Chemotherapy in advanced breast cancer

Impact

In this part of the thesis, we will explore the scientific impact of the conducted research, its relevance for specific populations as well as for society as a whole. Additionally, implementation of and innovation brought by our results, and the dissemination of our knowledge are discussed.

Advanced breast cancer (ABC) comprises both incurable locally inoperable or metastasized breast cancer, which remains, as of today, a largely incurable disease. When endocrine or targeted therapies are not efficient or not indicated due to the absence of receptors or pathways, or due to lacking responsiveness to these therapies, chemotherapy remains the backbone of treatment for ABC. Current and future research will focus on an increasing number of selective treatment options for the different subtypes of breast cancer, incorporating targeted drugs and immunotherapy. Thus, this is the perfect time to evaluate how we can optimize the use of currently available chemotherapy agents. To this end, this thesis discusses the optimal strategy to incorporate chemotherapy in the treatment of patients with ABC.

The results discussed in this thesis indicate that continuation of chemotherapy for up to eight cycles rather than scheduling a break after four cycles benefits survival and does not compromise the quality of the patient's life.[2-4] This could lead to a change in health policy, by initiating less variety in the chemotherapy scheduling for ABC in clinical practice. Guidelines currently already include the advice to continue chemotherapy as long as possible,[5] and this thesis might contribute to a better compliance with this recommendation. The challenge for clinical practice to successfully implement a continuous chemotherapy schedule will be tolerability. As discussed earlier, future research should focus on preferably oral, (low-cost) agents with limited cumulative toxicity as a background for targeted agents.

It should be noted that the differences found between the two treatment arms of the Stop&Go study in almost all outcome parameters were relatively small, which leaves room for additional considerations. When discussing a continued versus an interrupted chemotherapy approach with the patient, the physician should explain that continuous therapy has the possible benefits of prolonging survival with approximately a median of two to four months,[1,2] without a clinically relevant decline in quality of life (QoL).[3] Disadvantages of continuous

chemotherapy could entail more hospital visits for check-ups and treatment administration.[1,2] The alternative of intermittent scheduling entails less hospital visits and possibly less toxicity, but with a downside of a shorter disease free interval[1] and a slightly shorter survival.[2] Tailoring these conversations to the individual patient also requires taking into account the course and effects of previous treatments, besides the general condition and presence of co-morbidities, as real-world studies indicated that effects of previous treatments can predict effects of next-line therapy.[4]

By summarizing observational data this thesis showed that the choice of cytostatic agent(s) applied within the first three lines of chemotherapy has changed over time and does not fully comply with current guideline recommendations. Apparently, tolerability of treatment has become increasingly important to physicians and patients. Combined with the advice to continue chemotherapy as long as possible, it could well be that future guidelines will adapt their recommendations as to the preferable agents. If so, the recommendations would be to first exploit the more tolerable agents, for example oral capecitabine or oral vinorelbine, which can be continued for prolonged periods and be possibly combined with biological agents, before moving onto more toxic cytostatic agents that can only be given for a limited amount of time.

Additionally, this thesis pointed out that continuation of chemotherapy – combined with bevacizumab – as given within the Stop&Go study, led to additional costs that were not justified by the benefits gained in quality adjusted life years (QALYs) or survival. However, results were largely influenced by the costs of bevacizumab when taking the sensitivity results into account. Therefore we recommend to guide chemotherapy duration primarily on clinical effectiveness and quality of life rather than on cost aspects.
While cost-effectiveness is not equally important in all countries globally, nowadays even the wealthy countries are dealing with deficits in their healthcare budgets. With the aging global population which will require more and more healthcare, policy makers will increasingly have to rely on economic evaluations of care strategies to take reimbursement decisions. Currently we see that economic evaluations are mainly done with new treatment agents, while our thesis indicates that these economic evaluations might also provide valuable insights on the way approved treatments are scheduled or applied. For policy makers, and ultimately for the whole society, cost-effectiveness data on different

strategies in which the available treatments are being used could contribute to a more efficient use of the scarce healthcare budgets.

Data from The Southeast Netherlands Advanced Breast Cancer (SONABRE) Registry presented in this thesis contributes to a better understanding of factors influencing the QoL of patients with ABC. In the SONABRE Registry, data is collected of all patients with an ABC diagnosis since 2008. That is, data on breast cancer subtype, proportion of patients treated per treatment line, delivered therapies, and the clinical and QoL outcomes per treatment line. This type of information may assist patients in complex decisions regarding their care as they may live longer with the introduction of more effective therapies and thus facing more treatment choices. Furthermore, information about factors influencing the QoL of these patients could assist physicians in deciding whether the balance between QoL and pursuing extension of life is still maintained. The fact that we found a relationship between the QoL and the time patients still had to live, could be a signal for the treating physician to start a conversation about end-of-life care at which point chemotherapy is not beneficial to the patient anymore. More attention for end-of-life care and better timing of bringing up this conversation could improve a sound relationship between physicians and patients.

By evaluating the existing data on QoL in patients with ABC we found an important gap in our knowledge. There is a lack of real-world studies; especially prospective studies evaluating QoL longitudinally is scarce. Additionally, the methodology of assessing QoL within this patient population lacks conformity. Currently, the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Group is in the process of improving the Health-Related Quality of Life (HRQoL) questionnaires of patients with ABC. The group aims to develop a new module to supplement the EORTC QLQ-C30 core questionnaire that is specific to the HRQoL concerns of ABC patients. Another solution to provide more real-world data could be to provide measurements of QoL as part of daily care in clinical practice, for instance on regular basis before an outpatient visit, with an uniformly standardized questionnaire.
To facilitate the ease for patients and possibly improve response rate to these questionnaires, they could be distributed electronically on their phones or on a tablet at home or in the waiting room before they enter their appointment with their physician. In order to avoid excessive time spend on explaining questions and/or results, these questionnaires and their outcomes should be displayed

graphically e.g. making use of colors and day-to-day objects. This way, QoL data will be part of real-world patient care and improve the quality of care for these patients. Examples of this type of telemonitoring and their benefits on several outcome parameters including QoL already exist in other (chronic) diseases (e.g., inflammatory bowel disease,[5] diabetes and heart failure,[6,7] and chronic pulmonary diseases[7,8]), and would be especially valuable in a disease setting like ABC, where optimizing QoL is one of the major treatment goals. Moreover, a recent systematic review on the use of electronical care-tools for breast cancer patients reported that 'eHealth' tools are effective in improving QoL.[9] Interestingly, multi-component online services that made use of different new technologies (e.g. social media and online support groups, online platforms for organizing and managing therapy adherence, mobile apps for continual monitoring) were the most effective for improving QoL in breast cancer patients as they were able to address specific issues related to QoL such as social support, emotions and coping, and self-efficacy in health management.[9] These tools, using mediated communication and 'social' properties of new technologies, present opportunities to overcome logistic obstacles and provide social support that patients can access anytime. This review concluded that to promote usage of such tools, it is more important to focus on the patient's attitude and predisposition rather than on technical advancements.[9]
Sampling QoL-data in a way that is integrated in the patient's day-to-day life could give both physicians and patients better insights into which complaints are limiting the patient, when and how often they appear, whether they could be related to the treatment the patient is receiving and thereby assist in decision making involving these treatments.

In conclusion, this thesis confirms that the current recommendation to treat patients with ABC with chemotherapy continuously rather than interrupted should be the preferred strategy. For daily practice, the pros and cons of these strategies should be discussed to promote shared decision making. Treatment with low-toxic, oral agents such as capecitabine should be preferred in first line instead of more toxic agents like anthracyclines which should be held back for later lines of treatment. Future research should focus on the suitability of metronomic chemotherapy and whether combinations with biological agents are beneficial. Finally, suggestions are made for optimizing methodology regarding the measurement of QoL in ABC patients, and implementations of such strategies in daily practice.

Dissemination of knowledge

The findings reported on in this thesis were published in several international scientific peer-reviewed journals. An overview article regarding the primary outcome of the Stop&Go study was also published in Dutch in the National Journal for Oncology (NTvO).[10] The official member magazine of the Dutch Society for Medical Oncology (NVMO) called 'Medische Oncologie' also published an article in Dutch about findings of the Stop&Go study and how they affect daily practice.[11]

Additionally, results were presented at international as well as local scientific congresses. Respectively at the European Society for Medical Oncology (ESMO) congress in 2017,[12] the ESMO Breast Cancer congress in 2019,[13,14] the 3rd edition of the Dutch event for top clinical hospitals called 'STZ-event' in 2018, the 10th edition of the Dutch symposium called 'Borstkanker Behandeling Beter' in 2019, and several local scientific meets (from the Zuyderland Medical Centre, the Maastricht University Medical Centre +, the Erasmus Medical Centre, the Dutch Breast Cancer Research Group (BOOG), and GROW-school for Oncology and Developmental Biology from Maastricht University). Furthermore, both the ESMO and the American Society for Clinical Oncology (ASCO) issued an (electronic) press-release containing results from the Stop&Go study.[15,16]

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