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Chapter 1

General introduction and outline of thesis

Introduction

Breast cancer is the most common female affecting cancer type in the western world, responsible for 14% of cancer-related deaths in women.(1) In the Netherlands, annually 14.000 women are diagnosed with the disease. (2) In addition to the classical curative treatment modality of surgery, breast cancer treatment nowadays is multidisciplinary involving the addition of radiotherapy and pre- or postoperative systemic therapy, with the aim to achieve optimal control of possibly remaining metastatic tumor cells. This thesis focusses on the optimalization of preoperative systemic therapy for patients with breast cancer.

Chemotherapy

In the 1970s the concept of eradication of locoregional and micrometastatic disease by using systemic therapy as an adjunct to surgery has been developed.(3;4) Seminal randomized clinical trials were conducted in the 1980s, such as the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-13 trial, which showed improved survival in patients treated with adjuvant chemotherapy consisting of methotrexate and fluorouracil.(5) At the same time, interest increased in preoperative administration of systemic therapy (i.e. so called 'neoadjuvant therapy'). It was hypothesized this would result in a reduction in size of primary tumors, rendering more tumors feasible for lumpectomies instead of cosmesis deteriorating mastectomies.(6) Indeed, results from trials such as NSABP B-18 and the Preoperative Chemotherapy in Operable Breast Cancer (POCOB) trial of the European Organisation of Research and Treatment of Cancer (EORTC), comparing preoperative with postoperative chemotherapy, showed equivalent survival outcomes with an increase of breast conservation feasibility in women who were dependent on mastectomy in first instance.(7-9) As an additional benefit, locoregional control improved as the majority of node-positive patients experienced nodal downstaging to some extent. Later studies have shown that the incidence of a complete pathological remission induced by preoperative systemic therapy is associated with better long-term survival outcome.(10;11). A new generation approach to neoadjuvant studies makes use of the possible fast-tracked drug selection for evaluation in large adjuvant phase III studies for women with early BC.(12)

Hormonal systemic therapy

Approximately 60% of premenopausal and 80% of postmenopausal breast cancer patients have tumors expressing hormone receptors on cell membranes.(13) In these tumors, cell growth is positively influenced by the reproductive hormones estrogen and progesterone. Therapies designed to target this 'tumor-growth driving' mechanism date back to as early as 1895, when Sir George Thomas Beatson performed oophorectomies in breast cancer patients, inspired by the effect this action had on lactation in cows.(14) Almost a century later, in the 1980s, results from studies investigating another hormone-receptor targeted therapy

were reported, namely with the selective estrogen receptor modulator tamoxifen.(15;16) Today, the efficacy of hormonal therapy is well established. For many years, tamoxifen was the standard adjuvant hormonal therapy for postmenopausal women with hormone-receptor positive breast cancer, resulting in an absolute risk reduction of breast cancer recurrence of 13% and death of 9% after 15 years.(17) In recent years, the incorporation of aromatase inhibitors (AIs) into (neo)adjuvant endocrine treatment regimens has led to improvements in the (neo)adjuvant treatment of breast cancer. AIs function by decreasing the levels of circulating postmenopausal estrogens and possibly intra-tumoral estrogen through inhibition of the aromatase enzyme, which facilitates the conversion of androgens to estrogens.(18;19) Several studies have shown that sequential treatment with tamoxifen and AIs results in better survival than monotherapy with tamoxifen.(20;21) Also, equivalent survival has been observed in trials that compared sequential treatment with AIs and tamoxifen to AI monotherapy.(22;23) Likewise, neoadjuvant studies comparing AIs to tamoxifen in terms of clinical response have shown that AIs result in superior responses and improvement in breast conserving surgery feasibility.(24) Whereas in adjuvant trials it lasted many years to prove superiority of one endocrine-targeted agent over another, in the neoadjuvant setting conclusive endocrine trials were reported within a few years.

Patients treated with hormonal therapy are at risk for side-effects such as vasomotor symptoms (e.g. hot flashes/(night)sweating) and musculoskeletal problems. However these side-effects are in general considered less detrimental for quality of life than chemotherapy-associated side effects, such as hair loss, nausea/vomiting and complications caused by myelosupression.(25-28) Therefore, one of the major advantages of hormonal therapy is that it has a toxicity profile that is favorable compared to that of chemotherapy, making it a suitable treatment options for patients who are unfit for chemotherapy, such as elderly women with breast cancer.

Addition of zoledronic acid to systemic therapy

In 1889 Stephan Paget declared one of the earliest milestones in the understanding of cancer biology.(29) After careful observation of a large number of breast cancer cases, he found that breast cancer metastases developed far more often in the liver than in any other organ. On basis of this he postulated the so called 'seed-and-soil hypothesis': there may be specific features in organs, the 'soil', making them more susceptible for metastasis of tumor cells, the 'seeds', than other organs. He stated: "The best work in the pathology of cancer is now done by those who are studying the nature of the seed. They are like scientific botanists; and he who turns over the records of cases of cancer is only a ploughman, but his observation of the properties of the soil may also be useful." How does this hypothesis translate to our current understanding of breast cancer? In the past decade, evidence has accumulated suggesting that osteoclast inhibitory drugs such as bisphosphonates results in less bone-metastases and a better survival outcome in postmenopausal women with breast cancer.(30) By inhibiting resorption, bisphosphonates may render the bone microenviroment a less feasible 'soil'

for metastatic tumor cells.(31) The first prospective randomized trial that investigated this concept was the AZURE study (acronym for Does Adjuvant Zoledronic Acid reduce Recurrence in patients with high risk localized breast cancer), in which 3360 breast cancer patients received adjuvant systemic therapy with or without zoledronic acid.(32) Overall findings from this study did not support the use of zoledronic acid as adjuvant treatment. However, postmenopausal women did benefit from the intervention. A small subset of this study (n=205) also received neoadjuvant chemotherapy with or without zoledronic acid. (33) In patients who received zoledronic acid in addition to chemotherapy a doubling of the pathological complete response rate was observed compared to patients who were treated with chemotherapy only. On basis of this, the NEOZOTAC study was designed in order to investigate the possible beneficial effect of zoledronic acid in combination with chemotherapy on tumor response.

Overview of cohorts

All investigations that are reported in this thesis have been done using data from two prospective trials coordinated by the Leiden University Medical Center in close collaboration with the Dutch Breast Cancer Research Group (BOOG).

The NEOZOTAC trial:
The NEOadjuvant ZOledronic acid and TAC chemotherapy (NEOZOTAC) trial was conducted between 2010 en 2012 in 26 Dutch hospitals.(34) The study aimed to investigate the effect of the addition of zoledronic acid to neoadjuvant chemotherapy. Patients received TAC (docetaxel 75 mg/m2, adriamycin 50 mg/m2, and cyclophosphamide 500 mg/m2 i.v.) chemotherapy on day 1, with or without zoledronic acid (4 mg i.v. within 24 h after infusion of chemotherapy) followed by granulocyte colony-stimulating factor on day 2, every 21 days during six cycles. Zoledronic acid therapy was combined with daily supplements of 500 mg calcium and 400 IU vitamin D. Patients were eligible for inclusion in the study if they had stage II–III breast cancer. HER2-negativity of the breast cancer had to be histologically proven. Both hormone receptor-positive and -negative tumor status was allowed. Pre- and postmenopausal patients were eligible. 250 patients were included in this trial.

The TEAMIIa trial:
The TEAMIIa trial was conducted between 2007 and 2012 in 11 hospitals.(35) Originally the study was designed to compare the efficacy of 3 and 6 months of neoadjuvant hormonal therapy. However, due to unexpected slow accrual the study protocol was amended to a phase II study evaluating the efficacy of 6 months of neoadjuvant hormonal therapy with the AI exemestane. Patients were included in case of postmenopausal status and strongly ER-positive (>50%) stage I-III breast cancer. Patients were ineligible in case of evidence of distant metastases.

Outline of this thesis

Part I evaluates the possible role of zoledronic acid to neoadjuvant chemotherapy for enhancing anti-tumor response abd other issues concerning neoadjuvant chemotherapy. Part II is about neoadjuvant hormonal therapy and concentrates on extended duration of neoadjuvant hormonal therapy and aromatase-inhibitor specific adverse events.

Part I

Chapter 2 summarizes the current knowledge on the role of bisphosphonates in combination with systemic therapy and speculates on in which way it may be of value as an adjunct to neoadjuvant chemotherapy. **Chapter 3** describes the results of a prospective, multicenter randomized trial in which the rates of pathological complete responses were compared between patients with early breast cancer who were treated with combination neoadjuvant chemotherapy with or without zoledronic acid. In **chapter 4** this therapy is further investigated in a pooled data analysis of all international randomized trials in which zoledronic acid is combined with neoadjuvant chemotherapy. In order to evaluate tumor response in clinical trials (i.e. decrease of the tumor mass) accurate imaging modalities are necessary. In **chapter 5** the value of MRI as post-neoadjuvant treatment response assessment modality is investigated and discussed. The accuracy of MRI may be differential on basis of the hormonal and/or HER2-receptor status. We evaluated the concordance between tumor size as measured with MRI measures and the actual residual tumor size on the surgical specimen on a large cohort of HER2-negative patients. In **chapter 6** data are described on the effect of neoadjuvant chemotherapy on vitamin D levels and the association between these changes and therapy outcome. Evidence has accumulated suggesting that vitamin D levels are of prognostic value, presumably because of anti-proliferative mechanisms of vitamin D. We aimed to investigate whether vitamin D levels are also associated with response to neoadjuvant chemotherapy.

Part II

A systematic review on studies investigating response to neoadjuvant hormonal treatment with different treatment durations in postmenopausal breast cancer patients is presented in **chapter 7.** Findings from the prospective TEAMIIA trial investigating six months of neoadjuvant hormonal therapy in ER-positive breast cancer patients are described in **chapter 8.** As previously mentioned, hormonal therapy is associated with specific adverse events (e.g. hot flushes/musculoskeletelal complaints) associated with estrogen depletion. The study presented in **chapter 9** aimed to investigate whether the occurrence of aromatase inhibitor specific adverse events is associated with clinical response. Estrogen depletion by aromatase inhibitors is associated with specific adverse events such as hot flashes and musculoskeletal symptoms. As the anti-tumor mechanism of aromatase inhibitors is based on estrogen depletion, the occurrence of these specific adverse events may be a measure for treatment efficacy. Lastly, the results from this thesis are discussed and placed into context of future perspectives in **chapter 10.**

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