Chemotherapy in advanced breast cancer

Summary

Breast cancer has a large global burden being the most commonly diagnosed cancer in women and the leading cause of female cancer-related death. Despite revolutionary developments in the past 30 years, advanced breast cancer (ABC) remains largely incurable with a median overall survival of ~2-5 years depending on the tumor subtype. One of the major landmarks in the treatment of breast cancer is the introduction of targeted agents, which may be combined with either chemo- or endocrine therapies for their additive or synergetic effects. Currently, focus is shifting from treatment based on four major subtypes related to the hormone (HR)- and Human Epidermal Growth factor 2 (HER2)-receptors, to precision medicine based on individual genomic profiles. Additionally, the introduction of these new agents and treatment strategies will postpone treatment with chemotherapy. Eventually, most patients are in need of chemotherapy as it remains a competent treatment option as backbone or as an alternative treatment option. Therefore, it is the ideal time to assess and optimize the use of chemotherapy with the currently available agents. This thesis focused on the optimization of chemotherapy duration and scheduling with regard to clinical outcome parameters as progression-free survival (PFS), overall survival (OS), quality of life (QoL) and costs.

In **chapter 1** a general introduction to the subject and outline of the thesis is given. Most chapters are related to the Stop&Go study, a large Dutch national multicenter randomized controlled trial (RCT), comparing an intermittent, interrupted chemotherapy schedule to continuous scheduling of the same amount of chemotherapy cycles over two treatment lines. The Stop&Go study included patients from 43 centers affiliated with the Dutch Breast Cancer Research Group (BOOG) between December 2011 and March 2016. (**Part I**).

The primary outcome of the Stop&Go study is presented in **chapter 2**. Here we assessed whether the PFS of first-line intermittent treatment was non-inferior to continuous treatment with the same chemotherapeutic agents for patients with HER2-negative incurable locally advanced or metastatic breast cancer who had not received previous chemotherapy for advanced disease. Additional endpoints included OS and toxicity. Patients were randomized to two times four cycles of paclitaxel, with the second set of four only given at progression of disease after at least three months after the initial set of cycles, or to eight continuous cycles of paclitaxel chemotherapy. In both treatment arms, first-line chemotherapy was

combined with and followed by bevacizumab (maintenance) treatment until progression of disease, and also continued in the break in the intermittent group. A proportional-hazards regression model was used to estimate the hazard ratio (HR) of intermittent versus continuous scheduling. The upper limit of the two-sided 95% confidence interval (CI) for the HR was compared with the non-inferiority margin of 1.34. Analyses on the intention-to-treat population of 420 patients yielded a median PFS of 7.4 months (95%CI 6.4–10.0) for intermittent and 9.7 months (95%CI 8.9–10.3) for the continuous treatment arm, with a stratified HR of 1.17 (95%CI 0.88–1.57), indicating a lack of non-inferiority. The OS results supported this notion, with medians of 17.5 months (95%CI 15.4-21.7) versus 20.9 months (95%CI 17.8–24.0) for intermittent versus continuous treatment, and a HR of 1.38 (95%CI 1.00-1.91). Safety results revealed no relevant unexpected findings. These results are in line with previous ABC trials, which showed that continuously delivered, non-taxane based chemotherapy was more effective than chemotherapy delivered for a fewer number of cycles.

In clinical practice, patients with ABC generally receive multiple lines of treatment. In a disease as heterogeneous as ABC, this results in a high variety of treatment strategies in clinical practice, where the question remains as to which strategy is optimal after failure of first-line chemotherapy. The Stop&Go study also included a second-line study treatment. After allocation, participants were to receive the same treatment strategy (intermittent or continuous) both in first- and in second-line (no cross-over and no repeated randomization). In **chapter 3** of this thesis efficacy results for patients who were able to continue with second-line study treatment are given, as well as updated combined efficacy results for first- and second-line treatment. Of the 420 patients that started first-line treatment within the Stop&Go trial (210:210), a total of 270 patients continued on second-line study treatment (64% of all), which consisted of capecitabine in 201 patients and of non-pegylated liposomal doxorubicin in 69 patients, evenly distributed between the treatment arms. Median PFS of second-line treatment was 3.7 versus 5.0 months (HR 1.07; 95%CI 0.82-1.38) for intermittent versus continuous treatment. Second-line PFS was positively influenced by prior hormonal therapy for metastatic disease and longer first-line PFS duration, while triple-negative tumor status had a negative influence. Patients with a short time to progression (TTP) in first-line (≤10 months) had a higher probability of starting second-line treatment if they received intermittent compared to continuous chemotherapy (OR 1.97; 95%CI

1.02-3.80). For the 270 patients starting second-line study treatment, median combined PFS of first- and second-line treatment was 14.6 months versus 16.4 months for intermittent versus continuous treatment with a HR of 1.12 (95%CI 0.86-1.45). For second-line OS medians were respectively 10.9 and 12.4 months (HR 1.27; 95%CI 0.98-1.66). Median OS calculated from date of randomization was 21.0 versus 23.2 months with a HR of 1.27 (95%CI 0.98-1.66), for the patients who started second-line study treatment (n=270). In conclusion, although there was an absence of statistical significance, results showed a consequent and clear favorable trend for continuous treatment in all evaluated efficacy parameters.

Although both first- and second-line efficacy results from the Stop&Go study indicated continuous chemotherapy for ABC might be preferable, these benefits in efficacy should be carefully balanced against effects on QoL. After all, the treatment goal of ABC is to use the most effective strategy without pursuing disease control and (overall) survival benefit at the cost of QoL. **Chapter 4** reports on the QoL outcomes of patients within the Stop&Go study, as measured by the RAND-36 questionnaire every 12 weeks over a follow-up period of 30 months. The primary objective was to describe the course of physical and mental QoL for both treatment arms, and to estimate differences in changes from baseline in physical and mental QoL between arms. For the primary analyses, a Bonferroni correction was applied and p-values <0.025 were considered statistically significant. An effect size of 0.5 SD (5 points) was considered clinically meaningful. A total of 398 patients (95% of total Stop&Go population) were included in the analyses with a median follow-up of 11.4 months (Inter-Quartile Range (IQR) 5.6–22.2) and a median number of 4.3 (IQR 2.1–7.5) questionnaires per patient. Contrary to expectations, physical QoL declined linearly in the intermittent treatment arm causing a clinically meaningful difference of 5.40 points at 24 months (p<0.001), while scores in the continuous treatment arm stabilized after a small decline of ± 3.4 points at 12 months. Mental QoL was fairly stable and even improved with 1.58 (p=0.005) and 2.48 points (p<0.001) at 12 months for intermittent and continuous treatment respectively. When comparing treatment arms for both components of QoL in changes from baseline, the maximum differences were 2.46 (p=0.101) and 1.95 points (p=0.182) for physical and mental scores, both measured and 30 months follow-up and in favor of continuous treatment. In conclusion we found no statistically significant differences between intermittent and continuous first- and second-line chemotherapy for changes from baseline of both physical and

mental QoL in patients with HER2-negative ABC. But, when looking at the physical QoL scores in the treatment arms separately, the total decline was considered a clinically meaningful detrimental effect in the intermittent arm (decline >5 points on the component score) and a small, clinically not meaningful (<5 points) effect in the continuous arm.

Summarizing the outcomes of chapters 2 through 4 based on the national phase III Stop&Go trial leads to the overarching conclusion that continuous chemotherapy rather than a limited number of cycles should be preferred considering efficacy and QoL results. For a treatment strategy to be successfully implemented in clinical practice, impact of the associated costs should also be evaluated. In **chapter 5** we therefore assessed the costs and cost-effectiveness of the continuous over the intermittent treatment strategy. This economic evaluation used a healthcare perspective based on direct medical costs, survival and QoL as observed in the Stop&Go trial during study-treatment for up to 24 months after randomization. Patients who administered at least one QoL-measurement were included (n=402, 96% of total). Quality-Adjusted Life-Year (QALY) were estimated using the scores on the RAND-36 questionnaire. Differences in costs between study-arms were estimated using Mann-Whitney-U-tests. Incremental cost-effectiveness ratios (ICERs) were expressed in euros (2019) per QALY and per Life-Year (LY) gained. The estimated ICERs were compared to the maximal Dutch societal threshold of €80,000/QALY. Additionally, post-hoc sensitivity analyses, estimating costs and ICERs in case bevacizumab would not have been used in the Stop&Go study when assuming similar outcomes, were performed.
Analyses of the 402 patients showed that mean total costs of continuous treatment were €4,450 higher per patient compared to intermittent treatment. Continuous treatment yielded a mean survival improvement of 0.061 LY and 0.021 QALY, resulting in ICERs of €72,614/LY and €210,140/QALY gained. The probability that continuous treatment was cost-effective over intermittent therapy at the national willingness-to-pay level of €80,000/QALY was found to be 21.8%. However, without the costs for bevacizumab while assuming comparable outcomes, total costs would be €17,140 for continuous and €14,239 for intermittent treatment, leading to incremental costs of €2,901 and ICERs of €47,557/LY and €138,143/QALY gained respectively. Since results were largely influenced by the costs of bevacizumab when taking the sensitivity results into account we therefore recommend to guide chemotherapy duration primarily on clinical effectiveness and QoL rather than on cost aspects.

In conclusion, **Part I** of this thesis indicated that continuously delivered chemotherapy for 8 cycles during first- and second-line treatment was preferable compared with intermittently delivered chemotherapy in two sets of 4 cycles when looking at efficacy, in terms of PFS and OS, and QoL outcomes in patients with HER2-negative ABC.
The continuation of chemotherapy combined with targeted therapy as used within the Stop&Go study was not found to be cost-effective compared to intermittent therapy with the same drugs. However, bevacizumab is currently only used in selected cases. Therefore, taken together, the results from Part I of this thesis endorse current guideline recommendations to continue chemotherapy treatment in ABC without a scheduled interruption in treatment, for as long as effective and tolerated by the patient.

Real-life studies are relevant in addition to RCT's, as populations in clinical trials are not equivalent to the real-world population and thus results cannot be generalized. Accompanying the chapters of part I is a real-world study we performed on QoL within a cohort of ABC patients and the factors affecting this outcome (**Part II**).

Real-world studies could reveal specific needs of care that are currently insufficiently addressed in clinical studies. In **chapter 6** we analyzed QoL within a cross-sectional observational cohort of ABC patients. A total of 92 patients were included. After informed consent, they administered the EQ-5D-3L questionnaire during an outpatient visit with their treating oncologist. Utility scores could range between 0 and 1. The observed median utility score was 0.691 (IQR 0.244), whereby patients older than 65 years reported significantly worse median scores than younger patients (medians 0.638 versus 0.743; p=0.017). Moreover, scores were significantly worse for patients with versus those without comorbidity (0.620 versus 0.725; p=0.005). Other subgroups of patients defined by tumor characteristics, type of systemic treatment or metastatic sites had no significantly scores. The remaining survival (time between questionnaire and death) was correlated to the reported utility scores with lower values for shorter remaining survival time (correlation coefficient (r)=0.260, p=0.0252), especially in the subgroup <65 years (r=0.340, p=0.0169), whereas there was no significant correlation with shorter or longer time since metastatic diagnosis (r=-0.106, p=0.3136). In conclusion, the observation of a low QoL in an individual patient may be of guidance for clinical decision-making

including advanced care planning, as it may possibly indicate the final phase of life.

Closing Part II of this thesis is **chapter 7**, where a summary of literature regarding chemotherapy-containing regimens for the treatment of ABC is given. We aimed to provide guidance to optimize selection, sequencing and duration of chemotherapy for the currently available agents for clinical practice. Data from observational as well as randomized studies was used. Generally, first- and second-line chemotherapy-containing regimens yielded a median OS of around 2 years in studies underlying approval. Combining different chemotherapy agents resulted in better overall response rate (ORR) and PFS compared to single-agent chemotherapy, but without OS improvement and with greater toxicity. Therefore, single agent chemotherapy is considered the preferential approach nowadays. We noted that the efficacy was fairly comparable between (single) cytostatic agents, and relevantly increased when combining chemotherapy with immunotherapy or targeted agents. As to chemotherapy duration, longer treatment durations till 'unacceptable' toxicity in contrast to predefined treatment cycle numbers generated benefits in efficacy without detrimental impact on QoL within RCTs. Observational studies reported that chemotherapy was generally not given for more than 3-8 cycles in daily practice. After third-line chemotherapy, additional benefits of continuing next-line treatment were in general modest compared to those yielded by first- and second-line, but clearly these largely depend on individual patient factors. Although international guidelines recommend the use of anthracyclines or taxanes as first-line chemotherapy, physicians increasingly prescribe capecitabine or taxanes, where tolerability in addition to efficacy seems to play an important role.

In **chapter 8** a general discussion and glimpse on future perspectives based on findings from this thesis is given, followed by several additional chapters.