Chemotherapy-induced peripheral neuropathy

Summary of the results

The main objectives of this thesis were to gain knowledge about the severity and prevalence of chemotherapy-induced peripheral neuropathy (CIPN), the influence of CIPN on patients' quality of life (QOL) and the influence of chemotherapy administration on the development of CIPN. This thesis was subdivided into two parts. Part one addressed the prevalence and severity of CIPN symptoms, and the impact of those symptoms on the QOL among different cancer patients, at different time points after diagnosis. Part two addressed the influence of chemotherapy administration on the development of persistent CIPN. We investigated the influence of oxaliplatin administration on persistent CIPN in colorectal cancer (CRC) survivors. In addition, the influence of antimyeloma treatment with immuno-modulatory drugs thalidomide and lenalidomide, and the proteasome inhibitor bortezomib on persistent CIPN in patients with multiple myeloma (MM) was reported.

Part I - Chemotherapy-induced peripheral neuropathy and quality of life

This thesis started with a study investigating the occurrence and severity of CIPN symptoms induced by the frequently used platinum derivatives and taxanes median six months after cessation of chemotherapy, as patients with remaining complaints after six months are at risk of having irreversible CIPN (**Chapter 2**). Furthermore, the impact of these symptoms on daily functioning and QOL was investigated. A sample of 43 cancer patients, including colorectal, breast-, ovarian and prostate cancer, visiting the outpatient clinic of the Máxima Medical Center were included. The majority of patients demonstrated the occurrence of CIPN symptoms in the upper and lower extremities. Overall, most reported complaints included numbness and tingling in hands as well as feet, suffering from cold feet, and trouble distinguishing objects in the hands. Housekeeping difficulties were reported in 13% of patients and 21% of patients became more dependent on others because of the neurotoxicity. In addition, the overall QOL was negatively affected due to the impact of CIPN in 49% of patients.

After concluding that CIPN was very common in patients with different cancer types visiting the outpatient clinic in chapter 2, we wanted to explore those symptoms in more detail in a population-based sample of CRC survivors long after diagnosis (**Chapter 3).** The platinum derivative oxaliplatin, first successfully used in the management of advanced CRC, is nowadays also the regimen of choice for adjuvant treatment of patients with curatively resected node-positive CRC, with improved survival rates as a consequence. Because of the increasing prevalence of CRC, the

increased use of oxaliplatin, and because there is no therapy to treat CIPN, many patients keep being confronted with this debilitating side effect. Therefore, we investigated the prevalence and severity of CIPN, and its influence on QOL in a population-based sample of CRC survivors two to 11 years after diagnosis in **chapter 3**. The population-based Netherlands Cancer Registry (NCR) was used to select all CRC patients diagnosed between 2000 and 2009 in the Southeastern area of the Netherlands. Of the patients who were alive, 83% (n=1,643) of patients completed the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and its Chemotherapy-Induced Peripheral Neuropathy supplement (EORTC QLQ-CIPN20). Neuropathy-related symptoms were still often reported two to 11 years after diagnosis. Especially sensory symptoms in the lower extremities among those treated with oxaliplatin. Patients who received oxaliplatin more often reported tingling (29% vs. 8%; p=0.001), numbness (17% vs. 5%; p=0.005), and aching or burning pain (13% vs. 6%; p=0.03) in toes or feet compared to those not treated with chemotherapy. They also more often reported tingling toes or feet (29% vs. 14%; p=0.01) compared with those treated with chemotherapy without oxaliplatin. In addition, those with many neuropathy symptoms (e.g. upper 10%) reported statistically significant and clinically relevant worse QOL scores on all EORTC QLQ-C30 subscales (all p<0.01). In conclusion, this study showed that neuropathy symptoms are still often reported in CRC survivors two to 11 years after diagnosis, especially sensory symptoms among those treated with oxaliplatin. The neuropathy symptoms have a negative influence on patients' QOL.

Besides the effects of CIPN on the daily functioning and QOL among CRC survivors, we also studied these effects in patients with multiple myeloma (MM). Because of improved treatment and increased aging of the population, the prevalence of MM is increasing, and more patients are confronted with the side effects of its treatment. Currently dose modification or discontinuation in case of moderate symptoms of CIPN is the only way to prevent severe CIPN. Unfortunately, dose modifications can influence treatment response and therefore cautiousness is warranted. Many assessment tools for monitoring CIPN symptoms have been investigated, but they are not developed for use in clinical practice. In **Chapter 4** we validated the self-reported Indication Common Toxicity Criteria (CTC)-grading Peripheral Neuropathy (ICPNQ) questionnaire, which can be used in daily clinical practice. Furthermore, we examined the prevalence of CIPN and its influence on QOL in MM patients. One-hundred fifty-six patients with MM were included (65% response) on average 3.3 years after diagnosis. CIPN was often reported, and 65% of patients reported grades two or three neuropathy. The newly developed self-reported ICPNQ is a valid instrument to distinguish the highest CIPN CTC-grades from the lower CTC-grades in a population-based cohort of MM patients. Hence, the self-reported ICPNQ provides in the need to give a standardized indication regarding the CTC-grades of CIPN, overcomes the issue

of underreporting CIPN by clinicians, and can be incorporated easily in clinical practice. Patients with grade two with pain and grade three neuropathy combined reported statistically significant and clinically relevant worse QOL compared to patients who had neuropathy CTC-grades between zero to two without pain. This indicates that early dose modification based on a more reliable tool for CIPN measurements is needed.

Part II - Chemotherapy-induced peripheral neuropathy and the influence of chemotherapy administration

It is acknowledged that the degree of oxaliplatin-induced neuropathy (O-IPN) is dependent on cumulative dose, duration of administration and dose intensity. Nonetheless, this knowledge is mainly based on studies concerning the development of acute neuropathy instead of studies reporting about chronic neuropathy more than a year after treatment. Therefore, the influence of oxaliplatin administration on the development of chronic neuropathy remains unclear. A systematic literature review on the influence of oxaliplatin administration (e.g. cumulative dose, dose intensity, number of cycles and combination regimen) on the long-term prevalence of oxaliplatin-induced peripheral neuropathy (O-IPN) at least 12 months after termination of chemotherapy was performed in **chapter 5**. Fourteen articles (n=3,869 patients) were included and the majority of these studies were of high quality. They reported that O-IPN was still present in a great amount of patients ≥12 months after termination of therapy. Only six studies directly assessed the relationship between oxaliplatin administration and neuropathy. Of these studies, five did find a relation between neuropathy and higher cumulative dose, whereas one study did not find a relation. However, given the heterogeneous definitions and tools utilized in the studies of O-IPN, no firm conclusions could be drawn regarding oxaliplatin administration and the development of long-term O-IPN. Hence, we concluded that a higher cumulative dose is likely to be a predicting factor for the development of long-term O-IPN.

As no firm conclusions could be drawn on the influence of oxaliplatin administration on the development of long-term CIPN, additional information on the actually delivered oxaliplatin treatment for a subgroup of CRC survivors was collected (**Chapter 6**). In total 207 patients, diagnosed with CRC between 2000 and 2009, underwent adjuvant treatment with oxaliplatin. Those patients were on average 4.0 years since diagnosis, and were diagnosed with colon cancer stage III in 84%. Analysis demonstrated that a higher cumulative dose was associated with the development of long-term CIPN. Dose intensity and time delay did not influence CIPN. Patients with documented acute neuropathy during treatment receiving a dose

modification (reduction and/or interval prolongation) because of neuropathy (n=50) reported significantly worse sensory scores after adjustment for cumulative doses, than those who did not receive a dose reduction because of neuropathy (n=96). In conclusion, monitoring symptoms of neuropathy during treatment is important as the risk of developing persistent CIPN may only be reduced by decreasing the cumulative dose of oxaliplatin, whereas delaying chemotherapy cycles probably is not beneficial. In addition, patients receiving a dose reduction because of acute neuropathy, are still at risk of developing long-term CIPN.

Another group of patients in whom dose limiting neurotoxicity, referred to as CIPN, is a common adverse effect are the more vulnerable patients with MM. In **Chapter 7** the prevalence of self-reported chemotherapy-induced peripheral neuropathy (CIPN) symptoms, its association with sociodemographic and clinical characteristics, and the amount of treatment dose modifications and its influence on CIPN in a population-based cohort of MM patients was evaluated. In total 156 MM patients completed the EORTC QLQ-CIPN20 on average 3.3 years after diagnosis (65% response). Sociodemographic and clinical characteristics were available from the NCR and the Population-based Haematological Registry for Observational Studies (PHAROS). This study showed that considerable neuropathy was reported by more than half of MM patients, with 53% percent of patients reporting at least one and on average three neuropathy symptoms that bothered them ‘quite a bit’ or ‘very much’ during the past week. Tingling toes or feet were most reported. Multivariate analysis showed that thalidomide, and especially a higher received cumulative dose, was associated with the severity of neuropathy, whereas CIPN was not associated with age, sex, time since last course of therapy, number of prior therapies and comorbidity. Dose was modified in one third of the patients because of CIPN and in spite of this modified dose, patients still reported a trend towards higher neuropathy scores without altered response rates because of the dose modification. Therefore, modifying the dose at a lower level of CIPN as assessed with a more reliable assessment tool seems warranted.

General discussion

The prevalence of cancer is increasing as a result of growing incidence of cancer due to the aging population and increasing cure rates. Consequently, a paradigm shift has occurred in the field of cancer research. Whereas quantity of life was the primary goal at first, quality of life and patients’ well-being are rising in importance as more patients and cancer survivors are confronted with the consequences of cancer and its treatment and, furthermore, prognosis is already improving because of screening

programs and earlier referral with as a result a smaller absolute gain from adjuvant systemic treatments in some patients.[1] One of the growing topics in the field of research is the common dose limiting side effect CIPN, especially since no preventive method or treatment is available for this potentially disabling and irreversible adverse event of commonly used chemotherapeutic agents.

The burden of CIPN

It is assumed that CIPN has a negative influence on patients' QOL,[1] mainly because it may result in serious limitations in daily activities.[2,3] For example, symptoms such as tingling, numbness, and aching or burning pain in the fingers or hands may cause problems with regular activities such as buttoning up a blouse, writing with a pen, or opening a jar or bottle. Likewise, comparable symptoms in the toes and feet may cause problems with walking, climbing stairs or driving a car. Although it is assumed that CIPN can have a negative influence on patients daily functioning and therefore QOL, little has been published on the association between CIPN and QOL.[1,4] Many studies that described CIPN and QOL described them separately, and did not directly assess their relationship.[5-18] However, ten studies which evaluated the association between CIPN and QOL reported that CIPN negatively influenced patients' QOL,[19-27] and three other studies did not find an association.[28-30]
Nonetheless, it remains difficult to draw firm conclusions on this matter as the studies which evaluated the association between CIPN and QOL differed tremendously. To begin with, different approaches to assess CIPN were used whereas standardization of CIPN assessment, subjectively by patient-reported outcomes and/or objectively by physical examination or nerve conduction studies is essential for appropriate evaluation and comparison of studies. Further, the studies were also very heterogeneous in the applied study design, time since diagnosis, the included patient population and chemotherapeutic agents used,[19-30] which makes comparison between studies difficult. In this thesis (**Chapter 2, 3, 4**), it was observed that CIPN was frequently experienced in patients treated with platinum derivatives and taxanes, in CRC survivors treated with oxalipatin, and in patients with MM treated with immune-modulatory drugs thalidomide and lenalidomide, the proteasome inhibitor bortezomib and/or vincristine, even months to years after last treatment. It was also observed that those who reported the highest and therefore worst CIPN scores reported worse QOL compared with patients who reported less severe CIPN. These and findings from others suggest that severe CIPN is likely to be negatively associated with QOL. However, because of the diversity of the studied patient populations and differences in CIPN and QOL measurements, further research is warranted. In order to do so, the assessment of CIPN and QOL should become more standardized. Preferably

this assessment is easy to use in daily practice, and incorporate both a subjective patient-reported outcome and an objective measurement. In addition, to define a causal relationship between CIPN and QOL, these studies should preferably be prospective in nature assessing CIPN and QOL both before, during and after treatment.

Furthermore, besides reporting statistically significant differences in QOL and CIPN, it is also important to determine if these differences are of clinical importance. A statistically significant difference is a difference that is unlikely being caused by chance, and is purely based on mathematical considerations.[31] However, in health care a significant difference, made by an intervention for example, is not always considered a clinically important difference as the change is not considered meaningful and worthwhile for the patient.[31] Therefore it is important to determine which difference is, besides being statistically significant, also a clinically important difference for the patient and may lead to alteration in clinical decisions. In this thesis, the differences in QOL between patients with or without severe CIPN were, besides statistically significant, also clinically important to patients determined with Norman's 'rule of thumb', in which a difference of ≈0.5 SD points to a threshold of discriminant change.[32] The differences were varying from large to small clinical relevance according to the reported guidelines[32,33] (**Chapter 3, 4**). This was observed in both long-term CRC survivors and in the more vulnerable MM patients. Although we reported that those differences were clinically important, it remains difficult to determine if the impact of CIPN is the same in those different patient populations. The long-term CRC survivors may have other expectations of daily functioning and life, including social activities and work, compared with the frequently still actively treated patients with MM with considerably worse prognosis.

The burden of CIPN underestimated by flaws in clinical trials

QOL is not only determined by CIPN, but also by numerous other chemotherapy-induced toxicities, like fatigue, gastrointestinal and sometimes cardiovascular symptoms.[34] Two studies reported that fatigue, one of the most frequently observed and often debilitating toxicities of chemotherapy, was associated with other common side effects such as CIPN, and greater levels of fatigue were related with worse symptom severity.[35,36] In **chapter 3 and 4** of this thesis it was also shown that patients who reported the highest CIPN symptom burden also reported higher levels of fatigue and pain. These observations might indicate that not only certain toxicities are related, but also that they might worsen one another, and all together influencing patients' QOL. Mainly grades three or four adverse events are reported in randomized

clinical trials (RCTs), but grade one and two adverse events, which are already often underreported by clinicians,[37] are therefore also undervalued. Especially if the side effects are interrelated. In addition, not only the underreporting by clinicians of these subjective toxicities in clinical trials is of concern, also the scheduling of adverse event assessment during therapy is crucial. Adverse events are most frequently assessed before the preceding therapy, however shortly after chemotherapy toxicity levels are the highest. Accordingly, the burden of the adverse events for patients is probably even more during the treatment period than reported. Therefore, it should be mentioned that the burden of chemotherapy is not only determined by the severity of the adverse events, but also by the timeframe and combination of all adverse events together. Therefore, the burden of chemotherapy should better be expressed in the total number and level (including grade I and II) of experienced toxicities multiplied by the timeframe between cycles they report those side effects. In daily care this might be difficult to define, however an assessment tool to determine this total burden would be valuable.

Difficulties in the assessment of CIPN

The assessment of CIPN is a major topic of debate. Many assessment tools for measuring CIPN symptoms have been investigated, varying from objective measurements, physician-based grading scales, to subjective patient-reported outcome measurements.[38] However, there is no consensus on which factors, subjective or objective measurements, are most important in determining clinical severity of neuropathy.[38,39] Therefore, different measurements are used which makes comparison of CIPN symptom level between studies difficult.[38,39] In addition, the development of standardized measurements to assess the level and severity of CIPN is required in order to investigate strategies for the prevention and treatment of CIPN in a reliable way.

Furthermore, another issue is that the currently existing measurements are not developed for use in daily clinical practice, although this is highly needed as treatment may be modified based on a reliable tool.[38] Since the objective CIPN measurements are not patient friendly, time-consuming, expensive, and often not sensitive enough to detect beginning or mild CIPN, questionnaires are preferred.[39] Those questionnaires provide more insight into the subjective sensory symptoms and their influence on patients' daily functioning. Questionnaires capture issues which are not confirmed by the objective measurements.[37,38,40,41] However, it lacks objective confirmation and clinicians are reticent to base clinical decision making on patients experience only. Though, a recent study confirmed that clinicians tend to underreport

toxicities, and therefore the use of patient-reported outcome measurements was highly recommended in the assessment of adverse events.[37]
In addition, distinction between grades of CIPN remains difficult for clinicians.[40] Nonetheless, guidelines necessary to decide on dose modifications of chemotherapy in daily clinical practice are mainly based on the physician-based National Cancer Institute-Common Toxicity Criteria (NCI-CTC). Therefore, CIPN questionnaires, although recommended, are difficult to use for this purpose in daily clinical practice.[42] Dose modifications should only be applied with caution as they can influence treatment outcome. Therefore, it is of utmost importance that a simple, patient-friendly and reliable assessment tool, including patient-reported information, for daily clinical practice will be developed. One of this attempts are the patient-reported outcome (PRO)-CTCAE criteria in which patient-reported measurements are integrated in NCI-CTCAE criteria.[43,44] In **chapter 4** of this thesis, we present the self-reported Indication Common Toxicity Criteria-grading Peripheral Neuropathy Questionnaire (ICPNQ) as a valid instrument to distinguish the highest CIPN CTC-grades from the lower CTC-grades, which may be valuable for the decision to modify the dose of chemotherapy in patients with MM. Hence, this questionnaire provides in the need to give a standardized indication regarding the CTC-grades of CIPN, while it overcomes the concern of underreporting CIPN by clinicians. Therefore this is a valuable tool which can be used in daily clinical practice. To evaluate the ability to monitor the development of CIPN over time, and to compare the CTC-grades derived from this self-reported questionnaire with physician reported CTC-grades, further prospective evaluation of this instrument is needed.

Towards personalized medicine, identifying patients at risk of developing CIPN

At the moment, alternative dosing regimens and treatment modification schemes are the only way to prevent moderate CIPN to become more severe. Therefore, identifying patients at risk of developing CIPN is of major importance. In **chapter 5** and **6** of this thesis it was shown that a higher cumulative dose of oxaliplatin was associated with the development of long-term CIPN in CRC survivors. Therefore, monitoring symptoms of neuropathy during treatment is important as the risk of developing persistent CIPN may only be reduced by decreasing the cumulative dose of oxaliplatin on time. Nevertheless, not all patients receiving a certain cumulative dose of a neurotoxic agent develop CIPN. Additionally, the amount of symptoms and reversibility of CIPN varies strongly between patients. This could be explained by the findings of recent studies demonstrating that certain patients, who are treated with oxaliplatin, might be more at risk of developing CIPN due to variants in encoding

genes of ion channels in the central nervous system.[45-49] In addition, a Dutch study also suggested an interaction between myeloma-related factors and the genetic background of patients with MM in the development of CIPN, with different molecular pathways being implicated in bortezomib-induced and vincristine-induced peripheral neuropathy.[50]

As the area of genomics studies is still in its infancy and not routinely used in daily clinical practice, it is important to take into account other patient characteristics when deciding on the best treatment for a particular patient with the least toxicity. For instance, pre-existing neuropathy, age, alcohol abuse, and comorbidity such as diabetes mellitus are factors related to the development or aggravation of CIPN,[51,52] and the presence of those risk factors may therefore be a reason to restrain certain chemotherapies for some patients. Therefore, preferably for the start of chemotherapy patients should be screened for all those factors. Furthermore, an American trial showed that patients aged ≥70 with stage III colon cancer may not benefit from adding oxaliplatin to oral fluoropyrimidines in the adjuvant setting, and therefore CIPN may also be prevented.[53] Also the stage and predicted response rate of disease should be reckoned when choosing the best treatment. As mentioned above, the aim of medical treatment is not only prolongation of life, but also the preservation of its quality. For example, in **chapter 7** more than half of patients with MM were confronted with considerable neuropathy due to neurotoxic treatment and in spite of dose modification patients reported a trend towards higher levels of neuropathy. Due to improving overall survival patients are therefore confronted with this side effect for a longer period. Nevertheless, the curation rate of MM remains scarce.

Given that there is still no proven therapy for CIPN and due to the burden of CIPN on the daily lives of patients, identifying the clinical characteristics and genetic variations in patients who are prone to develop CIPN is of major importance. In that way, patients may benefit from personalized medicine as patients and clinicians together can decide to decrease the cumulative chemotherapy dose on time or restrain certain types of chemotherapy with the goal to prevent or minimize CIPN. This shared decision making should be taken under the condition that the patients have received proper information about the different treatment options and about CIPN and the consequences of this potentially severe side effect.

Prevention and treatment of CIPN

Recent practical guidelines could give no strong recommendations regarding the pharmacological prevention or treatment of CIPN.[39,54,55] Only a weak recommendation for duloxetine, gabapentin, or pregabalin for chemotherapy-induced neuropathic pain could be given. This is mainly because trials tend to be small and heterogeneous in patient population, the applied neurotoxic agent, and time of CIPN assessment.[39,54] In addition, the absence of a consensus in outcome measurements of CIPN, as earlier mentioned, makes comparison of studies and drawing firm conclusions on their results difficult. Consequently, recommendations on the management of neuropathic pain in cancer patients are usually based on studies concerning painful diabetic neuropathy, post-herpetic neuralgia and trigeminal neuralgia which are 'benign' neuropathic pain conditions.[56] However, CIPN is different from those forms of neuropathic pain with respect to pathophysiology and symptomatology, and therefore the development of a better suitable treatment is highly needed.[39]

Non-pharmacologic interventions are not considered in the recent guideline from the American Society of Oncology.[39] They state that a number of non-pharmacologic interventions have been investigated, but due to the paucity of RCTs the inclusion of those studies in the systematic review have been impeded.[39] However, given the lack of evidence for pharmacological treatment, non-randomized trials could also provide valuable information, and give a direction to future research.[57] For example, a Danish cohort study showed less CIPN in docetaxel treated patients who wore frozen gloves or socks.[58] Following this study, we hypothesized that wearing frozen gloves during chemotherapy could be effective in preventing CIPN in the hands. Frozen gloves may induce vasoconstriction and decrease uptake of chemotherapy due to less biochemical activity within the neuronal cells, and therefore cause less axonal damage. Therefore, we conducted a pilot study in 30 cancer patients that showed a trend with less neuropathic pain and discomfort in a frozen glove protected hand compared with a control hand.[59] We expended this pilot study to a multicenter, randomized controlled study to evaluate the efficacy of frozen gloves in the prevention of CIPN due to treatment with neurotoxic agents. Other investigated non-pharmacological ways of preventing or treating CIPN are the use of dietary supplements, scrambler therapy or rehabilitation programs. The most extensive investigated dietary supplements are the natural herbal Goshajinkigan (GJG) and antioxidant acetyl-L-carnitine (ALC).[60-66] GJG showed to cause less grade III CIPN in patients using GJG during chemotherapy in four Japanese studies[60-62] and results on ALC were encouraging in two studies, but less conclusive in others.[63-66] Nonetheless, a previous study reported that serum ALC concentrations were significantly lower in cachectic patients when compared to healthy volunteers.[67] Furthermore, fatigue among patients with cancer and with low serum-carnitine levels has reported to

become less after treatment with ALC.[68] Therefore, we suggest that this simple dietary supplement has to be investigated more thoroughly in which precise metabolic and pharmacokinetic analyses are required. Scrambler therapy, in which noninvasive cutaneous electrostimulation is used to treat neuropathic pain, showed a short-term reduction in pain in patients with CIPN in two small studies.[69,70] Those studies about the use of dietary supplements and scrambler therapy report encouraging results, nevertheless all those studies suffer from small sample sizes and heterogeneity in CIPN assessment, and therefore are not recommended at the moment.
Nowadays in the Netherlands, rehabilitation programs however are offered to cancer patients in standard cancer care, as they have demonstrated physiological and psychological benefits.[71,72] Nonetheless, most of the studies investigating rehabilitation programs were indeed also not RCTs, used small sample sizes and did not consider the special needs of patients with CIPN.[71,73] Only one small pilot study reported improved balance due to intensive rehabilitation in patients with CIPN.[72] Moreover, no trials investigated the effect of rehabilitation on coordination and muscle strength in cancer patients with CIPN. A Dutch systematic review, investigating the effect of whole body vibration on coordination and muscle strength, was not able to include patients with peripheral neuropathy due to chemotherapy.[73] Rehabilitation programmes performed in alternative populations, such as elderly or patients with diabetic peripheral neuropathy, have shown to be effective in diminishing the development of neuropathy.[74] In a recent study we reported that meeting the physical activity guideline is associated with less severe neuropathy in CRC survivors and therefore physical activity interventions are an interesting subject for future research in treating and preventing CIPN.[75] Therefore, studies investigating non-pharmacological interventions such as dietary supplements or rehabilitation modalities in patients with CIPN should be encouraged. Besides, those interventions can easily be incorporated in daily clinical care, and consequently are of particular interest.

In conclusion, prevention and treatment of CIPN remains unproven. Therefore, more studies investigating both pharmacological and non-pharmacological interventions to prevent or treat CIPN are required. Meanwhile, alternative dosing regimens, early detection and treatment modification schemes are necessary to limit CIPN. In addition, patients should be informed properly on the implications of this side effect which is illustrated by the quote of the 50-year old CRC patient in the introduction.

Future perspectives

In this current thesis it is shown that CIPN is a common dose limiting and potentially severe side effect of frequently used chemotherapeutic agents, which can be experienced until years after treatment with a negative influence on patients' QOL. With the increasing number of patients confronted with this side effect, and the fact that there is no proven therapy for CIPN, it is likely that more patients will be confronted with CIPN. Much is still unknown about this potentially disabling adverse event and the studies included in this thesis are just the first steps of a long journey in which still many facets need to be discovered. In Table 8.1 a summary is given of the current knowledge of CIPN, results of this thesis and the future perspectives. In summary, more research to explore CIPN is necessary.

To begin with, it is of major importance that we understand the underlying mechanisms of CIPN necessary to define potential targets for the prevention and treatment of CIPN, especially since an increasing amount of patients is confronted with the short- and long-term consequences of CIPN.

Furthermore, in order to investigate strategies for the prevention and treatment of CIPN it is vital to be able to assess the severity of CIPN in a reliable way. Future studies should therefore also focus on the development of a valid and reliable measurement to assess CIPN. This tool should, besides being a valid and reliable tool, be patient-friendly, responsive to change in CIPN, and easy to use in daily clinical practice. In addition, it should incorporate at least a patient-reported outcome measurement.

Moreover, studies investigating the influence of CIPN on patients' QOL and the burden of associated and lower grade adverse events are stimulated. Those studies should preferably determine not only statistically significant differences, but also report if these differences are clinically important to patients.

In addition, with personalized medicine becoming more integrated in future cancer care, it is important to identify risk factors for the development of CIPN. Therefore studies investigating the influence of sociodemographic and chemotherapy administration on the development of CIPN, and studies investigating genetic variations making patients more prone to develop CIPN are encouraged. Consequently in the future the best treatment for each individual patient with the least toxicity can be chosen after close consideration between patient and clinician.

Table 8.1 Summary of results presented within this thesis and future perspectives.

CIPN	What did we need to know?	Investigated within this thesis (chapter)	Results presented within this thesis	Future perspectives for research
			Part I	
Pathophysiology	The precise mechanism underlying CIPN.	Not included	Not included	Discovering the underlying mechanisms of CIPN necessary to define potential targets for the prevention and treatment of CIPN.
Prevalence and clinical manifestation	Short- and long-term clinical manifestation and prevalence of CIPN in different patient populations	2, 3, 4, 7	Common dose limiting side effect: In patients treated with platinum derivatives and taxanes 6 months after treatment Up to 30% of CRC survivors treated with oxaliplatin experience severe CIPN symptoms 2 to 11 years after diagnosis. 53% of patients with MM reported severe neuropathy symptoms up to 13 years after diagnosis. Most reported symptoms: Tingling, numbness and pain in the hands and/or feet, loss of strength in the hands, erection problems for men	Assessment of prevalence and severity of CIPN in a reliable, uniform way. Development of a valid and reliable measurement to assess CIPN. Clinical trials should also report all grades 1 and 2 side effects. The burden of side effects should better be expressed in the total number and level (including grade I and II) of experienced toxicities multiplied by the timeframe between cycles they report those side effects.
Diagnosis: Assessment tools	No consensus in diagnosis. What should a valid assessment tool incorporate?	4	Assessment tool should incorporate at least a patient-reported outcome. The self-reported ICPNQ may be a valuable tool which can be incorporated easily in clinical practice.	The development of a valid, uniform, patient-friendly and reliable measurement. Easy to use in daily clinical practice. It should incorporate at least a patient-reported outcome measurement to overcome underreporting by clinicians.
Influence of CIPN on QOL	Evidence is scarce. What is the influence of CIPN on patients' QOL?	2, 3, 4	CIPN has a negative influence on all the domains of daily functioning and QOL of CRC survivors and patients with MM. Further research is warranted because of the diversity of the studied patient populations and differences in CIPN and QOL measurements	More studies investigating the influence of CIPN on patients' QOL and the burden of associated and lower grade adverse events are warranted Studies should determine not only statistically significant differences, but also report if these differences are clinically important to patients.

Table 8.1 (continued)

CIPN	What did we need to know?	Investigated within this thesis (chapter)	Results presented within this thesis	Future perspectives for research
			Part II	
Influence sociodemographic and clinical factors on development of CIPN	What sociodemographic and clinical factors are relevant for the development of CIPN?	5, 6, 7	Oxaliplatin and thalidomide, and especially a higher received cumulative dose, was associated with the severity of neuropathy. CIPN was not associated with dose-intensity, age, sex, time since last course of therapy, number of prior therapies and comorbidity Dose was often modified because of CIPN in CRC and MM patients. Patients who received a dose modification because of CIPN still reported worse levels of CIPN at the long term	Identifying patients at risk of developing CIPN is of major importance in order to personalize cancer care e.g. sociodemographic, clinical and genetic variations.
Prevention	How can we prevent the development of CIPN?	6,7 General discussion	Modify dose on time	Pharmacological interventions to prevent/treat CIPN induced neuropathic pain/symptoms. Non-pharmacological options e.g. frozen gloves, dietary supplements (e.g. ALC), rehabilitation.
Treatment	How can we treat the symptoms of CIPN?	Not included General discussion		

ALC: acetyl-L-carnitine; CIPN: chemotherapy-induced peripheral neuropathy; CRC: colorectal cancer; ICPNQ: indication chemotherapy-induced peripheral neuropathy questionnaire; MM: multiple myeloma; QOL: quality of life.

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Samenvatting

(Dutch summary)

Samenvatting

In Nederland worden jaarlijks ongeveer 100.000 patiënten geconfronteerd met de diagnose kanker. Naast een operatie en bestraling is behandeling met medicijnen in de vorm van chemotherapie, een belangrijke hoeksteen in de therapie van vele vormen van kanker. De behandeling met chemotherapie wordt vaak vergezeld door vele bijwerkingen zoals misselijkheid, tekort aan bloedplaatjes en/of witte bloedcellen, en zenuwschade, ook wel chemotherapie-geïnduceerde perifere neuropathie (CIPN) genoemd. Deze zenuwschade, in het vervolg CIPN genoemd, is een veel voorkomende, potentieel ernstige en soms onomkeerbare bijwerking van bepaalde chemotherapieën die gebruikt worden in de behandeling van o.a. darm-, borst-, prostaat-, eierstok- of een vorm van witte bloedcelkanker. CIPN presenteert zich met verschillende klachten zoals tintelingen, gevoelloosheid, brandende pijn en/of een onaangenaam gevoel bij aanraking in de extremiteiten. De klachten beginnen meestal in de tenen en vingers, maar kunnen zich verder uitbreiden naar de gehele armen en benen. Bovendien, kan spierzwakte aan de armen en benen en autonome disfunctie, zoals erectiestoornissen of hartkloppingen, optreden. Deze klachten kunnen zo ernstig zijn dat ze leiden tot problemen met dagelijkse activiteiten zoals het dichtknopen van een blouse, vasthouden van een pen, of het openen van een pot of fles. Ook kunnen problemen met wandelen, traplopen of autorijden ontstaan. Soms is de uitwerking van deze bijwerking zo invaliderend dat het zelfs een reden is om helemaal te stoppen met de behandeling, waardoor mogelijk de effectiviteit van de behandeling in het geding komt.

Er komt steeds meer aandacht voor kwaliteit van leven binnen de oncologie, zowel bij patiënten waarbij kanker in een vroeg stadium van de ziekte wordt ontdekt als bij patiënten die ongeneeslijk ziek zijn verklaard. Het doel van de medische behandeling is niet alleen verlenging van het leven, maar ook het behoud van de kwaliteit ervan. Omdat steeds meer patiënten de diagnose kanker krijgen, het gebruik van chemotherapie toeneemt en de overleving van kanker verbetert, worden steeds meer patiënten geconfronteerd met de korte en lange termijn gevolgen van deze schadelijke bijwerking. Er is echter nog weinig bekend over de invloed van CIPN op de kwaliteit van leven van patiënten. Bovendien is er ondanks meerdere onderzoeken nog geen goede behandeling van de symptomen. Het is daarom van groot belang dat er meer inzicht komt in de symptomen en ernst van deze bijwerking en de invloed ervan op de kwaliteit van leven van patiënten. Bovendien is het van belang om te onderzoeken wat de invloed van chemotherapie toediening is op het ontstaan van deze klachten, zodat patiënten die kans maken op het ontwikkelen van blijvende klachten geïdentificeerd kunnen worden. Dit proefschrift is opgedeeld in twee delen. Deel één beschrijft het optreden en de ernst van de symptomen van CIPN, en de invloed van deze symptomen op de kwaliteit van leven bij patiënten met kanker, op verschillende tijdstippen na de behandeling. Deel twee beschrijft de invloed van

toediening van chemotherapie op de ontwikkeling van permanente CIPN bij patiënten met dikke darmkanker en witte bloedcel kanker.

Belangrijkste bevindingen van dit proefschrift

Deel 1- CIPN en de invloed op kwaliteit van leven

Het doel van **hoofdstuk 2** was het beschrijven van het optreden en de ernst van de symptomen van CIPN, veroorzaakt door veel gebruikte chemotherapieën in de behandeling van o.a. dikke darmkanker, borst- en eierstokkanker, 6 maanden na het beëindiging van deze behandeling. Bovendien werden de gevolgen van deze symptomen op het dagelijkse functioneren en de kwaliteit van leven onderzocht. In totaal hebben 43 patiënten met kanker van het Máxima Medisch Centrum vragenlijsten ingevuld over CIPN en kwaliteit van leven. De meerderheid van de patiënten rapporteerden CIPN symptomen in de bovenste (79%) en onderste extremiteiten (90%). De meest voorkomende klachten waren gevoelloosheid en tintelingen in zowel handen als voeten, koude voeten, en moeite met het onderscheiden van kleine objecten in de handen. Patiënten werden door deze klachten beperkt in het dagelijks leven. Problemen met het huishouden werden gemeld in 13% van de patiënten en 21% van de patiënten werden meer afhankelijk van anderen vanwege de CIPN symptomen. Bovendien werd de kwaliteit van leven negatief beïnvloed door de CIPN in 49% van de patiënten.
Door de stijgende leeftijd van de bevolking en de verbeterde behandelings-mogelijkheden voor dikke darmkanker is het aantal patiënten dat dikke darmkanker heeft of heeft gehad toegenomen. De introductie van het geneesmiddel oxaliplatin heeft een grote bijdrage geleverd aan deze verbeterde overleving. CIPN is echter een veel voorkomende bijwerking van oxaliplatin. Vanwege het toenemend aantal patiënten met dikke darmkanker, het toegenomen gebruik van oxaliplatin, en omdat er geen goede behandeling is voor CIPN, worden steeds meer patiënten geconfronteerd met deze bijwerking zowel op de korte als lange termijn. In **hoofdstuk 3** onderzochten we het optreden en de ernst van CIPN bij patiënten met dikke darmkanker op de lange termijn. Bovendien onderzochten we de invloed van deze bijwerking op de gezondheid gerelateerde kwaliteit van leven.
De Nederlandse Kankerregistratie, regio Zuidoost Nederland, werd gebruikt om alle nog levende patiënten met dikke darm kanker die in de periode tussen 2000 en 2009 werden gediagnosticeerd te selecteren en 1643 (83%) van hen namen deel aan het onderzoek. De dikke darmkankerpatiënten rapporteerden twee tot elf jaar na diagnose nog vaak neuropathie symptomen. Met name sensorische symptomen in de onderste ledematen werden vaak vermeld. Patiënten die zijn behandeld met oxaliplatin rapporteerden vaker symptomen als tintelingen (29% versus 8%),

gevoelloosheid (17% versus 5%), en pijn (13% versus 6%) in tenen en/of voeten in vergelijking met patiënten die niet met chemotherapie werden behandeld. Ze rapporteerden ook vaker tintelende tenen of voeten (29% versus 14%) vergeleken met patiënten die zijn behandeld met chemotherapie zonder oxaliplatin. Bovendien rapporteerden patiënten die veel neuropathie symptomen (top 10%) hadden een klinisch relevante slechtere kwaliteit van leven ten opzichte van patiënten die minder neuropathie symptomen hadden. Samenvattend laat deze studie zien dat neuropathie symptomen twee tot elf jaar na diagnose nog vaak worden ervaren door dikke darmkanker patiënten. Met name patiënten die behandeld zijn met oxaliplatin blijven veel sensorische neuropathie ervaren. De neuropathie symptomen hebben een negatieve invloed op de kwaliteit van leven van deze patiënten.

Een andere populatie patiënten die vaak geconfronteerd worden met de bijwerking CIPN zijn patiënten met multiple myeloom (MM), een vorm van witte bloedcel kanker. Deze patiënten worden behandeld met andere therapie dan de dikke darmkankerpatiënten, en CIPN is voornamelijk het gevolg van behandeling met de chemotherapieën bortezomib en/of thalidomide. Momenteel is er nog geen behandeling voor CIPN en het wijzigen van de chemotherapie dosis of zelfs het staken van de behandeling in geval van matige symptomen van CIPN is de enige manier om ernstige CIPN te voorkomen. Het staken of aanpassen van de chemotherapie dosis kan echter de uitkomst van de behandeling beïnvloeden en moet daarom met de nodige voorzichtigheid worden toegepast. Tot op heden zijn er echter geen hulpmiddelen ontwikkeld die in de dagelijkse praktijk gebruikt kunnen worden om te monitoren of een dosisaanpassing noodzakelijk is. Bovendien is er nog weinig bekend over het optreden van CIPN en de invloed van CIPN op de kwaliteit van leven bij patiënten met MM. In **hoofdstuk 4** bestudeerden we enerzijds de validiteit van een vragenlijst die gebruikt kan worden in de dagelijkse praktijk voor het monitoren van CIPN, en anderzijds de prevalentie van CIPN symptomen in patiënten met MM en de invloed van deze symptomen op hun kwaliteit van leven. Honderd-zesenvijftig patiënten (65% response), gediagnosticeerd met MM in de periode van 2000 tot 2014, vulden gemiddeld 3,3 jaar na diagnose vragenlijsten in. Meer dan de helft van de patiënten rapporteerden neuropathie symptomen en 65% van de patiënten rapporteerden neuropathie graad 2 of 3. De nieuw ontwikkelde vragenlijst ICPNQ (Indication Common Toxicity Criteria-grading Peripheral Neuropathy Questionnaire) bleek een waardevol instrument om onderscheid te maken tussen de hoogste en daarmee meest ernstige CIPN graderingen (graad 2 met neuropathische pijn of graad 3) en de lagere graderingen (graad 0 tot graad 2 zonder neuropathische pijn). In de dagelijkse klinische praktijk is het van groot belang om een onderscheid te maken tussen deze graderingen, omdat richtlijnen aan de hand van deze graderingen aangeven of een dosisaanpassing nodig is. Op het moment is er echter veel onderrapportage van CIPN door artsen en is het moeilijk voor de artsen om een

onderscheid te maken tussen deze graderingen. De ICPN is daarom een waardevol instrument dat zou kunnen worden gebruikt in de dagelijkse klinische praktijk.
Verder toonden we in deze studie aan dat de patiënten met de hoogste en daarmee meest ernstige CIPN graderingen (graad 2 met neuropathische pijn of graad 3) een klinisch relevante slechtere kwaliteit van leven hadden dan patiënten met minder ernstige CIPN. Daaruit kunnen we concluderen dat de neuropathie symptomen ook in deze patiëntpopulatie een negatieve invloed hebben op de kwaliteit van leven.

Deel 2- CIPN en de invloed van chemotherapie toediening

In de literatuur wordt beschreven dat de mate van neuropathie ten gevolge van behandeling met oxaliplatin afhankelijk is van de toegediende totale cumulatieve dosis en de dosis intensiteit. Deze kennis is echter voornamelijk gebaseerd op studies die de ontwikkeling van acute neuropathie tijdens de behandeling beschrijven. De invloed van oxaliplatin toediening op de ontwikkeling van persisterende neuropathie is echter onduidelijk. In **hoofdstuk 5** worden de resultaten van een systematische literatuurstudie beschreven. De literatuur met betrekking tot de invloed van oxaliplatin toediening (bijvoorbeeld de totaal ontvangen dosis ofwel cumulatieve dosis, dosis intensiteit, aantal cycli en combinatie regime) op de ontwikkeling van persisterende CIPN ten minste 12 maanden na het beëindiging van behandeling met oxaliplatin werd bestudeerd. Bovendien werd de methodologische kwaliteit van de studies beoordeeld aan de hand van vooraf opgestelde kwaliteitscriteria. Veertien artikelen (totaal 3869 patiënten) die voldeden aan de vooraf gedefinieerde inclusiecriteria werden geïncludeerd. De meerderheid van deze studies was van hoge kwaliteit. De studies toonden dat ≥12 maanden na het beëindigen van de behandeling met oxaliplatin CIPN nog frequent werd ervaren door patiënten. Slechts zes studies hebben de relatie tussen oxaliplatin toediening en de ontwikkeling van persisterende neuropathie onderzocht. Daarvan vonden vijf studies een verband tussen persisterende neuropathie en het toedienen van een hoge totale cumulatieve dosis. Eén studie vond geen relatie tussen persisterende neuropathie en de totale dosis chemotherapie die de patiënt heeft ontvangen. Gezien het feit dat de studies zeer heterogeen waren in de gebruikte hulpmiddelen om CIPN vast te stellen, patiënt populaties en de tijd van CIPN bepaling konden geen duidelijke conclusies getrokken worden met betrekking tot oxaliplatin toediening en het ontwikkelen van CIPN op de lange termijn. Echter, een hogere cumulatieve dosis is waarschijnlijk een voorspellende factor voor de ontwikkeling van CIPN op de lange termijn.
Om deze bevindingen te bevestigen hebben we in **hoofdstuk 6** de invloed van oxaliplatin toediening op de ontwikkeling van persisterende CIPN onderzocht in patiënten die dikke darmkanker hebben gehad. Uit de studie van hoofdstuk 3 selecteerden we de patiënten die adjuvant zijn behandeld met oxaliplatin. Vervolgens hebben we uit het medisch dossier van deze patiënten aanvullende gegevens

verzameld over de behandeling met chemotherapie. Uit de statistische analyses bleek dat het behandelen met een hogere totale dosis oxaliplatin gerelateerd was met het rapporteren van meer persisterende CIPN symptomen. Dosis per tijdseenheid en verlenging van het tijdsinterval tussen de kuren bleek geen invloed te hebben op de mate waarin CIPN werd ervaren op de lange termijn. Tevens bleek dat patiënten die tijdens de chemotherapiekuren een aanpassing van de oxaliplatin dosis hadden gekregen vanwege acuut ontstane neuropathie (50 patiënten) nog steeds meer klachten van CIPN rapporteerden op de lange termijn dan patiënten die geen dosisaanpassing nodig hadden vanwege neuropathie (96 patiënten). Op basis van deze bevindingen hebben we geconcludeerd dat het monitoren van CIPN symptomen tijdens de behandeling zeer belangrijk is, omdat het risico op het ontwikkelen van permanente CIPN enkel kan worden verminderd door het verlagen van de totale dosis oxaliplatin. Daarentegen had het uitstellen van de chemotherapiekuren waarschijnlijk geen invloed op de mate waarin neuropathie werd ervaren op de lange termijn. Daarnaast liepen patiënten die een aanpassing van de oxaliplatin dosis hadden gekregen vanwege acuut opgetreden neuropathie nog steeds het risico om permanente CIPN te ontwikkelen. Daarmee lijkt er een verband te bestaan tussen het optreden van de acute en de chronische vorm van neuropathie ten gevolge van behandeling met oxaliplatin.

De behandeling van MM is in de laatste decennia zeer sterk verbeterd na de introductie van thalidomide, lenalidomide en bortezomib. Deze behandelingen gaan echter wel gepaard met CIPN. In **hoofdstuk 7** hebben we onderzocht wat de invloed is van behandeling met neurotoxische therapie zoals thalidomide, bortezomib, lenalidomide en vincristine op de ontwikkeling van CIPN in patiënten met MM. In totaal hebben 156 patiënten met MM gemiddeld 3,3 jaar na diagnose de neuropathie specifieke vragenlijst, EORTC QLQ-CIPN20, ingevuld met een antwoordpercentage van 65%. Klinische karakteristieken van de patiënten waren beschikbaar via de Nederlandse Kankerregistratie en gedetailleerde behandelingsgegevens werden verkregen via PHAROS. Gegevens over chemotherapie regimes, remissiestatus ten tijde van de studie, en aanpassingen van de doseringen van de therapie werden verzameld. Analyses in deze studie toonden aan dat meer dan de helft van de patiënten met MM tenminste één en gemiddeld drie CIPN symptomen ervaarden die hen behoorlijk of heel veel ergerden in de afgelopen week. Behandeling met thalidomide, en met name een hogere toegediende dosis, bleek van invloed op de ernst van de neuropathie symptomen. De ernst van de CIPN symptomen bleek niet beïnvloed te worden door leeftijd, geslacht, tijd sinds de laatste therapie, aantal ontvangen therapieën, artrose en suikerziekte. Een dosis aanpassing was vaak noodzakelijk (65%). Patiënten die een dosis aanpassing hadden gekregen door klachten van CIPN rapporteerden desondanks een trend tot ernstigere motorische en sensorische neuropathie vergeleken met patiënten voor wie een dosis aanpassing was

toegepast met een andere reden of geen dosis aanpassing nodig was. De dosis aanpassingen leken geen invloed te hebben op de uitkomst van de behandeling van patiënten. Daarom lijkt de beslissing tot het aanpassen van de dosis vroeger in de behandeling gerechtvaardigd indien deze is gebaseerd om een betrouwbare manier om CIPN te monitoren. Toekomstig onderzoek moet zich dan ook richten op het gebruik van zelf-gerapporteerde vragenlijsten in de beslissing tot het wijzingen van de dosis, en op het bewerkstelligen van dosis aanpassingen bij minder ernstige CIPN symptomen zonder dat de uitkomst van de behandeling in het geding komt.

Tot slot, worden in **hoofdstuk 8** de belangrijkste bevindingen van dit proefschrift samengevat en bediscussieerd. Bovendien worden aanbevelingen gedaan voor toekomstig onderzoek. In dit proefschrift hebben we het optreden en de ernst van CIPN bestudeerd in verschillende patiënt populaties op verschillende tijdstippen na de diagnose kanker. We hebben kunnen concluderen dat CIPN een veel voorkomende bijwerking is van veel gebruikte cytostatica zoals platinum derivaten, taxanen, en middelen gebruikt voor de behandeling van MM. Bovendien heeft CIPN een significante en klinisch relevante negatieve invloed op de kwaliteit van leven van patiënten. In de toekomst dient nog veel onderzoek te worden gedaan naar CIPN. Met name de uitvinding van een hulpmiddel om CIPN te diagnosticeren en monitoren is van groot belang. Indien er een standaard methode is om CIPN vast te stellen kunnen ook betere, zeer noodzakelijke, studies worden gedaan naar zowel de preventie en behandeling, als naar de invloed op kwaliteit van leven. Verder is het van groot belang dat we patiënten kunnen identificeren die een verhoogd risico hebben op het ontwikkelen van CIPN.