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CHAPTER 16

GENERAL DISCUSSION

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General Discussion

Personalized medicine is the practice of using established and novel techniques to optimize the management of an individual patient’s disease based on unique patient and tumor characteristics whilst addressing personal needs and expectations in order to choose the most optimal treatment approach with the greatest possibility of achieving the best medical outcomes. With regard to breast cancer, rapid advances in biotechnology have enabled us to look more profoundly at the biological and disease processes taking place in each patient and her tumor. Consequently, the terms ‘personalized’ or ‘tailored’ treatment have been coined to describe treatment that is fitted to the individual patient, combining conventional clinical and non-clinical characteristics with more recent molecular markers and involving patients in the decisions pertaining to their cancer.

In postmenopausal, endocrine-sensitive, early breast cancer patients, personalized endocrine treatment is still relatively unknown. Thus far, it has not yet been possible to choose the most optimal endocrine therapy regimen based on the combination of tumor biological factors and personal characteristics including demographics, comorbidities, anticipated side effects, and quality of life (QOL) and lifestyle issues. Being able to determine the best endocrine therapy regimen may be difficult when all the elements that define a patient and her disease are not completely taken into consideration. Furthermore, continuous monitoring and updating of a patient’s prognosis based on subsequent events over time (such as disease events as well as other non-disease-related incidents) are needed as these may require re-evaluation of the prescribed treatment regimen. Aiming at successful therapy, whilst preventing over- or under-treatment, it is crucial to take into account all aspects of the individual patient and her disease. Above all, it is important to engage a patient in her own disease and treatment decision-making processes.

Predicting individual outcomes in breast cancer

Prognosis in medicine means estimating the probability or risk of a future outcome in an individual based on his or her characteristics. In daily clinical practice, a doctor will, directly or indirectly, make use of an array of elements to estimate the risk or probability of a certain outcome in an individual patient. In clinical trials, it is equally important to account for these characteristics using prognostic and predictive models in order to allow for more accurate estimations for individual patients. Using different cohorts of endocrine-sensitive, postmenopausal early breast cancer patients (Tamoxifen Exemestane Adjuvant Multinational (TEAM), Investigation on the Duration of Extended Adjuvant Letrozole (IDEAL), and TEAM IIA trials), we studied several prognostic and predictive factors associated with outcomes of endocrine treatment.\(^1,2\)

Tumor- and patient-specific factors

Endocrine-sensitive breast tumors, characterized by the expression of hormone receptors (estrogen receptor (ER) and/or progesterone receptor (PR)) on the cell surface, grow under the influence of estrogen and/or progesterone. In postmenopausal breast cancer patients, anti-estrogens (tamoxifen and aromatase inhibitors (AIs)) are the mainstay of endocrine treatment and, at present, are prescribed either as sequential treatment consisting of tamoxifen followed by an AI, or as upfront treatment with an AI for a total of 5 years.\(^2,6\)
Over the last few years, accumulating evidence is showing improvements in long-term survival when treatment with AIs is continued beyond the standard 5-year treatment period, although it is insufficiently clear for which patients extended adjuvant endocrine therapy is suitable, and the optimal duration thereof in terms of offering maximal survival benefit with minimal toxicities. Primarily, however, it is essential to emphasize the importance of successfully completing the initial 5-year treatment period in the absence of disease relapse and with the best possible prognosis, while taking into consideration individual QOL and treatment compliance issues. The studies included in this thesis largely focus on determining the best endocrine therapy regimen for each individual, based on different patient- and tumor-specific features.

Based on national and international treatment guidelines, adjuvant endocrine therapy is generally prescribed in patients whose tumors express a certain level of hormone receptors, although currently no distinction is made between quantitative hormone receptor expression with respect to preference for either a sequential or upfront endocrine treatment regimen. Analysis of Dutch and Belgian patients included in the TEAM trial showed a preferential treatment benefit for exemestane upfront in patients whose tumors displayed a relatively high level of ER expression (Allred score 7 and 8), while a sequential treatment regimen was more beneficial in tumors with lower levels of ER expression (Allred score ≤6)(chapter 3). In considering the mechanism for these findings, greater estrogen dependency and the reduction in ER expression during tamoxifen treatment may play an important role. In breast tumors, ER expression is heterogeneous and it is possible that, through clonal selection, primary treatment with tamoxifen allows for the selective survival of tumor cells lacking ER expression. As tolerability and effectiveness of tamoxifen treatment may diminish following ER down-regulation, the effect of switching to an AI may instigate a new and enhanced response that counters estrogen-induced tumor growth in patients with lower levels of ER expression. More detailed documentation and utilization of quantitative ER expression in the clinical setting could therefore provide further tailored treatment recommendations and improve outcomes for individual patients.

After menopause, the main source of estrogen is the body’s adipose tissue. A direct relationship has been established between body-mass index (BMI, kg/m²) and levels of circulating estrogens. As obesity is associated with heightened estrogen synthesis, as well as hormone-dependent breast cancer growth, it is conceivable that adiposity could contribute to lower efficacy of treatment with AIs. There have been several studies regarding the influence of obesity on survival after breast cancer. Our study of patients with available BMI data in the international TEAM trial did not show an association between BMI and survival. Furthermore, there was no evidence of a preferential treatment benefit for sequential or upfront endocrine treatment in different BMI categories. Some of the major trials comparing different endocrine therapy regimens have also touched upon the issue of BMI in relation to preferential treatment benefit, but results vary tremendously. A direct comparison of the results of these studies is limited by the diversity of BMI cut-off points, and a meta-analysis of the major studies would be justified. To add, a better insight into the role of adjusting the prescribed doses of endocrine treatment may also be relevant.
With respect to other, potentially modifiable, lifestyle factors, physical activity (PA) can play an important role in improving breast cancer outcomes. PA contributes to benefiting daily physical, emotional and social functioning, with a subsequent positive effect on QOL as well as reducing the burden of side-effects arising from endocrine treatment. Particularly in the aging population, a decline in physical functioning is also associated with decreased social functioning, subsequent worsening of QOL as well as increased mortality. Few studies, however, have addressed the role of PA in affecting breast cancer survival. In our systematic review (chapter 5), we found that PA significantly improved overall survival as well as breast cancer-specific survival in elderly patients. In addition, our analysis regarding PA in the TEAM-Lifestyle side-study (chapter 6) showed that overall survival improved in patients who were physically active before and after breast cancer diagnosis. In older patients especially, pre-diagnosis PA revealed better overall survival.

**Quality of life, treatment compliance and side effects**

In considering the individual breast cancer patient with an indication for adjuvant endocrine treatment, maximal effectiveness can only be achieved if the patient also maintains a good QOL while adhering to her prescribed treatment regimen. Side effects of adjuvant endocrine treatment can seriously hamper daily functioning and QOL of breast cancer patients, and are the greatest cause of non-compliance to endocrine treatment. Approximately half of all patients prescribed adjuvant endocrine treatment discontinue before the pre-designated end-date. As observed in our study on compliance to extended adjuvant endocrine therapy (chapter 9), an additional 20% of patients discontinue treatment in this setting. Considering that the goal of (extended) adjuvant endocrine therapy is to further improve individual survival outcomes, it is important to address alternative ways of reducing toxicities and improving compliance while maintaining maximal QOL and treatment benefit.

Insight into the different side effects associated with endocrine therapy and understanding its impact on QOL and daily functioning is essential, given the growing acceptance of extended adjuvant endocrine treatment durations (chapter 8). In clinical practice, it is important to carefully weigh potential treatment benefits against potential sacrifices in QOL and daily functioning. It is likely that a combination of patient- and/or tumor-biological as well as lifestyle mechanisms contributes to the presence and severity of AEs, and understanding the underlying mechanism for the manifestation of AEs in some, but not all patients is of much clinical interest.

When determining the optimal endocrine treatment strategy while maintaining QOL, a patient’s susceptibility to these specific AEs of treatment is seldom taken into account. With respect to AIs, several specific side-effects, including vasomotor symptoms (hot flashes, night sweats) and musculoskeletal symptoms, may derive from the body’s response to a further reduction in circulating estrogen levels. Accordingly, we predicted that specific side effects of endocrine treatment may be related to improved endocrine treatment outcomes, while taking into account confounders such as non-compliance. Longer survival was noted in patients who reported one or more specific AEs (vasomotor symptoms and/or musculoskeletal AEs) than
patients who did not report these symptoms (chapter 10 and chapter 11). Some critics have suggested that reporting is selective, and patients who report their AEs may be inherently different from patients who do not report these specific AEs. For example, patients who report specific side effects are more likely to engage in other healthy lifestyles, which could contribute to better outcomes than in women who do not report these symptoms. It is plausible, however, that the majority of reported side effects does not distinguish patients by their lifestyle habits. Bearing this in mind, we performed additional analyses which revealed that survival outcomes were still superior for patients with specific AEs when compared with patients who reported nonspecific AEs and patients who did not report any AE separately (data not shown).

Not all patients undergoing endocrine therapy will develop specific AEs, implying that AEs may also be the result of variable estrogen levels in AI-treated patients. Polymorphisms in the aromatase gene, CYP19A1, have been associated with differences in circulating estrogen concentrations previously, and may be related to the diversity of responses to AIs among breast cancer patients. CYP19A1 gene polymorphisms may thus play a causal role in the development of specific AEs. This hypothesis was tested in chapter 12, which revealed that specific AEs were more commonly reported by patients who expressed one of three CYP19A1 variants. Genetics-based treatment decisions have rapidly advanced in recent years and companies now market genetic tests (such as Oncotype DX and Mammaprint) capable of predicting added benefit of treatment based on a tumor’s genetic profile. With these tests, patients and doctors alike use this information to weigh potential treatment advantages with important lifestyle and QOL issues. For patients, it signifies more insight and fewer feelings of uncertainty about the risk of disease recurrence, and with this data, patients can better understand their disease process and actively engage themselves in the treatment decision-making process.

**Dynamic prediction**

The various studies described in this thesis demonstrated that several conventional and unconventional clinical factors are associated with predicting treatment success, QOL, and survival in postmenopausal, endocrine-sensitive early breast cancer patients. The majority of determinants that influenced individualized treatment decisions were based on patient- and tumor-specific features that were measured at the time of diagnosis or at the start of adjuvant endocrine treatment. In considering individualized treatment strategies, it is also important to re-evaluate a patient’s health and disease status during treatment and over time, using this knowledge to modify therapy where deemed necessary. As described in chapter 7, current statistical models still fall short of taking into account changes in a patient’s health status or the occurrence of specific events throughout the course of treatment, which may alter previously predicted survival outcomes. The following example illustrates our need for better prediction models for all cancer patients. We consider our 69-year-old postmenopausal breast cancer patient from chapter 7 who was diagnosed with a grade III, 1.5cm, ER- and PR-positive tumor two years earlier. At the time, she underwent breast-conserving surgery, adjuvant radiotherapy and chemotherapy, and started adjuvant endocrine therapy. During her regular yearly visit she tells that she is suffering a number of side effects and discusses the possibility of discontinuing
her endocrine treatment. At the time of diagnosis two years earlier, the woman and her physician solicited Adjuvant!\(^3\) to calculate her probability of being alive 10 years later. Without additional chemotherapy or endocrine therapy, this probability was 38.9%, and with additional chemotherapy and endocrine therapy meant an additional 12.7% chance of being alive 10 years later. What Adjuvant! could not take into account at that time was whether this patient’s survival probability would still be the same two years later. Does this woman still have a 38.9% chance of being alive 10 years after her initial breast cancer diagnosis? Two years earlier it was not possible to know whether this woman would suffer a relapse, or that she might discontinue endocrine treatment because of side effects that obstructed her QOL and daily functioning.

Time has shown to play a vital role in predicting as well as modifying survival outcomes, and in our endeavour to tailor treatment to the individual patient, the occurrence of events and the capacity for a patient’s health and disease status to change over time is frequently neglected. Furthermore, it is important to keep in mind that the individual’s QOL and daily functioning can be seriously affected by endocrine treatment, and dynamic prediction can help the patient and her doctor weigh the benefits and harms of discontinuing treatment against improvements in QOL. We have developed a clinically applicable dynamic prediction model which incorporates the key factor, time, into a survival model for breast cancer patients. Although external validation and fine-tuning of this prediction model needs to be performed, our analysis reiterates the importance of continuously re-evaluating the previously prescribed treatment regimens. It is our obligation as physicians to help patients weigh the benefits and detriments of treatment against mortality risk and personal preferences during this long-term treatment relationship in order to attain the best possible treatment advice, tailored to suit the individual’s needs.

Dynamic prediction can be considered a novel concept that provides more sophisticated estimates of survival probabilities based on a more realistic reflection of the course of a patient’s health and disease status over time. At present, we are developing a more refined, user-friendly, web-based dynamic prediction tool that can be accessed during clinical follow-up visits so as to re-evaluate and, where necessary, modify individual treatment recommendations. Implementing and improving dynamic prediction in current clinical practice entails expanding existing multidisciplinary as well as national and international collaborations in order to develop better models based on more extensive datasets. Ultimately, these models will help guide patients and clinicians during the course of treatment, not only with respect to breast cancer, but over the full scope of clinical oncology, and likely, other ‘chronic’ conditions.

**Pre-operative treatment**

The final part of this thesis is dedicated to pre-operative (neoadjuvant) systemic treatment for breast cancer patients and the role of the sentinel lymph node biopsy (SLNB) in this context. Neoadjuvant treatment allows for downsizing and downstaging of large (≥2cm) or locally advanced and/or inoperable primary tumors prior to surgical resection. In addition, neoadjuvant treatment provides the convenience of efficiently gaining insight into the effects of systemic treatment on various biochemical, molecular and histological
tumor features, on the basis of which valuable biomarkers can be identified and clinical decisions can be made.

In some patients, it can be challenging to determine the best neoadjuvant treatment regimen. Neoadjuvant chemotherapy may not be the most appropriate treatment option for elderly and/or frailer patients, as well as in patients whose tumors have high levels of ER expression. Especially in these kinds of patients, neoadjuvant endocrine treatment has been proposed as a valid alternative to neoadjuvant chemotherapy. In strongly endocrine-sensitive breast cancer patients, neoadjuvant endocrine therapy is gaining popularity, although there remains considerable uncertainty about issues such as the optimal treatment duration and the most suitable modality for response assessment. Neoadjuvant endocrine therapy trials have typically treated patients for 3 or 4 months prior to surgery, but emerging evidence suggests that longer treatment durations are feasible and that tumors continue to regress during longer treatment periods, without serious threats concerning safety and toxicity. In our phase II trial, we observed sustained tumor downsizing as well as more breast conservation (chapter 14). Similar results were described in our earlier review of the literature on neoadjuvant endocrine therapy (chapter 13), with maximal responses when treatment was extended beyond 3-4 months. Our results strongly suggest that treatment periods of at least 6 months should be sought after in clinical practice.

The role and timing of the sentinel lymph node biopsy (SLNB) as well as the axillary lymph node dissection (ALND) in the context of neoadjuvant treatment still prompts much debate, and clinical guidelines are largely lacking or inconclusive. The SLNB was originally introduced to accompany surgical tumor excision as a means of specifying disease stage and prognosis, as well as to guide further treatment decisions concerning systemic, locoregional and additional surgical intervention. As neoadjuvant treatment causes a shift in the timing of surgery, it may seem logical to perform the SLNB at the moment of primary surgery. Needless to say, some have argued that neoadjuvant chemotherapy can reduce staging accuracy of the sentinel lymph node, although the clinical implications may be slightly overstated. Potential undertreatment resulting from increased false-negative rates may not be as relevant, as the decision to administer systemic treatment has already been made and the risk of developing an axillary recurrence after a positive SLN without an additional ALND is low. Yet the risk of surgical over-treatment and the impact of additional comorbidity following surgical intervention is significant. With the advent of neoadjuvant systemic treatment as an important contributor to current breast cancer treatment, it is justified to adjust surgical treatment if downstaging of the tumor and axilla has occurred.

**Tailored endocrine treatment - a pursuable goal?**

“Individualization of drug therapy is an evolution, not a revolution”, was the statement by Lesko and Schmidt, who describe that ‘personalized’ apothecary practice dates back to 2600 B.C. as evidenced by medical texts and prescriptions written on clay tablets. Although up until the late 19th and early 20th centuries the concoction of formulations to treat the individual patient was common practice, the expansion
of our medical knowledge and intensified production of one-size-fits-all treatments made way for more efficient drug development and the evolution of evidence-based medicine which now sets the standard for new treatments. With the advent of evidence-based medicine, some critics convey that the use of clinical trials does not truly allow for personalized medicine as the majority of these trials maintain strict in- and exclusion criteria in which case only a certain subset of patients can be included and results cannot be applied to the more general population.\textsuperscript{42, 43}

Personalized medicine requires more than an overall cohort benefit. In modern medicine, we have reached a tipping point, where treatment decisions based on large clinical trials and overall treatment benefits for large groups of patients are replaced by more complex models targeting individual patients. In addition, the physician’s individual clinical expertise as well as the patient’s more active involvement with her condition in order to convey important issues driving individual preferences and maximizing the probability of successful treatment have become an integral part of a treatment plan.

In current clinical practice, there is a need for more accurate and easily accessible personalized prediction models that surpass the currently available selection of genetic tests such as Mammaprint and OncotypeDX.\textsuperscript{36} A major limitation of genetic tests is that they lack the capacity to account for issues associated with daily functioning in individual patients, including QOL, compliance, and side effects. We demonstrated that patients vary in their responses to endocrine therapy. The studies that make up this thesis show that we are capable of combining a wide range of patient- and tumor-specific features into a single model that offers opportunities to adjust treatment advice over time, aimed at further personalized medicine. Moreover, the presented dynamic prediction model can help empower individual patients to convey personal preferences and partake in their own treatment decisions in order to put into perspective side effects and QOL aspects beside treatment benefit. For the scientific community, the need for solid prediction models underlines the importance of further in-depth investigations and more large-scale collaboration to permit additional fine-tuning of our dynamic prediction model for an even broader target audience. Based on statistics, we can establish the best objective outcome for the disease, but based on an array of unique characteristics, we can provide the best care for the individual patient.


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40. ASCO Breast Cancer Guidelines. 2014. 1-1-2014. Ref Type: Online Source

