Tailoring adjuvant therapy for hormone receptor-positive breast cancer

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Chapter 11

General discussion

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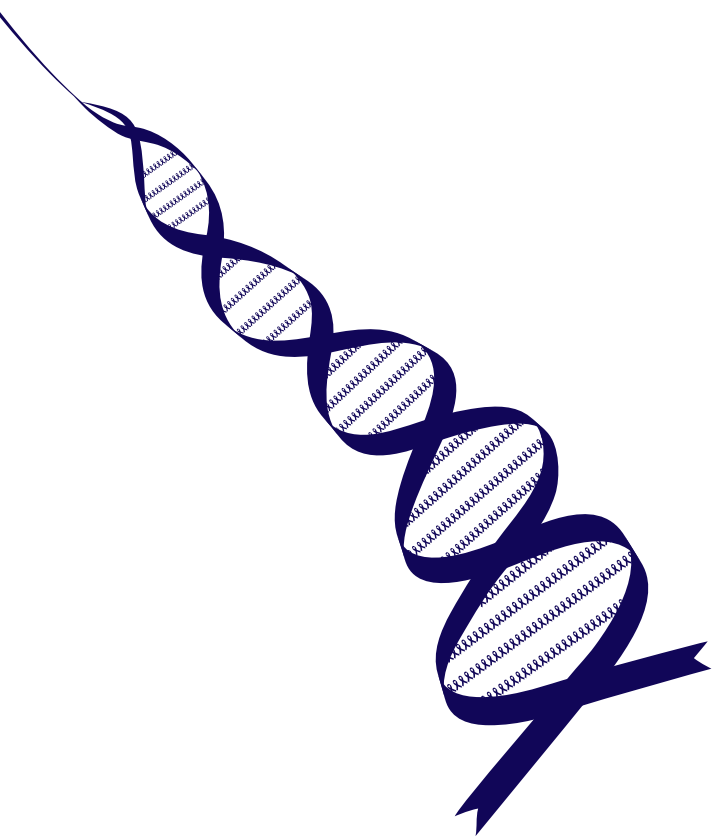

In the past decades, adjuvant endocrine therapy has increased substantially in popularity and has become one of the mainstays in the treatment of patients with breast cancer. Current international guidelines state that all patients with >1% of tumour cells expressing ER are eligible to receive adjuvant endocrine therapy.[1] Although the Dutch guidelines are a bit less stringent (>10% ER expression, and <2 cm and grade 1, or <1cm and grade 1 or 2 tumours are excluded), still the majority of ER-positive patients receives adjuvant endocrine therapy.[2-4] The treatment durations have escalated over the years. Starting initially with just a few months of adjuvant tamoxifen, trials have been performed studying up to 15 years of adjuvant endocrine therapy.[5]

Both the relative low threshold for ER-positivity and the increasing treatment durations contribute to the risk of overtreatment. In a meta-analysis performed by the Early Breast Cancer Trialists Collaborative Group (EBCTCG), 5 years of tamoxifen was compared to no adjuvant therapy. At 15 years after diagnosis, there was an absolute benefit of 12% in recurrences (45% vs 33%), and an absolute benefit of 9% (35% vs 26%) on breast cancer mortality.[6] However, this also suggests that for 88% of the patients there was no benefit of tamoxifen (55% because they wouldn't develop a metastasis anyhow, and 33% because they still develop a metastasis despite their therapy). Identification of these patients is crucial, either to de-escalate therapy for the ones that would not develop a metastasis even without therapy, or to escalate therapy for the patients that would develop a (late) metastasis despite their therapy. In this thesis, we have studied and discussed multiple aspects of tailoring this adjuvant endocrine therapy.

Extended adjuvant endocrine therapy

Extended therapy beyond 5 years is one of the strategies to escalate therapy, in order to prevent late relapses of HR-positive breast cancer. Especially after 5 years of tamoxifen, it is often considered to be standard of care, which is reflected in most international guidelines and is summarized in chapter 2. The leading study in this field is the MA.17 trial, which was published in 2003 by the group of Paul Goss in the New England Journal of Medicine.[7] In this study, over 5000 women who earlier received 5 years of tamoxifen, were randomized between 5 years of extended letrozole, or 5 years of placebo. At interim analysis after 2.4 years, the disease-free survival in the treated group was 93%, versus 87% in the placebo group (HR 0.57, 95% CI 0.43-0.75, p<0.001). Although impressive at first glance, the absolute differences in terms of

distant recurrences are less impressive. In the letrozole group 47 (out of 2593) patients had a distant recurrence (1.8%), in the placebo group 76 (out of 2594) had a distant recurrence (2.9%). Based on these absolute numbers, it can be questioned whether this 1.1% of absolute difference in distant metastasis justifies 5 years of additional therapy. This doubt is strengthened by the 5 year follow-up publication, which showed no significant difference in distant metastasis-free survival (HR 0.80, 95% CI 0.62-1.03, p=0.08) or overall survival (HR 0.98, 95% CI 0.78-1.22, p=0.85).[8] That DFS was still significantly improved in both analyses, is explained by the fact that death due to other causes was not included in the definition of DFS. Furthermore, prevention of local relapse and secondary breast cancer in the contralateral breast (which is not regarded as a treatment aim for systemic adjuvant therapy) also strongly influenced the differences in DFS.

In a recent meta-analysis, it was confirmed that in general the added effect of extended endocrine therapy is limited, especially when overall survival is used as outcome measure.[9] For recurrences, the same meta-analysis shows that the effect is isolated to patients with positive lymph nodes.[9] In chapter 3 of this thesis, we describe the results of the phase III IDEAL trial, in which postmenopausal patients with early HR+ breast cancer were randomized between either 2.5 or 5 years of letrozole, after finishing 5 years of regular adjuvant endocrine therapy. In this chapter, we conclude that longer (5 versus 2.5 years) extended therapy has little value for the full population (chapter 3). However, other groups studying extended endocrine therapy, suggested that for patients with node-positive disease, there might be a benefit of longer AI therapy after using sequential therapy of tamoxifen followed by an AI for 5 years.[10] In chapter 4, we describe a subgroup analysis in the IDEAL trial, in this particular subgroup (node-positive disease, pre-treated with tamoxifen followed by an AI). In this chapter, we have shown that a longer use of letrozole in this particular subgroup might be beneficial. Still, despite the significant value in node-positive disease, the absolute benefits of extended therapy remain small. Therefore, shared decision-making between patients and physicians plays a major role, balancing the (small) benefits and side effects.

Another reason why shared decision-making is particularly important for extended endocrine therapy, is the compliance to therapy. In the primary analysis of the IDEAL trial (chapter 3), we have shown that 25% of patients in the 2.5 years, and 45% in the 5 years group are unable to finish therapy, in majority explained by adverse events.

In chapter 5, we further investigated this phenomenon, by evaluating the factors associated to participating in the IDEAL, the factors associated to early treatment discontinuation, and the effect of early treatment discontinuation on survival outcome. We showed that factors associated to participation are high risk factors like a younger age and nodal status, whereas the factors associated to early discontinuation are more patient-centred factors like the type of earlier endocrine therapy, the amount of time between treatments, and the occurrence of side effects. Remarkably, we have shown that patients who decide to cease therapy after an adverse event, have an equal survival outcome compared to those who continue with therapy after an adverse event. This emphasizes the need for shared decision-based, personalized treatment regimes.

One of the outcomes that shows a consistency under extended endocrine therapy, is the lower occurrence of contralateral breast cancer, which was also shown in chapter 3. This preventive effect of endocrine therapy on the occurrence of new primary breast tumours is well studied, and has increasing popularity.[11] However, the differences in absolute and relative risk reductions play a major role in this discussion. One of the most well-known studies in the field of primary breast cancer prevention is the International Breast Intervention Study II (IBIS-II). They randomized 3864 patients between anastrozole or placebo. After 5 years, there was a 50% reduction in the incidence of breast cancers (32 vs 64 respectively). This absolute reduction of 32 cases represents an absolute decrease of 1.7%, which already sounds much less impressive. Combined with the fact that only ER-positive breast cancer is prevented, which in general has a more favourable prognosis (approximately 85-90% survival at 5 years), the effect on overall survival is almost non-existent. Therefore, we feel that the preventive effect of extended endocrine therapy should not be used as an argument for the use of (extended) endocrine therapy.

Biomarker-based personalized endocrine therapy

One approach to improve the effect of (extended) endocrine therapy is to identify the patients that will benefit most from it, using biomarkers. Or, vice versa, use biomarkers to identify the patients that will not benefit from it, so that other types of therapy can be considered. Roughly, there are two approaches in the development of biomarkers, which we will call biology-based and risk-based biomarkers.

The first approach, *biology-based biomarkers*, are biomarkers that are designed based on the biological mechanism of an intervention. A current example which is already widely used, is the tumor expression of hormone receptors (HRs). When these receptors are not expressed, endocrine therapy is not expected to cause any therapeutical effect. However, as shown in the previous section, the expression of hormone receptors is not a guarantee for treatment success. A possible mechanism to improve the use of information on the tumour expression of hormone receptors as predictive biomarkers for endocrine therapy, is described in chapter 6. By determining the activity of the ER-pathway, you could distinguish for which patients the estrogen receptor is not only expressed, but indeed active and therefore a suitable target for therapy. In chapter X, we adapted this procedure for evaluation in the TEAM IIA trial, in which patients were treated with neo-adjuvant endocrine therapy, we showed that non-response and progressive disease during therapy were associated to a lower baseline ER-pathway activity. Furthermore, in a public dataset, the decrease in ER-pathway activity was associated to therapy response. Therefore, this technique might be a way to monitor the efficacy of endocrine therapy, since the receptor pathway activity is expected to diminish upon successful treatment. Currently this is only applicable to the neo-adjuvant and metastatic setting, since these are the only settings with a tumour in situ for monitoring. However, with increasing utility of circulating tumour cells, this technique might become feasible for adjuvant therapies as well. Furthermore, future analyses are planned to assess whether a lack of decrease in ER-pathway activity might be explained by baseline mutations in ESR1, the gene coding for ER. If this is the case, patients with such a mutation might be spared from endocrine therapy since they will have no clinical response, and they should be treated with other types of adjuvant therapy (i.e. chemotherapy).

A second biology-based biomarker approach highlighted in this thesis, is the tumour-immune environment, specifically the *tumour-infiltrating lymphocytes* (TILs). TILs, and specifically CD8-positive TILs are effector cells of the adapted immune system, capable of targeting tumour cells which they recognize as being 'foreign' due to expression of tumour neo-epitopes. However, since TILs are depending on these neo-epitopes for their activation, tumours with a lower mutational load are usually considered to be less responsive against TIL-infiltration.

It has been shown that ER-positive tumours have a lower mutational load compared to ER-negative tumours.[12]o Therefore, it is no surprise that TILs have no prognostic

value in ER-positive disease, in contrast to ER-negative disease in which high numbers of TILs predict for a better survival.[13, 14] The lack of prognostic value of TILs in ER-positive disease was confirmed in this thesis in multiple cohorts (chapter 7 and 8). In contrast, TILs have prognostic capacities in ER-negative disease, in particular in triple-negative breast cancer (TNBC). [15-19] In chapter 8 we explored the role of FAS, a key mediator in cytotoxic T-cell based immunity, in the distinction between ER-positive and ER-negative disease. We showed that CD8-positive TILs only had prognostic value in the presence of FAS expression , and that FAS was expressed twice as frequent in ER-negative disease compared to ER-positive disease.

In chapter 7, we evaluated the predictive capacity of CD8-positive TILs in the Dutch population of the Intergroup Exemestane trial (IES), which randomized patients between tamoxifen or exemestane after 2-3 years of tamoxifen. In this analysis, we have shown a strong predictive value of TILs in ER-positive disease, with regard to a differential treatment response to either tamoxifen or an AI. Patients with low numbers of TILs had a more favourable prognosis when treated with an AI compared to tamoxifen, whereas patients with a high number of TILs had a similar prognosis on both treatments.

We have two different hypotheses for this observation. A first explanation might be a direct influence of endocrine therapy on lymphocytes in general, and TILs in particular. It is known that ER is expressed in lymphocytes, and the response in these cells to estrogen depletion (with an AI) might be different from the response to receptor modulation by tamoxifen.[20] This could theoretically lead to altered functionality of the TILs, and thereby a difference in clinical prognosis. The second theory to explain the findings of TILs as predictive markers for endocrine therapy, could be that the number of TILs are a proxy marker for the mutational load. Tumours with higher numbers of TILs have a higher mutational load[21], more resembling ER-negative tumours and less dependent on ER-signalling. In that case, the type of endocrine therapy would make little difference. In contrast, tumours with lower levels of TILs may have a lower mutational load, thereby being more dependent on ER-signalling. This strong ER dependency might magnify the differences between AIs and tamoxifen with regard survival benefits. Future studies will need to show which of these two theories explains our results best, and validation is required before this marker can be used in a clinical setting.

Risk-based biomarkers

Risk-based biomarkers are capable of discriminating between patients with a high or low risk of tumour recurrence. Even when the relative treatment benefit (hazard ratio) is equal in the low-risk and high-risk subgroup, the treatment will have an higher impact when the a priori chance of recurrence is higher. For example, when a group of patients with a 50% chance and a group with a 10% chance of recurrence a being treated with a therapy that has a hazard ratio of 0.5, the first group will have an absolute risk reduction of 25% (1 in 4 patients has a benefit), whereas the second group has an absolute risk reduction of only 5% (1 in 20 patients has a benefit). Therefore, selection of either high-risk or low-risk patients might help in selective escalating and de-escalating of endocrine therapy.

One of the most popular new strategies to identify patients with a lower or higher risk of recurrences, is the use of gene expression profiles (GEPs). These assays determine the risk of recurrence, based on the expression of selected genes in the tumour. These assays are thoroughly discussed in chapter 9 and 10. In chapter 9, we performed an elaborate systematic review, to assess the assay development, clinical validation, clinical utility, and economic value of the four most frequently used GEPs in Europe. In this review, we conclude that in particular OncotypeDX and Mammaprint are both well studied, having level IA evidence available from large randomized trials. In chapter 10, we comment on MINDACT, one of these large trials assessing the clinical functioning of the Mammaprint test together with traditional clinicopathological guidelines. In this letter, we emphasize the need for subgroup analysis and the selection of patients for which testing is the most beneficial, and ask for careful interpretation of the trial results.

The use of GEPs to select patients for endocrine therapy is still limited. Only recently, a relative small study using GEP in an old trial (1976-1990) randomizing between 2 years of tamoxifen and no endocrine therapy, showed that a group of ER-positive patients with ultralow risk had an excellent prognosis, even without endocrine therapy.[22] Upon validation, this or similar other assays could be used to identify the patients for who endocrine therapy can be safely withheld. On the other end, these assays could perhaps be used to identify the patients with a higher risk for tumour recurrence, who might benefit from extended endocrine therapy. This use will be the topic of further investigations, both in the IDEAL trial and in other studies.

Future perspectives

The trend of personalized and precision medicine in oncology is unstoppable, and will change the field completely. The field of breast cancer was one of the first to adopt personalized targeted medicine with endocrine and HER2-targeted therapy. This thesis has shown that for endocrine therapy a further personalization is likely and, upon validation of our findings, will lead to a more optimal treatment for every individual patient. However, there are some challenges which will need to be addressed before personalized endocrine therapy will become standard of care.

The first challenge will be to validate the initial results in a way, that can reliably be applied in the clinical setting. In the current situation, in which endocrine therapy regimes only become longer, especially de-escalation will be challenging. Prospective-retrospective studies, in which an earlier randomized trial is used to assess the predictive capacity of a new biomarker, is a popular method to validate a biomarker for treatment decisions. However, trials with ER-positive breast cancer, without any endocrine therapy in one arm (which would be needed to show the safety of biomarker-based de-escalation) are rare and usually old.[6] It can be questioned whether these cohorts are still representative enough for current practice. The validation of biomarker-based differentiation between tamoxifen and AIs might be easier, since these trials (like BIG 1-98 and ATAC) are more recent and are suited for validation.

A second challenge is the remaining risk of tumour recurrence beyond 5 years of standard endocrine therapy.[23] This thesis has shown that extending adjuvant therapy is not the solution for this problem, and there remains a continuous risk despite the extended therapy. A possible explanation might be that endocrine therapy is considered as cytostatic treatment, slowing down or stopping tumour growth without actually inducing cell death. Therefore, one extra step has to be taken in the field of endocrine therapy in order to use it as cytotoxic therapy. Whether this step will be taken using immunotherapy or ER-targeted cytotoxic therapy is not clear yet, and will take many years to develop.

Another challenge, which applies for personalized endocrine therapy but also for personalized medicine in general, is the validation of personalization as the most optimal treatment strategy. In classic evidence-based medicine, trials with thousands of patients are conducted, in which one arm is using the new therapy, and the other

arm is using standard therapy. However, the ultimate goal of personalized medicine, is that every treatment strategy is unique for every patient, and per definition therefore cannot be validated using 'regular' clinical trials. A work-around for this problem might be the development of trials that validate a treatment concept, instead of an individual therapy. In that case, you might randomize between 'therapy according to biomarker-protocol' and 'therapy according to standard protocol'. However, financing this kind of trials for personalized endocrine therapy conserving patient numbers would become complicated, since all (adjuvant) endocrine therapy agents are off-patent, and benefits for industry would be low. For the development of new personalized agents (e.g. combination inhibitors, tailored to the tumour molecular make-up), other problems arise when this new concept of protocol-based treatment validation would be used. In order to be accepted to the US and EU markets, individual agents now have to be registered with evidence from a registration trial, in which the new drug is showing superiority over standard therapy. However, when these agents are tailored to individual patients, these trials are impossible to conduct. The unregistered use of agents in protocol-based trials as described above, would therefore require a paradigm shift in evidence-based medicine and pharmaceutical regulations.

When these challenges are met, the future of endocrine therapy will become a personalized treatment strategy combining targeted cytostatic and cytotoxic approaches. Decisions whether endocrine therapy should be started will be made using clinical and genomic risk evaluations, whereas decisions which type of endocrine therapy will be most effective will be made using biology-based biomarkers like tumour lymphocyte infiltration and ER pathway activity. Combining both approaches will lead to more effective endocrine therapy strategy for every individual patient. Only when we are able to select the most optimal endocrine therapy, we will be able to determine the optimal duration for each approach. Until then, 5 years of adjuvant therapy is sufficient for the majority of patients, and extended endocrine therapy should only be considered for a small subgroup of high-risk, tamoxifen treated patients.

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