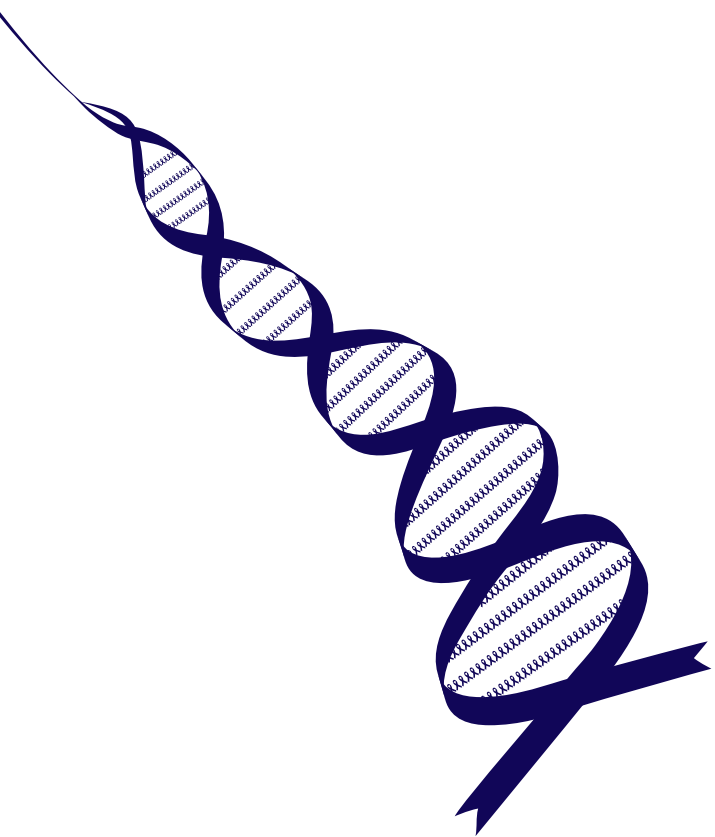
Tailoring adjuvant therapy for hormone receptor-positive breast cancer

Blok, E.J.

Chapter 1

General Introduction

E.J. Blok



Breast cancer epidemiology

With an annual incidence of 17.000 per year in the Netherlands, and 1.7 million worldwide, breast cancer is the most frequent malignancy in females, and the second most frequent cancer overall after lung cancer.[1] Over the past years, there is a steady increase in incidence, together with steadily improving survival rates. A major factor in the improving survival rates is the concept of (neo)adjuvant therapy.[2]

Currently, there are three cornerstones for the treatment of primary breast cancer: surgery, radiotherapy and systemic (neo)adjuvant therapy. The aim of surgery is to remove the primary tumour, thereby preventing future metastasis and locoregional complications. The aim of radiotherapy is the prevention of local and regional relapse, especially after breast-conserving surgery and in the presence of lymph node metastasis. The aim of adjuvant systemic therapy, either endocrine therapy, targeted therapy or chemotherapy, is to prevent relapse, in particular distant metastasis. In addition, the concept of neo-adjuvant therapy, in which systemic therapy is applied before the operation, also leads to tumour shrinkage. This could allow breast-conserving surgery, as well as axillary downstaging and provides knowledge about the sensitivity of the tumour towards the therapy.

Approximately 80% of all breast cancers are hormone-receptor positive, meaning that the tumour is expressing either the estrogen receptor (ER), progesterone receptor (PgR) or both.[3] With this expression, the tumour is capable of stimulating its own growth by receiving a higher amount of estrogen-dependent growth signals.[4]

Endocrine therapy

Already in the 19th century, the concept of endocrine sensitivity of breast cancer was discovered, when Col. Sir George Thomas Beatson performed an oophorectomy at three patient with advanced breast cancer, thereby reducing their metastases.[5] For decades, the oophorectomy became standard therapy for advanced breast cancer. In the 1960's and 70's, a first type of chemical endocrine therapy was first discovered. Tamoxifen, a selective estrogen receptor modulator (SERM) first developed as an oral anticonceptive, was shown to have growth inhibiting capacities in HR-positive breast cancer. Initially, this treatment was only used in advanced disease, to inhibit the growth of metastases. However, soon it was also discovered that preventive use of tamoxifen was able to lower the chance of disease recurrence.[6-9] It was established that 2 years, and later 5 years of tamoxifen was associated to a lower rate of recurrences.[10, 11]

In a post-hoc meta-analysis by the Early Breast Cancer Trialists Collaborative Group (EBCTCG), it was established that at 15 years after diagnosis, there was an absolute benefit of 12% on recurrence-free survival of tamoxifen 5 years (33% recurrence) versus no adjuvant endocrine therapy (45% recurrence).[12]

Meanwhile, a second class of endocrine therapy was being developed. Brodie et al first showed the concept of aromatase inhibition, in which the enzyme aromatase, which is responsible for the conversion from androgens to estrogens, is being inhibited.[13] In case of a postmenopausal patient, for which aromatase-dependent androgen conversion is the only source of estrogens, this would lead to a theoretical full depletion of estrogen, thereby preventing any activation of the estrogen receptor.

The Intergroup Exemestane trial (IES trial) was the first trial to directly compare the effect of tamoxifen and aromatase inhibitors, in this case exemestane. After 2-3 years on tamoxifen, patients were randomized between either completing 5 years of tamoxifen, or switching to exemestane to complete 5 years of adjuvant endocrine therapy. Both at 5 and 10 years follow-up, there was a significant improvement for disease-free (DFS) and overall survival (OS) for the switch to exemestane.[14, 15] The Arimidex, Tamoxifen, alone or in combination trial (ATAC) compared anastrozole and tamoxifen monotherapy, together with a third arm combining both agents. The combination arm was closed due to a lack of additional benefit. This study showed that for DFS and distant metastasis-free survival, there was a benefit of an AI over tamoxifen monotherapy.[16, 17] These results were confirmed by the Breast International Group (BIG) 1-98, which additionally showed that a sequential therapy of tamoxifen followed by an AI, was also superior over tamoxifen monotherapy.[18]>

The Tamoxifen and Exemestane Adjuvant Multicenter Trial (TEAM) compared exemestane monotherapy with a sequential scheme of tamoxifen for 2.5 years, followed by exemestane to complete 5 years of therapy. Both at 5 and 10 years of follow-up, this trial showed no difference in DFS or OS.[19, 20] In a recent meta-analysis performed by the EBCTCG, it was confirmed that there was a clinically and statistically significant benefit of both sequential therapy and AI monotherapy over tamoxifen monotherapy, both for DFS and OS. Moreover, a marginal benefit of AI monotherapy over sequential therapy was shown for DFS with an absolute risk reduction of 0.7% (HR 0.90, p=0.045), but not for OS (HR 0.89, p=0.11).[21]

Despite the success of adjuvant endocrine therapy, there is still a continuous risk for recurrences up to 15 years after diagnosis.[22] Therefore, the concept of extended (i.e. longer than 5 years) adjuvant endocrine therapy was developed. Initially, extended therapy was mainly studied in the context of extended 5 years of tamoxifen. After 5 years of tamoxifen, it was shown that extended therapy with either another 5 years of tamoxifen, or 5 years of an AI was beneficial in terms of disease-free survival, in particular in patients with node-positive disease.[23-25] However, the effect on overall survival was marginal, and not statistically significant when data were pooled in a meta-analysis.[26] After receiving an AI in the first 5 years of treatment, until date no study has shown that extended therapy has a significant benefit.

Biomarkers

In all studies mentioned above, it is apparent that there is only a small group of patients that benefits from (extended) adjuvant endocrine therapy. For example, when comparing 5 years of tamoxifen with no adjuvant therapy, the absolute reduction of 12% and the hazard ratio of 0.73 looks impressive, but also means that 88% of the patients is treated in vain.[12] This means that there is a lot of room for improvement. The guidelines for adjuvant therapy are relatively strict; both adjuvant chemotherapy and endocrine therapy are indicated quite easily, thereby lowering the risk for undertreatment. However, due to this approach many patients will be overtreated, which is especially concerning given the side effect profiles of adjuvant chemotherapy and endocrine therapy. Therefore, tailoring strategies are crucial in order to optimize adjuvant therapy, so that maximal benefits can be achieved with minimal harms.

Currently, the possibilities to tailor adjuvant (extended) therapy are limited. For adjuvant chemotherapy, the current tailoring strategies are mainly risk-based. In theory, patients with a higher risk of recurrence will benefit more from adjuvant chemotherapy compared to patients with a low risk of recurrence. Traditionally, clinicopathological factors like lymph node status, tumour size, receptor status, differentiation grade and age are used to determine the risk for recurrence. However, more recently, gene expression profiles have shown to be interesting prognostic tools, accurately predicting the risk for recurrence.[27, 28]

Besides the risk-based tailoring approach, there is also a biology-based approach to tailor therapy. For endocrine therapy, ER and PgR are used as biomarkers to tailor

endocrine therapy. However, since 80% of all breast cancer patients is either ER and/or PgR-positive, and all above-mentioned trials had ER and/or PgR-positivity as inclusion criterion, the level of tailoring reached with only ER and PgR is insufficient.

One factor that could provide a biology-based tailoring approach, next to the hormone receptors, is the immune system. It is well known that the immune system, and the adaptation of the tumour to the immunological burden, is crucial in the development, growth and metastasis of a tumor.[29] One of the many important aspects in the tumour-immune system interaction, are tumour infiltrating lymphocytes (TILs). Although many different subcategories of lymphocytes are present within a tumour, T-cells, and specifically CD8-positive cytotoxic T-cells, are the most abundant. It has been shown for triple-negative breast cancer, and HER2-positive breast cancer, that higher levels of TILs are associated to a better prognosis, and a higher success rate of adjuvant chemotherapy and HER2-targeted therapy.[30-37] Remarkably, this association was not observed for ER-positive breast cancer, in which TILs have no prognostic value.[38, 39] However, the predictive value of TILs on endocrine therapy has never been studied.

In this thesis we aimed to tailor adjuvant therapy, and in particular adjuvant endocrine therapy, using multiple approaches. We particularly focused on the benefits of extended endocrine therapy, and on new translational approaches for tailoring adjuvant therapy for postmenopausal patients with early breast cancer.

Outline of this thesis

Part I of this thesis is aimed at the clinical use of extended endocrine therapy.

Chapter 2 provides an overview of all the current evidence for extended therapy, and the prospectives of the trials that will be reported in the future. Chapter 3 describes the primary results of the multicentre phase III IDEAL trial, in which patients who received any kind of 5 years adjuvant endocrine therapy, were randomized between either 2.5 or 5 years of extended therapy. Chapter 4 provides a more detailed subgroup analysis of the IDEAL trial, trying to identify a clinicopathological subgroup for which there is a benefit of longer extended therapy. Chapter 5 describes which factors are associated to choosing to participate in the IDEAL trial, which factors contributed to treatment compliance, and the impact of treatment compliance on survival.

Part II of this thesis is aimed at tailoring both (neo)adjuvant chemotherapy and endocrine therapy, using biomarker-based approaches.

Chapter 6 describes the development and validation of a new platform, capable of assessing the activity of the estrogen receptor pathway. This platform was developed by determining the activity of downstream gene targets of the estrogen receptor, and thereby estimating the probability that the estrogen receptor is active. When the receptor is indeed active, it might predict for the benefit of endocrine therapy, whereas with an inactive pathway endocrine therapy would have little effect. Chapter 7 explores the use of tumour-infiltrating lymphocytes (TILs) as a prognostic marker in ER-positive breast cancer, and as a predictive marker for endocrine therapy. Chapter 8 further studies TILs as a prognostic marker, in combination with expression of the cell surface death receptor FAS. Chapter 9 provides a systematic review of gene expression profiles, in which the four major assays (Endopredict , MammaPrint, OncotypeDX, and Prosigna) are reviewed on the developmental procedure, prognostic and predictive capacities, clinical utility and the economic value of the tests. Chapter 10 provides a critical interpretation of the results of the MINDACT trial, a major clinical trial evaluating the use of MammaPrint in clinical practice.

Finally, a summary and discussion on the results of this thesis will be provided in chapter 11, addressing the future perspectives of tailoring adjuvant therapy.

References

1. Ferlay J, Soerjomataram IF, Dikshit RF et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012.(1097-0215 (Electronic)).
2. Narod SA, Iqbal J, Miller AB. Why have breast cancer mortality rates declined? Journal of Cancer Policy 2015;5:8-17.
3. Pritchard KI, Gelmon KA, Rayson D et al. Endocrine therapy for postmenopausal women with hormone-receptor positive her2-negative advanced breast cancer after progression or recurrence on nonsteroidal aromatase inhibitor therapy: a Canadian consensus statement. Current Oncology; Vol 20, No 1 (2013) 2013.
4. Osborne CK, Schiff R. Estrogen-Receptor Biology: Continuing Progress and Therapeutic Implications. JCO 2005;23(8):1616-1622.
5. Beatson G. ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES. The Lancet 1896;148(3803):162-165.
6. CONTROLLED TRIAL OF TAMOXIFEN AS ADJUVANT AGENT IN MANAGEMENT OF EARLY BREAST CANCER. The Lancet 1983;321(8319):257-261.
7. Fisher B, Costantino J, Redmond C et al. A Randomized Clinical Trial Evaluating Tamoxifen in the Treatment of Patients with Node-Negative Breast Cancer Who Have Estrogen-ReceptorGÇôPositive Tumors. N Engl J Med 1989;320(8):479-484.
8. Effects of Adjuvant Tamoxifen and of Cytotoxic Therapy on Mortality in Early Breast Cancer. N Engl J Med 1988;319(26):1681-1692.
9. Fisher B, Costantino J, Redmond C et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. N Engl J Med 1989;320:479-484.
10. Sacco M, Valentini M, Belfiglio M et al. Randomized Trial of 2 Versus 5 Years of Adjuvant Tamoxifen for Women Aged 50 Years or Older With Early Breast Cancer: Italian Interdisciplinary Group for Cancer Evaluation Study of Adjuvant Treatment in Breast Cancer 01. JCO 2003;21(12):2276-2281.
11. Tamoxifen for early breast cancer: an overview of the randomised trials. The Lancet 1998;351(9114):1451-1467.
12. Early Breast Cancer Trialists' Collaborative Group (. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-1717.
13. Jordan VC, Brodie AMH. Development and Evolution of Therapies Targeted to the Estrogen Receptor for the Treatment and Prevention of Breast Cancer. Steroids 2007;72(1):7-25.
14. Coombes RC, Hall E, Gibson LJ et al. A Randomized Trial of Exemestane after Two to Three Years of Tamoxifen Therapy in Postmenopausal Women with Primary Breast Cancer. N Engl J Med 2004;350(11):1081-1092.
15. Morden JP, Alvarez I, Bertelli G et al. Long-Term Follow-Up of the Intergroup Exemestane Study. JCO 2017;JCO.
16. Baum M, Budzar AU, Cuzick J et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 2002;359:2131-2139.
17. Cuzick J, Sestak I, Baum M et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol 2010;11:1135-1141.
18. The BIG 1-98 Collaborative Group. Letrozole Therapy Alone or in Sequence with Tamoxifen in Women with Breast Cancer. N Engl J Med 2009;361(8):766-776.
19. Derks MGM, Blok EJ, Seynaeve C et al. Adjuvant tamoxifen and exemestane in women with postmenopausal early breast cancer (TEAM): 10-year follow-up of a multicentre, open-label, randomised, phase 3 trial. The Lancet Oncology 2017;18(9):1211-1220.
20. van de Velde CJ, Rea D, Seynaeve C et al. Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. The Lancet 2011;377(9762):321-331.
21. EBCTCG. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. The Lancet 2015;386(10001):1341-1352.

22. Pan H, Gray RG, Davies C et al. Predictors of recurrence during years 5-14 in 46,138 women with ER+ breast cancer allocated 5 years only of endocrine therapy (ET). JCO 2016;34(15_suppl):505.
23. Davies C, Pan H, Godwin J et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. Lancet 2013;381:805-816.
24. Gray R, Rea D, Handley K. aTTom: Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years in 6,953 women with early breast cancer. J Clin Oncol 2013;31(supplements; abstract 5).
25. Goss PE, Ingle JN, Martino S et al. A Randomized Trial of Letrozole in Postmenopausal Women after Five Years of Tamoxifen Therapy for Early-Stage Breast Cancer. N Engl J Med 2003;349(19):1793-1802.
26. Ibrahim EM, Al-Hajeili MR, Bayer AM et al. Extended adjuvant endocrine therapy in early breast cancer: a meta-analysis of published randomized trials. Medical Oncology 2017;34(7):131.
27. Cardoso F, vant Veer LJ, Bogaerts J et al. 70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer. N Engl J Med 2016;375(8):717-729.
28. Sparano JA, Gray RJ, Makower DF et al. Prospective Validation of a 21-Gene Expression Assay in Breast Cancer. N Engl J Med 2015;373(21):2005-2014.
29. de Visser KE, Eichten A, Coussens LM. Paradoxical roles of the immune system during cancer development. Nat Rev Cancer 2006;6(1):24-37.
30. West NR, Kost SE, Martin SD et al. Tumour-infiltrating FOXP3(+) lymphocytes are associated with cytotoxic immune responses and good clinical outcome in oestrogen receptor-negative breast cancer. Br J Cancer 2013;108(1):155-162.
31. West NR, Milne K, Truong PT et al. Tumor-infiltrating lymphocytes predict response to anthracycline-based chemotherapy in estrogen receptor-negative breast cancer. Breast Cancer Res 2011;13(6):R126.
32. Denkert C, Loibl S, Noske A et al. Tumor-Associated Lymphocytes As an Independent Predictor of Response to Neoadjuvant Chemotherapy in Breast Cancer. JCO 2010;28(1):105-113.
33. Loi S, Sirtaine N, Piette F et al. Prognostic and Predictive Value of Tumor-Infiltrating Lymphocytes in a Phase III Randomized Adjuvant Breast Cancer Trial in Node-Positive Breast Cancer Comparing the Addition of Docetaxel to Doxorubicin With Doxorubicin-Based Chemotherapy: BIG 02-98. JCO 2013;31(7):860-867.
34. Loi S, Michiels S, Salgado R et al. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. Annals of Oncology 2014;25(8):1544-1550.
35. Salgado R, Denkert C, Demaria S et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs Working Group 2014. Annals of Oncology 2015;26(2):259-271.
36. Ali HR, Provenzano E, Dawson SJ et al. Association between CD8+ T-cell infiltration and breast cancer survival in 12 439 patients. Annals of Oncology 2014;25(8):1536-1543.
37. Adams S, Gray RJ, Demaria S et al. Prognostic Value of Tumor-Infiltrating Lymphocytes in Triple-Negative Breast Cancers From Two Phase III Randomized Adjuvant Breast Cancer Trials: ECOG 2197 and ECOG 1199. JCO 2014.
38. Mahmoud SMA, Paish EC, Powe DG et al. Tumor-Infiltrating CD8+ Lymphocytes Predict Clinical Outcome in Breast Cancer. JCO 2011;29(15):1949-1955.
39. Baker K, Lachapelle J, Zlobec I et al. Prognostic significance of CD8+ T lymphocytes in breast cancer depends upon both oestrogen receptor status and histological grade. Histopathology 2011;58(7):1107-1116.