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General introduction and outline of this thesis

Epidemiology

Breast cancer is the most frequently diagnosed cancer type and the leading cause of cancer death in women in Western countries.[1] In the Netherlands, 14,296 women were diagnosed with breast cancer in 2012 and eventually 3,197 died that year of breast cancer (http://www.cijfersoverkanker.nl). Through improved treatment modalities and a multidisciplinary approach, survival of breast cancer patients has improved. The five year survival rate for women diagnosed between 1995-2000 was 81%, and became 85% for women diagnosed between 2001 and 2005. Ten year survival rates for the respective time periods were 72% and 77%, respectively.

Treatment

Optimal curative therapy consists of a combination of different available treatment modalities, including locoregional therapy (surgery with or without radiotherapy), and systemic therapy (chemotherapy, endocrine therapy, and/or targeted therapy). International treatment guidelines (e.g. of the American Society of Clinical Oncology-ASCO, and the St. Gallen early breast cancer conference) have been developed aiming at optimal care based upon up to date evidence-based therapy as much as possible. There is strong evidence that treatment in accordance to guidelines results in improved outcome for breast cancer patients.[2] As adherence to guidelines is not mandatory and interpretation from international to national and/or local guidelines can differ, variations in treatment policies and implementation rates of new techniques among different countries and different hospitals can arise.

Over time, multidisciplinary breast cancer teams have been installed in hospitals. These teams consist of representatives of the involved specialities, namely oncologic surgeons, radiation-oncologists, medical oncologists, pathologists, radiologists, breast cancer nurses, and, on indication plastic surgeons, clinical genetics, psychologists, and research nurses. These local teams intend to coordinate, standardise, and ameliorate breast cancer care and outcome. It has been demonstrated that patients, advised and treated by a multidisciplinary team, received a different treatment compared to patients treated by a single specialist.[3,4] Moreover, the advices given by the multidisciplinary team were more in line with the guidelines as compared to those given by a single specialist, the latter particularly reflecting the own discipline.

Endocrine therapy

One of the systemic treatment modalities concerns endocrine therapy. The most commonly used drugs of endocrine therapy are anti-oestrogens, consisting of selective oestrogen receptor modulators (SERMs, eg Tamoxifen), selective oestrogen downregulators (SERDs, eg Fulvestrant) and aromatase inhibitors (AIs), consisting of non-steroidal agents (eg Anastrozole, Letrozole) and steroidal agents (eg Exemestane).

The first report concerning the activity of endocrine therapy in breast cancer patients was described in 1896 by Sir George Beatson.[5] He reported on a bilateral ovariectomy in a young patient with locally advanced breast cancer resulting in a complete disappearance of the disease. In the last century, the hormone oestrogen was identified and the oestrogen receptor (ER) was described by Dr Elwood Jensen.[6,7] In the nineteen sixties, tamoxifen was first introduced as an oral contraceptive and the anti-oestrogenic action through binding at the ER was established through Dr Craig Jordan and his team. The value of tamoxifen as adjuvant therapy for early breast cancer patients was studied as of the seventies of the 20th century. Initially, tamoxifen was studied in postmenopausal breast cancer patients with node positive disease irrespective of hormone receptor status, thereafter in all postmenopausal patients, including high-risk node negative breast cancer patients, and later also in premenopausal patients. Further, different time periods of use were studied, at first for two years, and later for five years. The favourable effect of tamoxifen regarding survival was established by the results of the meta-analyses of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).[8,9] In later analyses of this and other groups, it became clear that tamoxifen was mainly effective in hormone receptor positive patients. In addition, long term use of and continuing research regarding tamoxifen learned that use of tamoxifen was associated with an increased

risk of several side-effects, namely thromboembolic complications and endometrial cancer (see section side effects of endocrine therapy).[9-12]

Where tamoxifen blocks oestrogen binding at the ER, inhibition of the aromatase enzyme blocks the conversion from androgens to oestrogens, resulting in lowered oestrogen plasma levels in postmenopausal women. The first AIs were not selective and were associated with unwanted side-effects. With the development of the selective third generation AIs, another class of drugs became available and were widely studied, the more as the toxicity profile was acceptable. Nowadays, available drugs are the non-steroidal inhibitor anastrozole (Arimidex®) and letrozol (Femara®) which inhibit the synthesis of oestrogens by reversible competition with the aromatase enzyme. Later on, exemestane (Aromasin®) was developed as an irreversible steroidal inhibitor inactivating the enzyme by blocking the substrate-binding site.

The value of AIs regarding efficacy and safety was studies in three kinds of designs in the adjuvant setting, namely as upfront therapy, after two to three years of tamoxifen (switch or sequential design) and as extended therapy after five years of tamoxifen.

Upfront therapy

Two trials investigated AIs in the upfront setting, namely the Anastrozole, Tamoxifen Alone or in Combination" (ATAC) trial and the Breast International Group (BIG) 1-98 study, also named BIG FEMTA study.[13,14]

In the ATAC trial, postmenopausal women with early breast cancer suitable for endocrine therapy (not yet restricted to ER and/or progesterone (PgR) positive breast cancer) were randomised to anastrozole (n=3125) or tamoxifen (n=3116).[13] Of these, 2618 and 2598 respectively, were hormone positive. After a median follow-up of ten years (range 0-145 months), there were less recurrences in hormone receptor positive patients using anastrozole (HR 0.86%, 95%CI 0.78-0.95; $p = 0.003$) compared to patients using tamoxifen. There was no difference in overall survival (OS) ($p = 0.4$). The BIG 1-98 study was a four armed trial including a total of 8010 postmenopausal hormone positive early breast cancer patients and randomised between monotherapy with tamoxifen, monotherapy with letrozole (both for five years), and sequential therapy with either tamoxifen followed by letrozole or letrozole followed by tamoxifen.[14] After a median follow-up of 8.7 years, the disease free survival (DFS) as well as the OS were better for letrozole compared to tamoxifen (both $p < 0.001$).

Switch or sequential therapy after two to three years of tamoxifen

Resistance to tamoxifen (primary or secondary) has been observed. Switching from tamoxifen to an AI (sequential therapy) before resistance occur may therefore result in an improved efficacy. Additionally, the impact of adverse events of each drug alone in this way may be minimized. These rationales prompted to initiate studies investigating sequential therapy. In these studies, patients were randomised to two to three years of tamoxifen followed by two to three years of an AI or to five years with tamoxifen or an AI alone. The first studies randomised patients after two to three years of tamoxifen between prolongation of tamoxifen versus two to three years of an AI, the so-called late randomisation sequential study. Later on, patients were randomised before the start of endocrine therapy for either sequential therapy or monotherapy with tamoxifen or an AI, the so-called early randomisation sequential studies.

There are three late randomisation sequential studies, namely the Intergroup Exemestane Study (IES), the Italian Tamoxifen Anastrozole (ITA) and the Anastrozole-Nolvadex (ARNO) 95 trial.[15] Patients who were disease free after two to three years of tamoxifen, were randomised to continue tamoxifen or switch to exemestane in the IES and to switch to anastrozole in the ITA and ARNO-95 trial.[15,16] In the IES, at a median follow-up of 91 months, the switch to exemestane improved overall survival.

The early randomisation sequential studies are the Austrian Breast and Colorectal Cancer Study Group trial 8 (ABCSG 8), the BIG 1-98, and the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial.[14, 17, 18] These studies used the AI anastrozole, letrozol and exemestane respective-

ly. In the ABCSG-8, patients were randomised between five years of tamoxifen or two years of tamoxifen followed by three years of anastrozole. Chemotherapy was an exclusion criterion. After a median follow-up of 60 months, sequential therapy resulted in an improved distant relapse-free survival. In the BIG1-98 study, however, no statistically different in survival was demonstrated between the four arms. The TEAM trial will be discussed in "the outline of this thesis".

Extended therapy after five years of tamoxifen

Ongoing recurrences after completing five years of tamoxifen therapy is a persistent problem for women with endocrine sensitive early breast cancer. Therefore, several trials investigated extended therapy involving an AI: two with letrozole and two with exemestane. Letrozole was used in the National Cancer Institute of Canada Clinical Trials Group trial (NCIC CTG intergroup) MA.17 and MA.27 studies.[19] In the MA.17 study, postmenopausal patients who completed five years of tamoxifen were randomised between letrozole or an placebo for five years. Extended therapy with letrozole was superior to placebo with regards to DFS and OS. The MA.27 study randomised between anastrozole and exemestane after five years of tamoxifen. There was no difference in event free survival between the steroidal and nonsteroidal AI.

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-33 trial patients were randomised between exemestane of placebo after five years of tamoxifen.[20] This study was closed premature because of the results of the MA.17 study. The analyses showed a statistically improved in relapse-free survival.

Side effects of endocrine therapy

As mentioned above, use of endocrine therapy is associated with a risk of side-effects. Both tamoxifen and AIs have been associated with the risk of various menopausal symptoms. The most common side effects caused by tamoxifen are menopausal symptoms including hot flashes, vaginal dryness, low libido and mood swings. Other (more rare) side effects are thromboembolic complications and endometrial cancer.[10-12] However, tamoxifen has been shown to have positive effects on bone metabolism in postmenopausal women.[21]

In view of the different mechanism of action of AIs as compared to tamoxifen, the spectrum of adverse events also differs. The most commons side effects of AIs are tiredness, hot flushes and musculoskeletal symptoms (e.g. muscle cramps, joint pain, joint stiffness). Other side effects are more heart problems, negative effects on bone metabolism and status (decreased bone mineral density, increased rate of fractures) and negative effects regarding gynaecological symptoms and sexuality.[22-25] All these side-effects may negatively impact quality of life, and consequently influence treatment compliance and thereby survival.[26,27]

Prognostic and prediction models

Decisions about systemic (endocrine) therapy depend on prognostic and predictive factors dividing patients into different risk groups.[28] Strictly speaking, prognostic factors estimate the patient's risk of relapse in the absence of systemic therapy. Established prognostic factors for breast cancer recurrence are age at diagnosis, tumour size and grade, lymph node status and, hormonal and humane epidermal growth factor receptor 2 (HER2) status. For instance, more pathological positive lymph nodes are associated with a higher risk of recurrence. Predictive factors estimate the responsiveness of a patient/tumour to a specific treatment. Expression of ER is predictive for the efficacy of endocrine therapy while HER2 overexpression is predictive for the efficacy of anti-HER2 directed therapies.

Current prognostic markers are not optimal for risk assessment: breast cancer can recur in low-risk patients not receiving systemic treatment. Additionally, as the difference in survival between different therapies is small, the impact of side effects on quality of life may also be an important issue to deliberate the drug of choice for a specific treatment strategy. Novel factors are needed to further subcategorise patients for different systemic treatment regimens and therefore to improve tailored treatment.

Outline of this thesis

In this thesis several issues concerning postoperative endocrine treatment of hormone sensitive postmenopausal early breast cancer patients have been addressed. Most chapters are based on data of the TEAM trial. The TEAM trial is an open label, randomised international phase three trial originally designed to compare the efficacy and safety of five years of exemestane to five years of tamoxifen as adjuvant endocrine therapy for postmenopausal women with hormone sensitive breast cancer. During the conduct of the study, the interim data of the IES became available, and demonstrated a significantly improved DFS by switching patients to exemestane after two to three years of tamoxifen therapy, compared to the standard five years of tamoxifen treatment.[29] Also, the data of other AI studies pointed in a similar direction indicating superiority for treatment incorporating an AI above five years of tamoxifen. Therefore, the design of the TEAM trial was amended to compare five years of exemestane alone versus sequential therapy with 2½-3 years of tamoxifen followed by 2-2½ years of exemestane.

The TEAM trial was activated in nine countries: Belgium, France, Germany, Greece, Ireland, Japan, the Netherlands, United Kingdom and the United States of America. In the Netherlands, the study was activated in the majority of Dutch hospitals and the central data management was performed at the Datacentre of the department of Surgery of the Leiden University Medical Centre.

The results published in 2011 showed no superior effect of exemestane above sequential therapy.[18]

Part I Patterns of Care

In **chapter two**, we explored differences in local therapy between the different TEAM countries. In **chapter three**, we explored the locoregional as well as the systemic therapy differences between the different Dutch comprehensive cancer centres.

PART II Aspects of endocrine therapy

In **chapter four**, an overview is given of the different switching strategies and trials concerning adjuvant endocrine therapy in postmenopausal hormone sensitive early breast cancer patients. In the next chapters, the side effects of adjuvant endocrine therapy in patients included in the TEAM trial are addressed: in **chapters five** the effect on bone health, in **chapter six** the effect on breast density, in **chapter seven** the effect on quality of life of patients, and finally, in **chapter eight**, the association with physical activity, body weight as well as quality of life.

PART III Biomarkers for prognosis

In **chapter nine and ten** several biomarkers were investigated as candidates for new biomarkers to improve more tailored treatment for early breast cancer patients.

Finally, **chapter eleven** summarises the research data of the above mentioned articles and provides a general discussion and gives suggestions for clinical practice.

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