy; Burkitt's disease promptly recurred again. Kolb et al.²⁶ reported a transient response in one of two lymphoma patients treated with donor lymphocyte infusion for recurrence after allogeneic BMT.

In an attempt to investigate this concept further, we have explored the use of withdrawal of immunosuppressants and donor lymphocyte infusions for patients in whom disease recurs after allogeneic BMT. Withdrawal of cyclosporine or tacrolimus was effective in four of nine patients studied. It resulted in two complete and two partial responses. Donor lymphocyte infusions were administered to three patients who did not respond to cyclosporine withdrawal. A minimal response was observed in one of the three. We have previously also reported a complete response to donor lymphocyte infusion in a patient with refractory chronic lymphocytic leukemia, a similar disease.^{27,28} Among leukemia patients, the response to donor lymphocyte infusion depends on disease histology.⁶ Based on the low recurrence rates after allogeneic BMT for low-grade lymphoma, similar differences in sensitivity to GVL effects may be true among lymphoma subtypes.⁹ Our observations on the effect of cyclosporine withdrawal however are currently too limited to allow such conclusions.

In conclusion, immune modulations may induce graft-versus-lymphoma effects that result in tumor regression in different histologic subtypes of lymphoma. Therapeutic strategies aimed at exploiting such effects should be further evaluated in a systematic fashion.

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Chapter 9

Syngeneic hematopoietic stem-cell transplantation for non-Hodgkin's lymphoma: a comparison with allogeneic and autologous transplantation-the lymphoma working committee of the International bone marrow transplant registry and the European group for blood and marrow transplantation

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Abstract

Purpose

To compare results of syngeneic, allogeneic, and autologous hematopoietic stem-cell transplantation for non-Hodgkin's lymphoma (NHL).

Patients and Methods

The databases of the International Bone Marrow Transplant Registry (IBMTR) and the European Group for Blood and Marrow Transplantation were used to identify 89 NHL patients who received syngeneic transplants. These patients were compared with NHL patients identified from the IBMTR and the Autologous Blood and Marrow Transplant Registry who received allogeneic (T-cell depleted and T-cell replete) and autologous (purged and unpurged) transplants.

Results

No significant differences in relapse rates were observed when results of allogeneic transplantation were compared with syngeneic transplantation for any histology. T-cell depletion of allografts was not associated with a higher relapse risk, but was associated with improved overall survival for patients with low-grade and intermediate-grade histology. Patients who received unpurged autografts for low-grade NHL had a five-fold ($P=0.008$) greater risk of relapse than recipients of syngeneic transplants, and recipients of unpurged autografts had a two-fold ($P=0.0009$) greater relapse risk than patients who received purged autografts. Among low-grade NHL patients, the use of purging was associated with significantly better disease-free survival ($P=0.003$) and overall survival ($P=0.04$) when compared with patients who received unpurged autografts.

Conclusion

These analyses failed to find evidence of a graft-versus-lymphoma effect, but do provide indirect evidence to support the hypothesis that tumor contamination may contribute to lymphoma relapse, and that purging may be beneficial for patients undergoing autologous hematopoietic stem-cell transplantation for low-grade NHL.

Introduction

Several studies have shown lower relapse rates after allogeneic transplantation for non-Hodgkin's lymphoma (NHL) when compared with autologous transplantation. These results could be explained by lack of tumor contamination, or by selection bias favoring patients with better prognostic characteristics. However, many investigators have hypothesized that a graft-versus-lymphoma effect is the most likely explanation for this finding.

High-dose therapy followed by autologous hematopoietic stem-cell transplantation has become accepted therapy for certain NHL patients. However, autologous transplantation is associated with the potential risk of reinfusing malignant cells. This has led to trials involving removal of contaminating cells from the autograft. Several of these methods of manipulation (purging) can eliminate significant numbers of tumor cells from the graft. There is indirect evidence for a clinical benefit from purging, although benefits have not been conclusively demonstrated.

Comparisons of syngeneic and allogeneic bone marrow transplantation for leukemia support the existence of a graft-versus-leukemia effect. We reasoned that a comparison of syngeneic and allogeneic NHL transplants could also provide insights into whether a similar graft-versus-lymphoma effect exists. We also reasoned that a syngeneic transplant is representative of an uncontaminated autograft, and consequently, a comparison of syngeneic and autologous transplants could provide indirect evidence regarding the potential contribution of tumor contamination to relapse after autologous transplantation for NHL. This study was undertaken to compare relapse rates after syngeneic, autologous, and allogeneic hematopoietic stem-cell transplantation for NHL.

Patients and methods

Data sources

The International Bone Marrow Transplant Registry (IBMTR) comprises more than 400 transplantation centers that contribute data on allogeneic and syngeneic hematopoietic stem-cell transplantations to a Statistical Center at the Health Policy Institute of the Medical College of Wisconsin. The Autologous Blood and Marrow Transplant Registry (ABMTR) comprises more than 250 transplant centers that report data on autotransplantations to the same institution. Approximately 40% of allogeneic transplantations worldwide and more than 50% of autologous transplantations in North and South America are

registered with the IBMTR/ABMTR.^{1,2} Consecutive transplantations are reported and compliance is monitored with on-site audits. The European Group for Blood and Marrow Transplantation (EBMT) comprises 436 transplantation centers in Europe and associated members from non-European countries. Data are checked by the Statistical Office of the EBMT at the University College of London Hospitals and at random site visits. The registry accrues data on transplantations from participating centers, and requests basic patient and clinical information and annual follow-up on all patients. Additional data are requested if patients are included in a study. Institutions were contacted on three occasions to obtain data for this study before the variable was coded as missing or unknown.

Patients

This study included NHL patients who received high-dose therapy followed by syngeneic, autologous, or HLA-matched sibling allogeneic transplants between 1985 and 1998, and were reported to the IBMTR, ABMTR, or EBMT. Syngeneic transplants reported to the IBMTR and EBMT were checked for overlap. These patients were then compared with autologous and allogeneic transplant recipients from the IBMTR/ABMTR. Nonmyeloablative allogeneic transplants were excluded.

Lymphoma classification evolved during the study period and specific histologic criteria were applied to ensure comparability of diagnoses. Only patients with a descriptive histologic classification conforming to the Working Formulation were included.³ Entities such as mantle-cell lymphoma and marginal zone lymphoma that are only recognized in the Revised European-American Lymphoma or WHO classification systems were excluded.^{4,5} Follicular large-cell lymphoma and large-cell immunoblastic lymphoma were classified as intermediate grade.

End points

The primary end point was relapse, defined as persistent or recurrent NHL in patients surviving at least 28 days after transplantation. Patients were also analyzed for disease-free survival and overall survival. Disease-free survival was defined as survival without evidence of NHL. Patients with persistent disease were classified as experiencing relapse at day 28, even if they did not subsequently progress. Overall survival was defined as the interval between transplantation and death from any cause. Surviving patients were censored at the date of last contact.

Statistical analysis

Patient-, disease-, and transplantation-related variables for cohorts were compared using the χ^2 statistic for categorical variables and the Kruskal-Wallis test for continuous variables. Univariate probabilities of disease-free and overall survival were calculated using the Kaplan-Meier estimator.⁶ The log-rank test was used for univariate comparisons of survival curves.⁷

Probabilities of relapse and transplantation-related mortality were calculated using cumulative incidence curves to accommodate competing risks.⁸ Transplantation-related mortality, defined as death during continuous remission or death in the first 28 days after transplantation, was used as a competing risk factor for estimation of relapse. Ninety-five percent CIs for all probabilities and *P* values of pairwise comparisons were derived from pointwise estimates and calculated using standard techniques.⁹

Cox proportional hazards models were constructed for each histologic subtype. The primary covariate analyzed was graft type (syngeneic, allogeneic T-cell depleted, allogeneic T-cell replete, autologous purged, and autologous unpurged). The following factors were also analyzed in the multivariate analyses for their association with relapse and their potential confounding effect on the associations between relapse and type of transplantation. The first set of categories were patient-related factors at the time of transplantation: age (<40 v $\geq$ 40 years) and sex. The second set of categories were disease-related factors at diagnosis: histology (low grade v intermediate grade v high grade). The third set of categories were disease-related factors at the time of transplantation: disease sensitivity (chemotherapy sensitive v resistant v unknown or untested), presence of bone marrow involvement at diagnosis or transplantation, and disease status (first remission v never in remission v second remission v first relapse v second relapse v unknown). The fourth set of categories were transplantation-related factors: year of transplantation (1985 to 1989 v 1990 to 1995 v 1996 to 1998), conditioning regimen (containing total-body irradiation [TBI] v not containing TBI), graft source (blood v marrow), and use of hematopoietic growth factors within 7 days of transplantation. A separate category for missing data was created for each covariate included in the multivariate analysis whenever applicable. Allogeneic transplants were analyzed for the effects of acute graft-versus-host disease (GVHD) and chronic GVHD entered as time-dependent covariates. We tested the proportional hazards assumption for each factor in the Cox model using time-dependent covariates.¹⁰ When this indicated differential effects over time (nonproportional hazards), models were constructed that broke the posttransplantation course into two periods using the maximized partial likelihood method to find the most appropriate breakpoint. After time-varying effects were modeled, the final multivariate model was built using a forward stepwise model selection approach. Each model contained the main effect (syngeneic [as the reference

group], allogeneic T-cell depleted, allogeneic T-cell replete, autologous purged, or autologous unpurged transplant). The inclusion of the main effect allowed us to examine differences in the outcome risk by type of transplant while controlling for other significant covariates. Factors significantly associated with the outcome variable at the 5% level were kept in the final model. First-order interactions were examined between the type of transplant and all significant prognostic factors. Examination for center effects used a random effects or frailty model.¹¹ We found no evidence of correlation between transplantation center and any outcomes. All *P* values are two-sided.

Results

Patient characteristics are presented in Table 9.1. Allogeneic transplant recipients were younger. All groups had a higher percentage of males. Allogeneic recipients were more likely to have high-grade histology and autologous transplant recipients were more likely to have intermediate-grade and low-grade histology. Allogeneic transplant recipients were also more likely to have a history of marrow involvement. The groups were similar with respect to systemic symptoms at diagnosis, stage at diagnosis, and disease status at transplantation. Allogeneic recipients were more likely to have untested or unknown sensitivity and were more likely to have received TBI conditioning. Bone marrow was used for most of the allogeneic transplants and purged autografts, whereas most unpurged autografts were performed with peripheral blood. A variety of purging and T-cell–depletion methods were used.

Among patients receiving purged autografts, 214 grafts (57%) were purged with 4-hydroperoxycyclophosphamide or mafosfamide, 44 grafts (12%) were purged with positive selection techniques, 31 grafts (8%) were purged with monoclonal antibodies, and 87 grafts (23%) were purged with other pharmacologic agents. Among patients receiving T-cell–depleted allografts, 40 grafts (34%) were T-cell depleted with elutriation, 31 grafts (26%) were T-cell depleted with sheep red cells and/or soybean lectin, 29 grafts (24%) were T-cell depleted with monoclonal antibodies, and 19 grafts (16%) were T-cell depleted with other methods.

The median follow-up for syngeneic transplants, unpurged autologous transplants, purged autologous transplants, T-cell–replete allogeneic transplants, and T-cell–depleted allogeneic transplants was 44 months (range, 4 to 186 months), 36 months (range, <1 to 125 months), 46 months (range, 3 to 128 months), 48 months (range, 2 to 174 months), and 60 months (range, 3 to 159 months), respectively. The interval between diagnosis and transplantation was not significantly different when syngeneic transplants were compared with other transplant types.

Table 9.1 Patient characteristics.

Characteristic	Syngeneic		Autologous Unpurged		Autologous purged		Allogeneic T-cell-replete		Allogeneic T-cell-replete	
	No.	%	No.	%	No.	%	No.	%	No.	%
No. of patients	89		2,018		376		774		119	
Age	Median	42		48		47		33		37
	Range	4-68		11-68		6-71		2-62		5-62
Male	51	57	1,232	61	230	61	495	64	69	58
Karnofsky performance status										
≥90%	30	34	1,203	60	272	72	440	57	92	77
<90%	27	30	712	35	55	15	313	40	16	13
Unknown	32	36	103	5	49	13	21	3	11	10
Histology										
Low-grade	30	34	427	21	160	42	189	24	36	30
Intermediate-grade	31	35	1,417	70	180	48	194	25	26	22
High-grade	28	31	174	9	36	10	391	51	57	48
"B" symptoms at diagnosis										
Absent	39	44	1,191	59	244	65	402	52	55	46
Present	24	27	787	39	124	33	255	33	39	33
Unknown	26	29	40	2	8	2	117	15	25	21
Stage at diagnosis										
I to II	18	20	578	29	97	26	137	18	25	21
III to IV	57	64	1,417	70	277	73	566	73	73	61
Unknown	14	16	23	1	2	1	71	9	21	8
Bone marrow involvement at diagnosis or transplantation										
Absent	57	64	1,816	90	285	76	255	33	32	27
Present	9	10	121	6	20	5	186	24	16	13
Unknown	23	26	81	4	71	19	333	43	71	60
Sensitivity to chemotherapy										
Sensitive	50	56	1,464	72	280	74	308	40	31	26
Resistant	13	15	316	16	63	17	110	14	13	11
Untreated or unknown	26	29	238	12	33	9	356	46	75	63
Disease status at transplantation										
Primary induction failure	22	25	449	22	64	17	194	25	27	23
CR1	18	20	238	12	53	14	150	19	32	27
≥CR2	14	16	319	16	74	20	140	18	19	16
Rel 1	24	27	650	32	82	22	168	22	14	12
Rel 2	6	7	171	8	30	8	53	7	11	9
Not assessable	5	5	191	10	73	19	69	9	16	13
TBI for conditioning	25	28	557	28	225	60	559	72	107	90
Type of graft										
Peripheral stem-cell	23	26	1,359	67	48	13	92	12	—	—
Bone marrow	66	74	659	33	328	87	682	88	119	100
Growth factor given within 7 days posttransplantation	26	30	1,155	61	146	44	246	33	24	22
Year of transplantation										
1985-1989	17	19	86	5	31	9	177	23	36	30
1990-1992	23	26	392	19	137	36	255	33	20	17
1993-1995	22	25	884	44	145	38	183	25	56	47
1996-1998	27	30	656	32	63	17	149	19	7	6

CR=complete remission; Rel=relapse; TBI=total-body irradiation

Relapse

The cumulative incidence of relapse for each type of transplant is displayed in Figure 9.1. Results of the multivariate analysis of factors independently associated with relapse risk are listed in Table 9.2.

Figure 9.1 Cumulative incidence of relapse after transplantation for all patients according to type of transplant. (A) Low-grade histology, (B) intermediate-grade histology, (C) high-grade histology.

Low-grade NHL patients who received allogeneic transplants did not have a significantly lower relapse risk than patients who received syngeneic transplants. Furthermore, there were no significant differences in relapse probability between patients who received T-cell-depleted and T-cell-replete allografts (relative risk [RR], 0.98; $P=0.97$). When compared with syngeneic transplants, unpurged autologous transplant recipients had a significantly higher risk of relapse (RR, 4.93; $P=0.008$).

Recipients of purged autologous transplants had a three-fold higher relapse risk than syngeneic transplant recipients, although this difference was not statistically different ($P=0.10$). Recipients of unpurged autografts had a significantly greater risk of relapse than patients who received purged autologous transplants (RR, 1.82; $P=0.0009$).

Table 9.2 Multivariate analysis: relapse.

	No. of patients	Relative risk of relapse	95% CI	P
Low-grade				
Syngeneic ^{ab}	26	1.00		
Allogeneic T-cell-depleted	34	1.49	0.32 to 6.88	0.61
Allogeneic T-cell-replete	165	1.46	0.41 to 5.13	0.56
Autologous purged	143	2.70	0.81 to 9.02	0.10
Autologous unpurged	394	4.93	1.52 to 15.94	0.008
Intermediate-grade^{ac}				
Syngeneic	30	1.00		
Allogeneic T-cell-depleted	23	1.80	0.68 to 4.75	0.24
Allogeneic T-cell-replete	173	1.12	0.52 to 2.42	0.78
Autologous purged	154	1.04	1.53 to 3.22	0.26
Autologous unpurged	1,399	1.88	0.93 to 3.82	0.08
High-grade^{ad}				
Syngeneic	28	1.00		
Allogeneic T-cell-depleted	57	1.01	0.41 to 2.46	0.99
Allogeneic T-cell-replete	373	0.99	0.46 to 2.12	0.98
Autologous purged	36	1.60	0.62 to 4.13	0.33
Autologous unpurged	169	1.68	0.78 to 3.61	0.19

^a Model stratified by disease status at transplantation and year of transplantation; ^b other significant variable: chemotherapy-sensitive versus chemotherapy-resistant to initial chemotherapy (relative risk [RR], 1.99; 95% CI, 1.39 to 2.83; $P=0.0002$). Pairwise comparison between T-cell-replete versus T-cell-depleted allogeneic transplants; RR, 0.98; $P=0.97$; autologous unpurged versus purged (RR, 1.82; $P=0.0009$); ^c other significant variable: chemotherapy-sensitive versus chemotherapy-resistant to initial chemotherapy (RR, 1.84; 95% CI, 1.52 to 2.23; $P=0.0001$). Pairwise comparison between T-cell-replete versus T-cell-depleted allogeneic transplants; RR, 0.62; $P=0.21$; autologous unpurged versus purged (RR, 1.23; $P=0.12$); ^d other significant variable: chemotherapy-sensitive versus chemotherapy-resistant to initial chemotherapy, (RR, 2.49; 95% CI, 1.56 to 3.97; $P=0.0001$). Pairwise comparison between T-cell-replete versus T-cell-depleted allogeneic transplants (RR, 0.99; $P=0.97$); autologous unpurged versus purged (RR, 1.05; $P=0.89$).

No significant differences in relapse risk were identified when allogeneic transplants for intermediate-grade NHL were compared with syngeneic transplants. An increased risk of relapse was not associated with T-cell depletion. Patients who received unpurged autografts had a higher risk of relapse than did syngeneic transplant recipients, although this difference was not statistically significant ($P=0.08$). Among patients with intermediate-grade NHL, there were no significant differences in relapse risk when results of unpurged and purged autologous transplants were compared (RR, 1.23; $P=0.12$).

Among patients with high-grade histology, there were no significant differences in relapse risk when allogeneic, autologous, and syngeneic transplants were compared. There were no significant differences when T-cell-depleted and T-cell-replete allogeneic transplants were compared, and no significant differences between unpurged and purged autografts.

For allogeneic transplant recipients who survived at least 90 days, the relapse rate at 1 year was estimated to be 20% (95% CI, 14% to 26%) for patients who developed chronic GVHD, as compared with 17% (95% CI, 13% to 22%) for patients without chronic GVHD ($P=0.41$). When time-dependent Cox regression was used, the RR of relapse for patients with chronic GVHD was 0.82 (95% CI, 0.52 to 1.28; $P=0.39$) when compared with patients without chronic GVHD. There was no evidence of graft-versus-lymphoma effects associated with acute GVHD or chronic GVHD, and this was true for all grades of lymphoma.

Disease-Free Survival

The actuarial disease-free survival for each type of transplant is shown in Figure 9.2. Results of the multivariate analysis of factors independently associated with disease-free survival are listed in Table 9.3.

Figure 9.2 Actuarial probability of disease-free survival after transplantation for all patients according to type of transplant. (A) Low-grade histology, (B) intermediate-grade histology, (C) high-grade histology.

Low-grade NHL patients who received allogeneic transplants who were not T-cell depleted had significantly worse disease free survival than did syngeneic transplant recipients (RR, 3.12; $P=0.006$). The former also had a trend toward poorer disease free survival, when compared with patients who received T-cell-depleted allografts (RR, 1.70; $P=0.08$). Patients who received unpurged

autologous transplants had significantly worse disease free survival than those who received syngeneic transplants (RR, 2.28; $P=0.04$). When compared with patients who received purged autografts, patients who received unpurged autologous transplants also had significantly lower disease-free survival (RR, 1.59; $P=0.003$).

Table 9.3 Multivariate analysis: disease-free survival.

	No. of patients	Relative risk of treatment failure	95% CI	P
Low-grade ^{ab}				
Syngeneic	26	1.00		
Allogeneic T-cell-depleted	34	1.83	0.72 to 4.64	0.20
Allogeneic T-cell-replete	165	3.12	1.40 to 6.98	0.006
Autologous purged	143	1.43	0.63 to 3.24	0.39
Autologous unpurged	394	2.28	1.04 to 4.99	0.04
Intermediate-grade ^{ac}				
Syngeneic	30	1.00		
Allogeneic T-cell-depleted	23	1.60	0.75 to 3.38	0.22
Allogeneic T-cell-replete	173	1.85	1.05 to 3.26	0.03
Autologous purged	154	1.21	0.68 to 2.14	0.52
Autologous unpurged	1,399	1.32	0.77 to 2.25	0.32
High-grade ^{ad}				
Syngeneic	28	1.00		
Allogeneic T-cell-depleted	57	1.17	0.60 to 2.27	0.64
Allogeneic T-cell-replete	373	1.04	0.58 to 1.84	0.90
Autologous purged	36	1.31	0.63 to 2.75	0.47
Autologous unpurged	169	0.98	0.54 to 1.79	0.96

^a Model stratified by disease status at transplantation and year of transplantation; ^b other significant variable: chemotherapy-sensitive versus chemotherapy-resistant to initial chemotherapy (relative risk [RR], 1.58; 95% CI, 1.17 to 2.13; $P=0.003$). Pairwise comparison between T-cell-replete versus T-cell-depleted allogeneic transplants (RR, 1.70; $P=0.08$), autologous unpurged versus purged (RR, 1.59; $P=0.003$); ^c other significant variable: chemotherapy-sensitive versus chemotherapy-resistant to initial chemotherapy (RR, 1.84; 95% CI, 1.55 to 2.18; $P=0.0001$). Pairwise comparison between T-cell-replete versus T-cell-depleted allogeneic transplants (RR, 1.16; $P=0.61$); autologous unpurged versus purged (RR, 1.09; $P=0.46$); ^d other significant variable: chemotherapy-sensitive versus chemotherapy-resistant to initial chemotherapy (RR, 1.91; 95% CI, 1.29 to 2.82; $P=0.001$). Pairwise comparison between T-cell-replete versus T-cell-depleted allogeneic transplants (RR, 0.88; $P=0.80$); autologous unpurged versus purged (RR, 0.75; $P=0.56$).

Patients with intermediate-grade NHL who received allogeneic transplants that were not T-cell depleted had significantly poorer disease-free survival than recipients of syngeneic transplants (RR, 1.85; $P=0.03$). No significant differences in disease-free survival were observed when recipients of T-cell-replete and T-cell-depleted allogeneic transplants were compared (RR, 1.16; $P=0.61$). No significant differences in disease-free survival were seen when results of autologous and syngeneic transplants were compared, or when purged and unpurged autologous transplants were compared (RR, 1.09; $P=0.46$).

Among patients with high-grade histology, no significant differences in disease-free survival were noted when autologous or allogeneic transplants were compared with syngeneic transplants. No advantages were associated with T-cell depletion or purging.

Overall Survival

The actuarial survival for each type of transplant is shown in Figure 9.3. Results of the multivariate analysis of factors independently associated with survival are listed in Table 9.4.

Figure 9.3 Actuarial probability of overall survival after transplantation for all patients according to type of transplant. (A) Low-grade histology, (B) intermediate-grade histology, (C) high-grade histology.

Low-grade NHL patients who received allogeneic transplants that were not T-cell depleted had significantly worse survival than patients who received syngeneic transplants (RR, 2.87; $P=0.006$). These patients also had significantly poorer survival than patients receiving T-cell-depleted allogeneic transplants (RR, 1.88; $P=0.005$). No survival differences were seen when autologous and syngeneic transplants were compared, although lack of purging was associated with poorer survival when purged and unpurged autologous transplants were compared (RR, 1.55; $P=0.04$).

Table 9.4 Multivariate analysis: overall survival.

	No. of patients	Relative risk of death	95% CI	P
Low-grade^{ab}				
Syngeneic	30	1.00		
Allogeneic T-cell-depleted	36	1.52	0.63 to 3.69	0.35
Allogeneic T-cell-replete	189	2.87	1.36 to 6.06	0.006
Autologous purged	160	0.80	0.37 to 1.74	0.57
Autologous unpurged	427	1.24	0.60 to 2.57	0.57
Intermediate-grade^{ac}				
Syngeneic	31	1.00		
Allogeneic T-cell-depleted	26	1.85	0.88 to 3.92	0.11
Allogeneic T-cell-replete	194	2.19	1.22 to 3.91	0.008
Autologous purged	180	1.33	0.74 to 2.40	0.34
Autologous unpurged	1,417	1.25	0.71 to 2.18	0.44
High-grade^{ad}				
Syngeneic	28	1.00		
Allogeneic T-cell-depleted	57	1.47	0.76 to 2.86	0.27
Allogeneic T-cell-replete	391	1.30	0.73 to 2.31	0.37
Autologous purged	36	1.47	0.72 to 3.00	0.29
Autologous unpurged	174	0.92	0.50 to 1.68	0.79

^a Model stratified by disease status at transplantation and year of transplantation; ^b other significant variable: chemotherapy-sensitive versus chemotherapy-resistant to initial chemotherapy (relative risk [RR], 1.70; 95% CI, 1.26 to 2.29; $P=0.0004$). Pairwise comparison between T-cell-replete versus T-cell-depleted allogeneic transplants (RR, 1.88; $P=0.005$); autologous unpurged versus purged (RR, 1.55; $P=0.04$); ^c other significant variable: chemotherapy-sensitive versus chemotherapy-resistant to initial chemotherapy (RR, 1.92; 95% CI, 1.63 to 2.26; $P=0.0001$). Pairwise comparison between T-cell-replete versus T-cell-depleted allogeneic transplants (RR, 1.18; $P=0.03$); autologous unpurged versus purged (RR, 0.94; $P=0.61$); ^d other significant variable: chemotherapy-sensitive versus chemotherapy-resistant to initial chemotherapy (RR, 1.50; 95% CI, 1.02 to 2.20; $P=0.04$). Pairwise comparison between T-cell-replete versus T-cell-depleted allogeneic transplants (RR, 0.88; $P=0.55$); autologous unpurged versus purged (RR, 0.63; $P=0.06$).

Patients with intermediate-grade NHL who received allogeneic transplants that were not T-cell depleted had significantly poorer survival than syngeneic transplant recipients (RR, 2.19; $P=0.008$). In addition, a comparison of T-cell-replete and T-cell-depleted allogeneic transplants showed poorer survival when T-cell depletion was not used (RR, 1.18; $P=0.03$). No significant survival differences were observed when autologous and syngeneic transplants were compared, and no survival advantage was associated with purging. There were no significant survival differences when autologous or allogeneic transplants were compared with syngeneic transplants. No survival advantages were associated with T-cell depletion or purging.

Discussion

The first part of this study was designed to look for evidence of a graft-versus-lymphoma effect. Relapse rates after allogeneic hematopoietic stem-cell transplantation for NHL are lower than relapse rates after autologous transplantation.¹²⁻¹⁷ However, survival advantages are not seen with allogeneic transplantation because of higher transplantation-related mortality. Lower relapse rates following allogeneic transplantation suggest that a graft-versus-lymphoma effect exists. However, these differences might also be explained by other factors such as lack of tumor contamination in the allograft.

We reasoned that comparing syngeneic transplantation with allogeneic transplantation would eliminate the confounding variable of tumor contamination and provide more definitive evidence for the existence of a graft-versus-lymphoma effect, in the same way that graft-versus-leukemia effects were demonstrated.¹⁸ Studies of syngeneic transplantations for NHL are limited. Investigators from Seattle compared autologous, allogeneic, and syngeneic bone marrow transplantations in 100 lymphoma patients.¹⁹ No significant differences in relapse rate or disease-free survival were identified, but only 13 syngeneic transplantations were studied and two of these patients had Hodgkin's disease.

The multivariate analyses in our study failed to show a lower risk of relapse when allogeneic and syngeneic transplants were compared. Furthermore, there were no significant differences in relapse between T-cell-depleted and non-T-cell-depleted allografts, although T-cell depletion was associated with survival advantages in patients with low-grade and intermediate-grade histology. The analyses also failed to show a lower relapse rate in patients who developed GVHD.

Our failure to find evidence of a graft-versus-lymphoma effect must be examined in light of clinical evidence supporting this effect derived from comparisons of autologous and allogeneic transplants and the fact that graft-versus-lymphoma effects have been demonstrated in some animal models.²⁰ The existence of a graft-versus-lymphoma effect is also supported by reports of lymphoma regression when immunosuppression is withdrawn following relapse after allogeneic transplantation,²¹⁻²³ and by reports of response to donor leukocyte infusion.^{24,25} Finally, lower rates of relapse or progression have been reported in patients who develop chronic GVHD after allogeneic transplantation for NHL.²⁶

Although this study does not provide evidence for a graft-versus-lymphoma effect, it is possible that this analysis lacked statistical power to show a difference in rates of relapse between allogeneic and syngeneic transplants. However, no trends in favor of this association were noted. A graft-versus-lymphoma effect might be obscured by an increased frequency of adverse

prognostic factors, such as chemotherapy resistance, in recipients of allogeneic transplants, although adjustment for prognostic factors in the multivariate analyses did not alter the results. Our analysis is also hampered by missing data, which made it impossible to include certain variables in the multivariate analyses. However, statistical adjustments for missing data did not indicate that this accounted for the results. For known prognostic factors, such as performance status, we included a category for missing data in the models. This allowed us to make adjustments to the fullest extent of the data available to us and to ensure that no patient cases were discarded, as would be necessary in a matched-pair analysis. Moreover, even with a more complete database, the use of case-matching does not improve statistical power when compared with regression analysis using all available patients.^{27,28} Although important variables such as history of marrow involvement, disease status, and chemotherapy sensitivity were included in the analyses, it is possible that allogeneic transplant recipients were more likely to have unidentified adverse prognostic features because this is not a randomized study.

Our results raise the hypothesis that lower relapse rates after allogeneic transplantation for NHL may be largely explained by other factors such as lack of tumor contamination of the autograft, and that graft-versus-lymphoma effects may not be as powerful as previously suspected. If true, an obvious implication is that the utility of nonmyeloablative allogeneic transplantations may need to be reconsidered.²⁹ However, it must also be noted that the 5-year cumulative incidence of relapse after syngeneic transplantation was only 9% for patients with low-grade histology. This result is similar to the relapse rate after allogeneic transplantation in this series, as well as other reports of allogeneic transplantation for low-grade NHL.^{15,16,30} The similarly low rate of relapse after syngeneic and allogeneic transplantation suggests that long-term disease-free survival may be a result of the high-dose preparative regimen. This observation also suggests that graft-versus-lymphoma effects might be difficult to detect after high-dose therapy, and that effects could become more evident with less intensive conditioning regimens.

The second part of this study was a comparison of syngeneic and autologous hematopoietic stem-cell transplantation for NHL. Gene marking studies have shown that tumor contamination may contribute to relapse after autologous transplantation for acute myelogenous leukemia, chronic myelogenous leukemia, and neuroblastoma.³¹⁻³³ Although this has not been demonstrated for NHL, indirect evidence suggests that tumor contamination might also contribute to relapse.

The first evidence comes from reports of rapid disseminated relapse after autologous bone marrow transplantation for aggressive NHL.^{34,35} Other evidence comes from studies showing lower relapse-free survival after autologous marrow transplantation in NHL patients whose marrow contains

clonogenic tumor cells.³⁶ Additional evidence supporting the importance of tumor contamination comes from studies showing better survival in patients who received autografts that did not contain detectable tumor cells after purging.³⁷ Another analysis showed a lower incidence of relapse after autologous hematopoietic stem-cell transplantation for NHL when more aggressive purging was used.³⁸ Finally, a case-matching study comparing purged and unpurged autologous transplants showed that low-grade NHL patients who received purged autografts had significantly better survival.³⁹

We reasoned that a syngeneic transplant is similar to an uncontaminated autograft and a comparison would provide another way to indirectly study whether tumor contamination contributes to relapse. A previous comparison of syngeneic and autologous bone marrow transplantations found no significant differences in relapse or disease-free survival in lymphoma patients.¹⁹

The multivariate analyses in our study showed a five-fold greater risk of relapse when results of unpurged autologous transplantations were compared with syngeneic transplantations for low-grade NHL. In addition, recipients of unpurged autologous transplants had a significantly greater risk of relapse than those who received purged autografts. In low-grade NHL, purging was also associated with improved disease-free and overall survival. Among patients with intermediate-grade histology, those receiving unpurged autografts had a two-fold higher risk of relapse than did recipients of syngeneic transplants, although this difference was of borderline statistical significance, and was not associated with improved survival.

Only one trial has prospectively studied the value of purging autologous transplants for NHL.⁴⁰ A preliminary analysis showed no significant differences in disease progression or survival between purged and unpurged transplants. Other analyses also failed to show a benefit from purging.^{39,41,42} Most relapses after autologous transplantation for NHL occur at sites of prior disease, suggesting that treatment failure most likely is due to inadequacy of high-dose therapy, rather than tumor contamination.

Nevertheless, our analyses provide additional indirect evidence that tumor contamination of the autograft may contribute to relapse after autologous hematopoietic stem-cell transplantation for low-grade, and possibly intermediate-grade, NHL. It is possible that a syngeneic graft-versus-lymphoma effect could explain these results.⁴³ However, it seems unlikely that this effect is important given the lack of evidence for an allogeneic graft-versus-lymphoma effect in our study, although a potent syngeneic graft-versus-lymphoma effect might make it impossible to identify an allogeneic graft-versus-lymphoma effect in this analysis. A syngeneic graft-versus-lymphoma effect could also explain the observed differences in relapse rate between syngeneic and autologous transplants.

In summary, this analysis failed to show evidence of a graft-versus-lymphoma effect. In contrast, this analysis provides additional evidence to suggest that tumor contamination can contribute to relapse after autologous hematopoietic stem-cell transplantation for low-grade, and possibly intermediate-grade, NHL. Although registry-based analyses are hindered by treatment heterogeneity and missing data, our results suggest the possibility that absence of tumor contamination accounts for some of the differences in relapse that have been attributed to a graft-versus-lymphoma effect when autologous and allogeneic transplants for NHL have been compared. Our results suggest that *in vitro* purging, positive selection,⁴⁴ or *in vivo* purging⁴⁵ may be beneficial, although randomized trials are the only way to prove the value of these approaches. In rare instances when a syngeneic donor is available, this may be the preferred type of transplant.

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Chapter 10

General discussion

Stem cell transplantation in follicular lymphoma:
progress at last?

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Abstract

Follicular non-Hodgkin's lymphomas usually present in advanced stage and although frequently are chemotherapy-sensitive remain incurable using conventional approaches. Treatment options are evolving rapidly and now include targeted therapies such as monoclonal antibodies. Recent studies, including the EBMTR-sponsored 'CUP Trial' (conventional Chemotherapy, Unpurged autograft, Purged autograft), demonstrate that for patients under age 60 years with recurrent chemotherapysensitive disease, autologous stem cell transplantation (ASCT) provides a survival benefit over conventional therapy. Allogeneic stem cell transplantation (alloSCT) has become a more effective option. Although incorporation of TBI into the preparative regimen may increase treatment-related mortality (TRM), relapses appear to be reduced compared to a chemotherapy-alone regimen. Reduced-intensity alloSCT procedures are now being performed at an increasing rate, in part due to a lower risk for TRM. Until more data are available, however, reduced-intensity alloSCT should be considered only in cases where myeloablative conditioning is contra-indicated. There are no clear means for choosing ASCT vs alloSCT, a decision influenced by the amount of residual tumor, disease-responsiveness, degree of marrow involvement and extent of prior chemotherapy. ASCT or alloSCT in first remission remains an investigational procedure. Future considerations include incorporation of novel preparative regimens, in vitro purging techniques, antilymphoma vaccines, post transplant immunotherapy and ex vivo-manipulated donor lymphocyte infusions.

Introduction

Follicular non-Hodgkin's lymphoma (NHL) comprises approximately one-third of all lymphomas with about 80% of patients having advanced-stage disease at diagnosis.¹ Paradoxically, this chemotherapy-sensitive disorder is generally incurable using conventional means. Median survivals are 8–10 years even in advanced-stage disease, but the annual mortality rate is approximately 6% per year. Prognosis of individual patients is difficult to predict, and use of prognostic scoring systems such as the Age-Adjusted International Prognostic Index (IPI) is of limited value although more recent data indicate that the Follicular Lymphoma International Prognostic Index (FLIPI) may be helpful.^{2,3} After initial treatment and first recurrence, the natural history of follicular NHL is a continuum of successive relapses of progressively shorter duration and ultimately death from the underlying disease.^{4,5} Conventional chemotherapy has limited or no impact on survival; immunotherapy with agents such as interferon likely has modest impact but often is poorly tolerated and therefore not widely used.^{6–9} Newer treatments such as the monoclonal antibodies rituximab, tositumomab (Bexxars) and ibritumomab tiuxetan (Zevalin®) have excellent activity and a favorable side-effect profile. It will be years, however, before any impact on survival will become apparent. Highdose chemotherapy with autologous stem cell transplantation (ASCT) or allogeneic stem cell transplantation (alloSCT) represents an alternative treatment approach. Advantages of stem cell transplantation include the potential favorable impact upon survival, while disadvantages are toxicity and an adverse side-effect profile.¹⁰ In this article, we will review the current status of ASCT and alloSCT for follicular NHL.

Autologous stem cell transplantation: indications and results

ASCT for recurrent disease

Conventional dose chemotherapy for the treatment of patients with recurrent follicular NHL is likely to produce remissions but of shorter duration each time. Several phase II studies suggest, however, that salvage treatment followed by consolidation with ASCT can prolong disease-free survival (DFS) in relapsed disease patients. Freedman et al.¹¹ reported the largest single institution experience. A total of 153 patients were treated using autologous bone marrow purged in vitro with anti-B-cell monoclonal antibody. At a median follow-up of 5 (range 2–13) years, the 8-year DFS and overall survival (OS) were estimated as 42 and 66%, respectively. Table 10.1 lists the major phase II trials that

showed similar results using different hematopoietic stem cell sources, ex vivo purging methods, highdose conditioning regimens and follow-up periods.^{11–27} All trials suggested an improved median duration of PFS compared to historic controls treated with conventional chemotherapy; a fraction of patients attained prolonged PFS. On the other hand, with longer follow-up, recurrence rates of over 50% were generally observed and questions remain as to whether the durable responses were due to a treatment effect vs patient selection. Comparisons with historic controls suggesting that transplant results in improved survival were not entirely convincing.^{19,28}

The EBMTR-sponsored CUP trial (conventional Chemotherapy, Unpurged autograft, Purged autograft) conducted between 1993 and 1997 is the only prospective, randomized trial to address the role of ASCT in prolonging PFS and OS in patients with follicular NHL.²⁴ Due to slow accrual, the trial was closed after enrollment of 140 of a planned 250 patients. In all, 65% of patients were in first relapse, the remainder in subsequent relapses. Patients were given three initial cycles of chemotherapy (usually a CHOP-like regimen) and 89 patients who attained at least a partial response were randomized to one of three treatment arms: further conventional chemotherapy, ASCT using purged and ASCT using unpurged autografts. Too few patients were entered to assess the effect of ex vivo purging. PFS and OS at 2 years after transplant for both patient groups randomized to ASCT were 55 and 71% compared to 26 and 46%, respectively, for those receiving conventional chemotherapy.²⁴ Hazard ratios for survival and PFS were 0.3 and 0.4, respectively, when comparing conventional chemotherapy with ASCT. These data are highly statistically significant and demonstrate that ASCT provides an important survival benefit in patients with chemosensitive recurrences of follicular NHL and currently should be considered a treatment of choice in this situation.

ASCT as consolidation of first remission

ASCT also has been used for low-grade NHL patients in first complete or partial remission in order to prolong or render such remissions permanent. Several phase II trials are summarized in Table 10.2.^{15,26,28–36} The trial reported by Freedman et al.²⁹, enrolled advanced disease stage patients who had responded to CHOP chemotherapy and underwent consolidation with Cy/TBI and ASCT. Although durable responses were observed, the investigators reported a continuous risk of disease recurrence. Horning et al.³⁰ used a similar strategy, but described improved disease recurrence risk and survival after ASCT compared to a historic control group (30 vs 70% estimated 10-year risk of disease recurrence and 84 vs 62% estimated 10-year survival). Additionally, the results recently reported by Corradini et al.³¹ were similar.

Table 10.1 Autologous transplantation performed in relapsed disease or partial remission.

Author, ref.	Pt. no	Conditioning	In vitro purging	Stem cell source	Median follow-up (mo)	PFS	OS	Early TRM (%)	Comments
Freedman et al ¹¹	153	Cy/TBI	Anti-B MoAB+C0	BM	96	42% at 8 years	66% at 8 years	01	18 secondary malignancies (12 MDS)
Colombat et al ¹²	42	Cy/TBI or BEAM	Purging in 40% BM pts.	BM 88%, PB 12%	43	58% at 43 mo	83% at 43 mo		
Bierman et al ¹³	100	Cy/TBI or BEAM	None	BM 13%, PB 87%	31	44% at 48 mo	65% at 48 mo	8	Two secondary MDS
Apostolidis et al ¹⁴	99	Cy/TBI	Anti-B MoAB+C0	BM	66	63% at 66 mo	69% at 66 mo	4	12 secondary hematologic malignancies
Voso et al ¹⁵	41	Cy/TBI 80%, BEAM 20%	CD34+selection in some pts.	PB	44	43% at 44 mo	72% at 44 mo	4	5% secondary malignancies
Bastion et al ¹⁶	48	Cy/TBI	None	PB	21	53% at 21 mo	86% at 21 mo		One secondary MDS
Weaver et al ¹⁷	49	Bu/Cy or BEAC	None	PB	42	35% at 42 mo	55% at 42 mo	8	BuCy equivalent to BEAC
Berglund et al ¹⁸	22	BEAC/TBI	MoAB in nine pts.	BM	74	72% at 74 mo	81% at 74 mo		50% transformed NHL
Brice et al ¹⁹	83	TBI 71%, BEAM 29%	CD34 (22%)	PB 73%, BM 27%	44	42% at 60 mo	58% at 60 mo		29% transformed NHL
Verdonck et al ²⁰	18	Cy/TBI	None	BM	36	22% at 24 mo	33% at 36 mo		
Cervantes et al ²¹	34	Cy/TBI 91%, BEAM 9%	Anti-B MoAB+C0	BM 70%, PB 27%, both 3%	40	18% at 24 mo	37% at 60 mo	4	
Cao et al ²²	49	Cy/TBI/V/P 78%, Cy/BCNU/V/P 22%	Anti-B MoAB	BM 39%, PB 61%	66	44% at 48 mo	60% at 48 mo		
Van Besien et al ²³	587	TBI 184 (31%) non-TBI 413 (69%)	None	BM 89 (15%), PB 508 (85%)	41	31%	55%	4	TRM increases to 8% at 5 years
Van Besien et al ²³	131	TBI 44 (34%), non-TBI 87 (66%)	MoAB 11%, CD34+ selection 21%, in vitro chemotherapy 68%	BM 100 (76%), PB 31 (24%)	49	39%	62%	8	TRM increases to 14% at 5 years
Schouten et al ²⁴	65	Cy/TBI	Anti-B MoAB (50%)	BM	69	52%	72%		Randomized study
Molina et al ²⁵	58	Cy/V/P and either BCNU or TBI	None	PB	62	42% at 60 mo	67% at 60 mo	2	Two secondary MDS
Seyfarth et al ²⁶	22	Cy/TBI 38%, BEAM or Bu/Cy 62%	CD34+selection in 95%	PB	48	38% at 48 mo	73% at 48 mo		
Stein et al ²⁷	36	Cy/V/P/TBI 75%, CBV 25%	None	BM 93%, PB 7%	NS	NS	53%	15	One secondary MDS

PFS=progression-free survival; OS=overall survival; MoAB=monoclonal antibody; VP=etoposide; BM=bone marrow; PB=peripheral blood; early TRM=treatment-related mortality, usually defined as occurring within 100 days after ASCT; NS=not stated; BEAM=BCNU/etoposide/cytarabine/melphalan; BEAC=BCNU/etoposide/cytarabine/cyclophosphamide; BuCy=cyclophosphamide/BCNU/etoposide, mo=months.

The encouraging phase II data summarized in Table 10.2 led several groups to develop multi-center, randomized studies comparing ASCT consolidation vs interferon maintenance or observation. The German Low Grade Lymphoma Study Group randomized chemosensitive indolent (mostly follicular) NHL patients younger than 60 years in first partial or complete remission to ASCT vs maintenance interferon therapy.³² A total of 240 follicular NHL patients were evaluable for the comparison of ASCT vs interferon maintenance. At a median follow-up period of 4.2 years, 31 relapses (27.2%) were observed in the ASCT study arm and 76 (60.3%) in patients receiving IFN maintenance. In addition, five deaths occurred in remission (four patients in the ASCT study arm and one in the IFN group). Accordingly, the PFS was significantly different in the two study arms. In patients receiving ASCT, the PFS was 79.1% after 2 years (95% confidence interval 71.4-86.9%) and 64.7% after 5 years (95% confidence interval 54.6-74.8%) in comparison to only 52.7% (95% confidence interval 43.8-61.7%) after 2 years and 33.3% (95% confidence interval 24.3-42.3%) after 5 years in the IFNa study arm ($P<0.0001$). This trial, however, does not have sufficient follow-up to assess the impact of ASCT on (OS). The French GOELAM group also reported, in preliminary fashion, that ASCT decreased recurrence rates but did not have any effect on long-term survival.³³ This finding may be due to the fact that patients undergoing ASCT appeared at increased risk for the development of myelodysplastic syndrome (MDS).³⁷ In the absence of a demonstrated survival benefit, the data do not support ASCT in first remission for follicular NHL patients outside of a clinical trial.

Transformed follicular NHL

Over time a considerable percentage of follicular NHL patients develop disease transformation. Such patients are often treated in a manner similar to large cell NHL patients, but tend to have a poor prognosis and are considered incurable. Early reports indicated ASCT to be ineffective in this patient group.³⁸ Subsequently, improved patient selection resulted in better overall outcome and has led to ASCT as consolidation treatment after reinduction therapy. Table 10.3 illustrates several small studies indicating that consolidation with ASCT can induce durable remissions in some patients.^{18,22,31,39-42} In fact, some larger retrospective analyses suggest a survival benefit of ASCT in the setting of transformation that might be comparable to results in nontransformed follicular NHL or diffuse large cell NHL.⁴¹⁻⁴³ For example, in the case-matched report from the EBMTR, a subgroup of patients with chemosensitive minimal residual disease prior to an ASCT had an overall 5-year survival of 69%.⁴¹

Table 10.2 Autologous transplantation performed in first complete remission.

Author, ref.	Pt. no	Conditioning	In vitro purging	Stem cell source	Median follow-up (mo)	PFS	OS	Early TRM (%)	Comments
Voso et al. ¹⁵	70	Cy/TBI	CD34+ selection (10%); none (90%)	PB	44	78% at 44 mo	86% at 44 mo	5	
Seyfarth et al. ²⁶	33	Cy/TBI 79%, BEAM 21%	None	PB	48	76% at 48 mo	92% at 48 mo		
Freedman et al. ²⁹	77	Cy/TBI	Anti-B MoAB+Co	BM	45	63% at 3 years	89% at 3 years	3	Five secondary hematologic malignancies
Horning et al. ³⁰	37	Cy/TBI/VP	Anti-B MoAB+Co	BM	78	60% at 10 years	86% at 10 years	5	Two secondary hematologic malignancies
Corradini et al. ³¹	40	Mitoxantrone/melphalan	None	PB	90	57% at 12 years	60% at 12 years	1	11 pts. had transformed follicular, three secondary hematologic malignancies
Lenz et al. ³²	140	TBI/Cy	None	PB	53	65% at 60 mo	NS	1	Randomized trial; 6.6% secondary MDS in transplant group 37
Colombat et al. ³³	27	Cy/TBI	CD34+ selection or anti-B	PB	72	55% at 72 mo	64% at 72 mo		Randomized trial; MDS increased in transplant group
Bociek et al. ³⁴	43	Not stated	MoAB+Co	PB	36	36% at 60 mo	63% at 60 mo		Original not available
Gonzalez-Barca et al. ³⁵	15	Cy/TBI	Immunomagnetic purging	BM 9, PB 6	56	83% at 56 mo	NS	13	6/8 BM PCR negative for BCL-2
Linossier et al. ³⁶	42	TBI 48%, non-TBI 52%	BM 36%	BM 88%, PB 12%	43	66% at 43 mo	83% at 43 mo		No prognostic factors identified

Early TRM=treatment-related mortality occurring in the first year after transplant. For other abbreviations, see Table 10.1 footnote.

Table 10.3 Studies using ASCT in transformed follicular lymphoma

Author, ref.	Pts. no	Conditioning	Stem cell source	Median follow-up (mo)	PFS	OS	Early TRM (%)	Comments
Berglund et al. ¹⁸	11	BEAC/TBI	PB	74	72% at 74 mo	81% at 74 mo		
Cao et al. ²²	17	Cy/TBI/VP 47%, Cy/BCNU/VP 53%	PB 59%, BM 41%	64	48% at 48 mo	50% at 48 mo	NS	
Corradini et al. ³¹	11	Mitoxantrone/melphalan	PB	90	54% at 10 years	NS		
Foran et al. ³⁵	27	Cy/TBI	PB 11%, BM 89%	29	52% at 48 mo	50% at 102 mo	7	Two secondary MDS
Friedberg et al. ⁴⁰	27	Cy/TBI	BM purged anti-B MoAB	36	46% at 60 mo	59% at 60 mo	0	Four secondary MDS
Williams et al. ⁴¹	50	TBI-containing 70%, non-TBI 30%	BM 62%, PB 38%	59	30% at 60 mo	51% at 60 mo	12	Three secondary MDS
Chen et al. ⁴²	35	VP/IMEL/TBI	BM 46%, PB 29%, both 25%	52	31% at 60 mo	37% at 60 mo	20	Three secondary MDS

Technical considerations

Several technical aspects of ASCT such as choice of hematopoietic stem cell source, *ex vivo* purging, conditioning regimen and aspects of supportive care may have a considerable influence on the outcome of transplant and ideally should be investigated in prospective, randomized studies. For a variety of reasons, including the large number of patients required, considerable expense of such an undertaking and requirement for prolonged follow-up, these aspects of care generally have not been addressed in this fashion. Definitive answers to questions of the optimal preparative regimen or optimal stem cell source therefore are not possible. Some recommendations can be provided by comparison of individual study results, case-control studies and best perhaps from multivariable analysis of large observational data sets.

Conditioning

Transplant conditioning regimens for ASCT in follicular NHL can be classified into three variants: TBI-containing, high-dose BCNU-based (BEAC, BEAM, CBV) and busulfan-based (Bu/Cy, Bu/VP16). Largely for historic reasons, TBI-containing or BCNU-based regimens most commonly are used in follicular NHL. Both an EBMTR study and IBMTR analysis indicated that use of TBI might be associated with an increased treatment-related mortality (TRM). Williams et al.⁴¹ in the EBMTR noted an 18% TRM (nine of 50) in transformed follicular NHL patients undergoing ASCT; all nine patients received TBI. van Besien et al.²³ in the IBMTR noted nearly a two-fold lower TRM in the 553 patients who received a non-TBI preparative regimen compared to the 348 subjects given TBI ($P=0.008$). On the other hand, TBI in the preparative regimen was associated with a statistically significant decrease in the rates of disease recurrence ($P=0.02$).

These observations, while far from definitive, suggest that TBI is a particularly effective, but a rather toxic treatment for follicular lymphoma and provide a rationale for the further development of radio-labeled monoclonal antibodies as part of conditioning regimens for transplant.⁴⁴ In a single-center, phase II study reported by Gopal et al.,⁴⁵ 98 individuals with follicular lymphoma transplanted using conventional-dose ASCT (70% received a TBI-containing regimen) were compared to 27 patients transplanted using high-dose chemotherapy and radioimmunotherapy (¹³¹I-anti-CD20 monoclonal antibody, tositumomab). The estimated 5-year OS and PFS were 67 and 48%, respectively, for those subjects given radioimmunotherapy conditioning compared to 53 and 29%, respectively, for conventional ASCT. Further, 100-day TRM was only 3.7% in the radioimmunotherapy group vs 11% in the conventional group; both groups had similar probabilities of secondary MDS/AML. Interesting preliminary data

regarding the use of ^{186}Re -labeled anti-CD20 followed by autogous stem cell rescue recently were reported by a German Group.⁴⁶

In vitro purging

Most patients with follicular NHL present in advanced disease stage and often with morphologic evidence of marrow involvement.⁴⁷ Even in patients with histologically normal marrow, occult marrow involvement can usually be demonstrated by PCR technique.⁴⁸ It is likely that these lymphoma cells contaminating the stem cell infusate contribute to relapse after ASCT. While direct evidence for this hypothesis is lacking, several lines of indirect evidence support this concept. First, several groups have demonstrated that presence of occult stem cells in the graft correlates with risk of disease recurrence.^{49–52} Further, Gribben et al.⁵³ used PCR technique to detect lymphoma cells in the circulation within hours after infusion of stem cells containing occult lymphoma cells. Third, in other hematologic malignancies such as AML, ALL and CML, a direct contribution of the graft to disease recurrence has been demonstrated by gene-marking experiments.^{54,55}

Ex vivo technologies to decrease tumor contamination include 'positive' selection,⁵⁶ that is, the *in vitro* enrichment of the graft for CD34 cells, a marker presumably lacking on lymphoma cells, as well as 'negative' selection, that is, the removal of tumor cells by exposure to lymphoma-specific antibodies.^{50,51,57}

These methods have been extensively investigated and several phase II studies suggest that effective purging is of clinical benefit. For example, the group from the Dana Farber Cancer Institute found that successful *in vitro* purging was associated with dramatically improved freedom from relapse in follicular NHL patients undergoing ASCT.^{11,29} Furthermore, Ladetto et al.⁵² showed that successful *in vivo* purging (i.e., the generation of PCR-negative harvests after intensive induction chemotherapy) was associated with improved PFS. Fouillard et al.,⁵⁰ using various purging methods, also found a correlation between *ex vivo* graft treatment and outcome. Only one group failed to find a correlation between PCR status of the infusate and recurrence.¹⁴ The obvious corollary of these findings is that occult lymphoma cells contribute to recurrence in tumor-contaminated grafts. The absence of a satisfactory control group in these studies, however, makes it impossible to rule out the alternative explanation, namely that the ability to achieve a tumor-free graft is a surrogate for chemotherapy sensitivity. The CUP trial attempted to address this issue in a prospective fashion, but low patient numbers limited the study's power.²⁴ The best, albeit indirect, evidence concerning the role of a tumor-free graft comes from several registry analyses. A case-control study from EBMTR demonstrated an improved PFS in patients given purged rather than unpurged autografts for follicular NHL.⁵⁸ A group of 270 patients given purged (marrow)

ASCT were compared to 224 casematched unpurged (marrow) ASCT patients. Patients with low-grade NHL did not have a significantly improved PFS if the bone marrow was purged ($P=0.1757$); however, they did have a significantly improved OS ($P=0.00184$). This increased OS was found to be associated with non-TBI conditioning and also with the purged patients undergoing transplantation at large transplant centers ($P=0.0016$). More recently, a retrospective IBMTR study identified stem cell purging as an independent predictor for relapse, PFS and OS ($P=0.03$) in multivariate analysis.²³ The hazard ratio for disease recurrence after purged transplant was 75% of that after unpurged transplantation. Third, a case-control study by Bierman et al.⁵⁹ comparing syngeneic transplants, purged ASCT and unpurged ASCT showed that syngeneic transplants had a very low recurrence rate. When compared with syngeneic transplants, unpurged ASCT had a significantly higher (nearly five-fold) risk of relapse ($P=0.008$); recipients of purged ASCT had a threefold higher relapse risk than syngeneic transplant recipients, but this difference was not statistically significant ($P=0.10$).⁵⁹ We interpret these data as indicative of the importance of providing a tumor-free graft. Current technology limits the efficiency of graft purging. For example, in the Dana-Farber series, persistent marrow involvement could be detected in almost half the patients after negative selection with a panel of monoclonal antibodies.^{11,29} In addition to positive and negative *in vitro* selection, *in vitro* chemotherapy exposure has been used for purging of stem cells.⁶⁰ This technique, while of historic and perhaps clinical interest, has fallen out of favor because of its complexity, the associated nonselective damage to normal progenitors and the subsequent delay in hematopoietic recovery after graft re-infusion. More recently, rituximab has also been used as an '*in vivo* purging' agent. Pilot studies indicate that rituximab administration may eliminate PCR-detectable cells in a significant proportion of hematopoietic cell harvests but may be associated with late neutropenia and serious infection.⁶⁰⁻⁶² Whether transplant outcome will be improved by collecting PBSC after exposure to rituximab remains to be demonstrated. Several novel purging technologies are currently undergoing early evaluation. For example, the anti-CD133 monoclonal antibody targets a primitive stem cell population and is being evaluated for positive stem cell selection.⁶³ Others are using pulsed electric fields to deplete tumor cells from a graft selectively.⁶⁴

Late toxicities of ASCT: MDS and treatment-related leukemia

Although early morbidity is considerable, advances in supportive care significantly reduced the immediate treatment-related mortality associated with ASCT, even in elderly patients. On the other hand, late treatment-related side effects, such as MDS or secondary acute myeloid leukemia (sAML), occur at a 5 to 15-fold increased incidence.^{65,66} The etiology of post transplant MDS is

complex and is related to a combination of host-related factors, prior treatment and conditioning. Micallef et al.⁶⁷ reported upon 230 follicular NHL patients given cyclophosphamide and TBI followed by ASCT. At a median follow-up of 6 years, 27 (12%) developed therapy-related MDS or AML 4.4-8.8 years after transplant; prior fludarabine therapy ($P=0.009$) and older age ($P=0.02$) were associated with the development of the secondary malignant processes. Others have related the risk of secondary MDS to pretransplant treatment with etoposide or radiation⁶⁸ or to pretransplant exposure to mechlorethamine or chlorambucil.⁶⁹ Excessive doses of radiation in the conditioning regimen may also be associated with increased risk for secondary MDS.⁶⁹ Interestingly, some studies have shown that clonal chromosomal abnormalities can often be detected in the graft of patients who have developed MDS after transplant^{70,71} The outcome for patients who develop treatment-related MDS/AML is usually is quite poor.^{72,73}

Allogeneic stem cell transplantation

Myeloablative transplantation

The exact role of alloSCT in follicular NHL remains somewhat difficult to define. AlloSCT was initially used in patients thought not candidates for ASCT due to the extent of disease or marrow involvement; investigators believed that the allogeneic or graft-versus-tumor effect would eradicate disease via adoptive immunotherapy.⁷⁴⁻⁸² Several retrospective studies suggest that alloSCT is associated with a very low relapse rate and might be a curative treatment for follicular NHL (Table 10.4)^{23,77-82} but that the benefit of alloSCT is at least partially offset by high TRM. The IBMTR reported data on 904 follicular NHL patients who during the period 1990 and 1999 underwent either ASCT or alloSCT.²³ A total of 176 (19%) patients underwent alloSCT, 131 (14%) were given purged ASCT and 597 (67%) received unpurged ASCT. The 5-year TRM rates were 30, 14, and 8% and recurrence rates were 21, 43, and 58% after alloSCT purged ASCT, and unpurged ASCT, respectively. Furthermore, the 5-year probabilities of survival were 51, 62, and 55% after alloSCT, purged ASCT and unpurged ASCT.²³ This communication confirms the high TRM yet low recurrence rate associated with the use of alloSCT and overall similar long-term patient survivals compared to ASCT. These data do not allow practitioners to make decisions for individual patients regarding the use of alloSCT vs ASCT; such treatment recommendations continue to be guided by physician judgment. Over the past decade, advances in supportive care and better patient selection have resulted in improved outcomes for alloSCT (Figure 10.1).²³ Also, the risk of secondary MDS after alloSCT is negligible.

Table 10.4 Selected studies using myeloablative conditioning and allogeneic transplantation for follicular lymphoma

Author, ref.	Pt. no.	Conditioning	Stem cell source	Median follow-up (mo)	PFS	OS	TRM	Relapse (%)	Comments
van Besien et al ²³	176	TBI 120 (66%), non-TBI 56 (32%)	BM 135 (77%), PB 41 (23%)	36	45% at 60 mo	51% at 60 mo	24% at 12 mo		Transplants between 1980 and 1999
Stein et al ²⁷	15	CyTBI 93%	BM 93%, PB 7%	60	NS	15%	53%	33	
van Besien et al ⁷⁷	113	TBI 84%, non-TBI 16%	BM	25	49 at 36 mo	49 at 36 mo	40% at 36 mo	16	Transplants between 1984 and 1995, one-third with small lymphocytic lymphoma
Peniket et al ⁷⁸	231	Varied regimens	NS	60	43%	51% at 48 mo	38% at 48 mo	25	Case-matched showing high TRM but low relapses
Mandigers et al ⁷⁶	15	CyTBI	BM and TCD	36	67%		33%	13	T-cell-depleted transplant.
Verdonck ⁸⁰	15	CyTBI		25	70%	70%	27%	0	T-cell depletion
Toze et al ⁸¹	16	NS	BM 100%	29	56%		25%	0	Four unrelated donors and 12 sibling donors
Forrest et al ⁸²	24	Bu/CyTMEI 92%	BM 16, PB 8	28	78% at 28 mo	78% at 28 mo	21%	0	No relapses noted

Early TRM=treatment-related mortality occurring in the first year after transplant; Bu/CyTMEI=busulfan/cyclophosphamide with/without melphalan. For other abbreviations see Table 10.1 footnote.

Table 10.5 Studies using reduced-intensity conditioning and allogeneic transplant for follicular lymphoma.

Author, ref.	Pts. no	Conditioning	Stem cell source	Median follow-up (mo)	PFS	OS	Early TRM (%)	Comments
Seattlea	9	Flud/TBI 200	PB	412	7	8	0	
Khoury and Champlin ⁸³	20	Flud/CY	PB	21	80%	80%	20	64% cumulative incidence at chronic GVHD
Faulkner et al ⁸⁴	28	BEAM Campath	PB	16	69%	74%	16	No extensive chronic GVHD
Robinson et al ⁸⁵	28	Flud/alkylator (92%), BEAM Campath 8%	PB	NS	29%	39%	39	Higher than expected TRM and relapse

Early TRM = treatment-related mortality occurring in the first year after transplant; Flud = fludarabine. For other abbreviations see Table 10.1, footnote.
^aPersonal communication by MB Maris, FHCRG.

We currently recommend alloSCT as the preferred therapy for recurrent NHL patients who are aged 50 years or less and who have an HLA-identical sibling donor. Use of a TBI-based conditioning regimen may be preferred due to the decreased recurrence rate associated with that modality.

Figure 10.1 Probabilities of survival after HLA-identical sibling transplantation by year of transplantation (reproduced with permission, American Society of Hematology, Blood 2003; 102: 3521–3529).

Reduced-intensity transplantation

Reduced-intensity conditioning regimens, considered less toxic, are being used at increased frequency. The underlying hypothesis of such a strategy is that fewer patients will develop TRM and graft-versus-lymphoma effects will result in curing a greater percentage of patients. Interesting preliminary results indicate that this premise may be the case (Table 10.5).^{83–85} Khouri and Champlin⁸³ reported their experience in 49 NHL patients of median age 55 (range 21–68) years, including 20 follicular and 15 transformed NHL. Eight patients had disease relapse after a prior ASCT. At a median follow-up of 19 (range 5–52) months, actuarial survival is 79%. PFS is 85% for the indolent and 60% for the transformed NHL patients. The potency of graft-versus-lymphoma effects is underscored by the sometimes spectacular responses to donor lymphocyte infusion (DLI). For example, Mandigers et al.⁸⁶ reported that two poor-risk, relapsed low-grade NHL patients failing T-cell-depleted sibling-matched allografts re-entered durable complete remission after DLI from the original donors. Still, the considerable risks and toxicity associated with chronic GVHD cannot be underestimated and long-term follow-up on such studies is lacking. Robinson et al.⁸⁵ reported preliminary results of an EBMT analysis of nonmyeloablative transplantation in lymphoma. The low-grade NHL patients had a disappointing 39% TRM and 29% PFS at 1 year after transplant, to a large extent due to GVHD and opportunistic infections. Paradoxically, some of

the best reported results involve in vivo or in vitro T-cell-depleted transplants such as the recent experience of using BEAM-alemtuzumab reduced-intensity alloSCT in which 70% of low-grade NHL patients are alive at 4 years.⁸⁴ The role of reduced-intensity alloSCT hopefully will be established by a recently activated trial conducted by the Blood and Marrow Transplant Clinical Trials Network comparing ASCT vs alloSCT in follicular NHL patients.

Future directions

The limitations of ASCT transplantation include disease recurrence and risk of secondary MDS. Future improvements are likely to focus on incorporation of targeted monoclonal antibodies into the preparative regimen and post transplant period, novel stem cell purging strategies and use of anti lymphoma vaccines or other forms of therapy in the post transplant period. These studies will be carried out in patients with recurrent disease and, if successful, could be extrapolated for use earlier in the course of the disease. Studies in alloSCT will focus on minimizing treatment-related complications that likely will include newer GVHD prevention approaches, use of new graft-versus-lymphoma maneuvers and incorporation of more advanced techniques of donor lymphocyte infusion (Table 10.6).

Table 10.6 Future directions.

Autograft
Incorporation of targeted monoclonal antibody therapy to preparative regimen and post transplant therapy
Novel in vitro purging techniques
Use of antilymphoma vaccines post transplant or other post transplant immunotherapy
Allograft
Minimizing treatment-related complications
Newer GVHD prevention approaches
Use of new graft-versus-lymphoma maneuvers
Advanced donor lymphocyte infusion techniques

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Chapter 11

Conclusion

"There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know."

Donald Rumsfeld

Exercice 11.1. Soit f une fonction continue sur $[a, b]$. On pose $F(x) = \int_a^x f(t) dt$. Montrer que F est dérivable sur $[a, b]$ et que $F'(x) = f(x)$.

$$\begin{aligned} F'(x) &= \lim_{h \rightarrow 0} \frac{F(x+h) - F(x)}{h} \\ &= \lim_{h \rightarrow 0} \frac{\int_a^{x+h} f(t) dt - \int_a^x f(t) dt}{h} \\ &= \lim_{h \rightarrow 0} \frac{\int_x^{x+h} f(t) dt}{h} \end{aligned}$$

Conclusion

Episodes of stagnation in medicine alternate with moments of rapid progression. Much of this has to do with the convergence and maturation of new technologies into new so called "medical platforms", that allow new areas of discovery and investigation. Examples of such platforms include the development of cellular pathology in the mid nineteenth century, the development of combination chemotherapy in the sixties and seventies, monoclonal antibody technology in the seventies, molecular biology, stem cell support for autologous transplants and so forth. More subtle, but equally important advances include those in radiology or the development of sophisticated statistical techniques for clinical trial design and interpretation. This is a heady time for those interested in lymphoma. Our understanding of its biology has dramatically improved in the past decades and new technologies, in particular gene arrays, promise exponentially increase knowledge. The immediate payoff for the clinician may be an improved ability to accurately predict prognosis (i.e. better prognostic scores) and to more accurately predict who might benefit from treatment. Over time, it is hoped that basic knowledge will translate into further rational drug development. Monoclonal antibody therapies constitute excellent examples of such development.

Numerous new drugs are now available that promise to improve the outcome of patients with follicular lymphoma and that provide new opportunities for clinical research. But opportunity also creates new problems and questions. Specifically questions abound on how to test individual drugs, how to accommodate testing of all of them and how to integrate the old treatments with the new.

The experience with interferon serves as a reminder of the complexities of drug development in follicular lymphoma. Unexplained discrepancies in results between randomized studies led to major delays in development of the drug and, for all practical purposes, its abandonment in the US, despite convincing data for its effect on survival. A recent meta-analysis of randomized studies suggests that dosing and potential interactions with various conventional chemotherapies are important determinants of the effects of interferon. The type of chemotherapy it is combined with affects its relative benefit.

Because of such complexities, prospective studies should be carefully designed, conducted and interpreted in a dispassionate manner, with minimal interference by either commercial or career mediated bias. While the randomized study remains the gold standard for drug development, it is not always possible, and much might be gained from incorporating novel designs in clinical studies as well as by incorporation of correlative studies. Ongoing study of the clinical relevance of surrogate markers remains of value because it

continues to have the potential for shortening the required length of follow-up for future studies.

The role of complicated treatments such as autologous or allogeneic transplantation in follicular lymphoma also requires rethinking.¹ In our opinion, these treatments continue to be of interest, because more than any other treatment, they hold the potential for cure in follicular lymphoma. For patients under the age of 60, the German Lymphoma Study Group continues to study the role of autologous transplantation after initial conditioning with CHOP-Rituximab chemotherapy.² Further follow-up of this trial will demonstrate whether there is an additive or synergistic effect between rituximab and autologous transplant on outcome of follicular lymphoma; or possibly whether the benefit of autotransplant is neutralized by that of rituximab. Stem cell purging as a method of reducing the risk of disease recurrence, after autologous transplantation also deserves further study. Allogeneic transplantation still has too much toxicity and is not widely applicable because of issues of donor availability. Until these issues are solved to a significant degree, allogeneic transplantation should be offered only in the absence of alternative treatment options. Whether complex treatments such as transplant will still be used twenty years from now is impossible to predict. Even if they are no longer considered practical treatments, the study of these technologies will have contributed considerably to stem cell and lymphoma biology.

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Samenvatting

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Samenvatting

De eerste beschrijving van folliculair lymfoom dateert van 1925. Het klinisch beeld was nagenoeg compleet tegen het begin der jaren veertig. De aandoening wordt gekenmerkt door wijdverbreide lymfknoopaantasting en een uiterst variabel verloop. De gemiddelde overlevingsduur bedraagt ongeveer tien jaar na het tijdstip van diagnose, maar de overleving kan enorm variëren van patiënt tot patiënt. Ongeveer 20% van de patiënten sterven in de eerste vier jaar.

Hoofdstuk 1 is een korte geschiedenis van folliculair lymfoom. De diagnose berustte gedurende lange tijd uitsluitend op de typische morfologie, maar er was weinig gekend over de natuur van deze aandoening. In de jaren 70 werd de B-cel origine van folliculair lymfoom herkend, en kort daarna de essentiële rol van de bcl-2 gen mutatie in de pathogenese. Dit heeft dan over de voorbije jaren geleid tot de ontwikkeling van uiterst specifieke therapieën, die hier kort worden samengevat. In de rest van het proefschrift bespreek ik de rol van allogene transplantatie als één van een aantal mogelijke behandelingsmethodes. Maar veel vragen over biologie blijven onbeantwoord. Men weet nog maar weinig over de rol van eventuele bijkomende mutaties in de pathogenese en in de modificatie van het ziektebeeld. Er is ook weinig bekend over de etiologie van deze aandoening die nochtans lijkt toe te nemen in frequentie.

De volgende hoofdstukken zijn retrospectieve studies over de rol van allogene transplantatie in folliculair lymfoom. Hoofdstuk 2 was een analyse van allogene transplantaties voor lymfoom in MD Anderson tussen 1981 en 1994. Patiënten met agressief en hooggradig lymfoom hadden een hoog risico zowel voor recidief als voor complicaties. Patiënten met laaggradig lymfoom daarentegen hadden een veel betere prognose. Hoofdstuk 3 is een meer gedetailleerd analyse van tien patiënten die allogene transplantatie ondergingen in MD Anderson Cancer Center in Houston, Texas. Deze studie en een latere follow-up van dezelfde patiënten (hoofdstuk 3) werd gepubliceerd in het Journal of Clinical Oncology.

Allogene transplantatie voor folliculair lymfoom blijft gewoonlijk beperkt tot jongere patiënten met HLA-identieke familiale donoren. Als een gevolg hiervan is het aantal patiënten zeer beperkt en zijn prospectieve studies bijna onmogelijk. De analyse van databestanden was daarom de meest realistische methode ter confirmatie van mijn originele data. De volgende drie hoofdstukken zijn studies die uitgevoerd werden in samenwerking met het International Bone Marrow Transplant Registry (IBMTR), in Milwaukee, Wisconsin. Zij slagen

hebben data van ongeveer 75% van alle beenmerg of stam cel transplantaties in de wereld. In de IBMTR studies bevestigden we dat de kans op recidief na allogene transplantatie uiterst beperkt is. Onze eerste studie, (hoofdstuk 5) gepubliceerd in 1998, besloeg vooral patiënten behandeld in de jaren tachtig. In deze groep vonden we een onaanvaardbaar hoog risico voor fatale complicaties (Treatment-related mortality –TRM). In een latere studie (hoofdstuk 6) van patiënten die in de jaren '90 getransplanteerd werden, was de frequentie van complicaties duidelijk veel lager. We vonden ook dat het risico voor complicaties afhankelijk was van de gezondheidstoestand van de patiënt, zijn of haar leeftijd, en de chemotherapie sensitiviteit van het lymfoom. Allogene transplantatie wordt dikwijls gebruikt voor patiënten die een recidief hebben na een vroegere autologe transplantatie. We hebben ook dit scenario bestudeerd in de IBMTR (hoofdstuk 7) en vonden dat ook in deze situatie de chemotherapie sensitiviteit van het lymfoom van groot belang was.

Door deze studies en een aantal studies van andere groepen werd het duidelijk dat allogene transplantatie veruit de meest efficiënte methode is ter genezing van folliculair lymfoom. Maar het risico voor ernstige en vaak fatale complicaties is een grote beperking van deze behandelingsmethode. Complicaties tengevolge van acute of chronische afstotingsverschijnselen (graft vs host disease) zowel als de conditioneringtherapie zijn hiervoor verantwoordelijk. Om vooruitgang te boeken moet de transplantatietechnologie verbeteren. Dit kan in zekere mate gebeuren door een beter begrip van hoe allogene transplantatie werkt. Is het de intensieve radiochemotherapie van de conditionering die nodig is voor genezing, of zijn de immunologische graft-versus-lymphoma effects het belangrijkste? Hoofdstukken 8 en 9 bestaat uit twee artikelen die deze vraag op een klinische manier proberen te beantwoorden. In een eerste studie, een analyse van patienten met recidief na allogene transplantatie, tonen we duidelijk het bestaan aan van GVL-effecten. Maar in een belangrijke IBMTR studie van syngene transplantatie, toonde Dr. Bierman aan dat GVL effecten niet essentieel zijn voor permanente genezing na allogene transplantatie.

Hoofdstuk 10 is een overzichtsartikel van studies in allogene en autologe transplantaties voor folliculair lymfoom. In hoofdstuk 11 speculeer ik tenslotte over de huidige en toekomstige rol van transplantatie in de behandeling van folliculair lymfoom.

Dankwoord

Dankwoord

Dit proefschrift is een samenvatting van meer dan tien jaar werk in klinisch onderzoek en klinische zorg. Het is onmogelijk allen te vermelden. Klinische hematologie en stamceltransplantatie is een complexe onderneming en velen behoeven dank om mijn werk mogelijk te maken. Ik vernoem hier vooral de mensen die mij meest geholpen hebben in mijn loopbaan.

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In Brugge heb ik mijn opleiding beëindigd. Het was een tijd om bij te leren in klinische hematologie en hematopathologie van collega's met een enorme ervaring. Mijn dank aan Achiel Van Hoof, Arnold Criel, Melanie Hidajat en Dries Louwagie.

Toen ik naar Texas kwam beloofde het diensthoofd, Al Deisseroth me dat ik miljonair zou worden in Houston. Ik ben dat nog steeds niet. MD Anderson was toen (en is nog steeds) de tempel van empirische klinische research in hematologie. Hun aanpak en onderliggende filosofie, hebben een grote invloed gehad op mijn carrière. Teveel vrienden om allemaal te noemen, maar mijn dank gaat vooral uit naar Dick Champlin, toen mijn baas en nog altijd raadgever, en mijn collega's en goeie vrienden Sergio Giralte en Rakesh Mehra.

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Mijn ouders hebben door hun voorbeeld, mij het belang ingeprent van hard werken, nieuwsgierigheid en ruimdenkendheid. Aan hen draag ik dit werk op. Mijn broers en zussen, waren mijn tweede lijn van opvoeders en voorbeelden. Ik ben opgegroeid met jullie als "rolmodel". Altijd was er iets nieuws, te zien of te horen of was er iemand in een ander ver land of in een andere taal. Dat maakte de stap naar de USA relatief gemakkelijk.

Ok-kyong, Herman, Sam en Leen. Teveel te danken, om hier in een paar regels te vertellen. It's great to have you....

Curriculum vitae

Curriculum vitae

Koen van Besien werd geboren op 1 mei 1959 te Tiegem in West-Vlaanderen. Na de kandidaturen geneeskunde in Namen vervolgde hij zijn studies in Leuven waar hij ook de eerste jaren assistentschap inwendige geneeskunde deed. In 1987 vertrok hij op uitnodiging van Guido Tricot en Ron Hoffman naar Indianapolis voor verdere opleiding in hematologie en oncologie. Van 1990 tot 1992 werkte hij in Brugge met Dries Louwagie en Achiel Van Hoof. Daarna vertrok hij met zijn gezin naar Houston, Texas. In het MD Anderson Cancer Center van 92 tot 97 begon hij zich, op vraag van Richard Champlin specifiek te interesseren in de behandeling van lymfomen. Hij woont sinds 97 in Chicago waar hij de transplantatie afdeling leidt, eerst aan de University of Illinois en sinds 2001 aan de University of Chicago.

Hij is gehuwd met Ok-kyong Chaekal, ook oncologe. Ze hebben drie kinderen: Herman, Sam en Leen.