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General discussion

Introduction

Breast cancer is the most frequently diagnosed type of cancer among women, both in developed and developing regions.[1] The majority of patients is postmenopausal at diagnosis and has hormone sensitive tumours, implying that patients may benefit from endocrine therapy, both in curative and in metastatic setting. In the last twenty-five years, the treatment of patients with hormone-sensitive early breast cancer has largely changed as more treatment options became available, while over the last decade more tailored treatment was aimed at. This has resulted in an improved prognosis.[2-4] Nevertheless, part of breast cancer patients will develop recurrent disease, especially late recurrences can occur in hormone sensitive disease while the various therapies may be associated with side effects which can affect quality of life.

The research described in this thesis was designed to gain further insight in optimal treatment of early breast cancer patients, especially in postmenopausal women with hormone sensitive tumours. Most studies in this thesis has been performed in the context of the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial. This international phase III trial compared the value of postoperative endocrine therapy with tamoxifen for 2-3 years followed by exemestane (an aromatase inhibitor, AI) for 3-2 years (totalling five years) with that of exemestane alone for five years in postmenopausal women with hormone sensitive early breast cancer. Overall, the trial included almost 10,000 patients of which approximately 3,000 were enrolled in the Netherlands and Belgium.

Patterns of care

Improvement and individualisation of cancer therapy is an ongoing process. In patients with breast cancer, large randomised controlled trials have been performed comparing new therapies with the current standards of care. In February 2014, there were a total of 70 breast cancer trials registered at www.trialregister.nl and 1,700 at www.cancer.gov/clinicaltrials. In most trial protocols, the new strategy or intervention is well described and it is stated that the standard treatment should be according to the guidelines. This has also been the case for the international TEAM trial regarding surgery, radiotherapy and chemotherapy. Therefore, we were interested in patterns of care with respect to the non-trial related breast cancer therapy in TEAM participants.

It is generally accepted that adherence to guidelines and working in a breast cancer team should be stimulated in order to improve the quality of breast cancer care. These multidisciplinary teams can support adherence to the guidelines and it appears that recommendations given by such a team are more in line with the guidelines as compared to advices given by a single specialist.[5-7] Nowadays, all Dutch hospitals have such a team. Notwithstanding these multidisciplinary teams present in the Netherlands and other countries participating in the TEAM study, we observed quite some differences between countries in what is considered "standard treatment" and "according to the current guidelines" regarding locoregional treatment and chemotherapy, and even within the Netherlands large regional differences were noticed, as is described in chapters 2 and 3.

In our opinion, the following aspects could have played an important role hereby.

Firstly, at the time that the TEAM trial was open for inclusion of patients, not all hospitals had a breast cancer team.

Secondly, the age of a patient is probably an important factor: younger patients are willing to accept more aggressive therapies in contrast to older patients. Moreover, physicians are inclined to give more aggressive treatments to younger patients, in contrast to older patients. In the TEAM trial, a higher age at diagnosis was associated with less breast conserving surgery, less radiotherapy and less chemotherapy. Even after adjustment for stage of disease and country, older patients received less intensive therapy.

Thirdly, differences will continue to exist because of cultural and geographical variations. This may partly explain the differences in the number of mastectomies in patients with mainly small tumour size performed in France and the United States of America (USA) (19% and 51% respec-

tively).[8] In the USA, the distance to a radiotherapy department may be longer than in France.[9] Possibly, the fear of a claim, which stimulates a more defensive attitude in medical decision making, can also play a role, in particular in the USA. Unfortunately, we did not collect information concerning breast reconstruction after mastectomy as this may have influenced the surgical approach.

Fourthly: the participation in clinical trials can vary in various regions and/or countries which can cause a delay in implementing new standards of care in those centres not participating in clinical research. For instance, in the TEAM trial, the rate of axillary lymph node dissection was different between the countries. This difference may have been due to a different timing of the routine implementation of the sentinel lymph node procedure: earlier implementation of the sentinel lymph node procedure will have reduced the number of axillary lymph node dissections.

It may be questioned whether it really is an issue that some differences in patterns of care do exist, and will continue to exist as long as patients are properly informed on the current standards by a breast cancer team. Our pattern of care studies have been performed using data collected on the clinical record forms (CRF) of the TEAM trial. A lot of data was not recorded in detail on the CRF, such as the advice of a multidisciplinary breast cancer team, logistical problems such as the distance to a radiotherapy department and/or the preference of the patient herself and her family.

Currently, more and more is registered and working groups are established aiming at improving quality of care and cancer outcome. In the Netherlands, a working team of the national breast cancer organisation of the Netherlands (NABON) has developed a set of quality indicators for the treatment of breast cancer including indicators for internal quality improvement and for external accountability. This set is a dynamic set; it can be adjusted based on experience and the validity and reliability of the indicators. At this moment, central registration for some indicators has been initiated, and will be implemented for others in the future. Another Dutch working group is the SONCOS (Stichting ONCologische Samenwerking) (www.soncos.org). This collaborative group of surgical oncologists, medical oncologists and radiation oncologists developed a dynamic document on requirements to comply with for hospitals treating breast cancer patients. Further, the European Society of Breast Cancer Specialists (EUSOMA) also defined a set of quality indicators which should be routinely measured and evaluated in order to confirm that the clinical outcome reaches the requested standards.[10] This set contains 17 main quality indicators: seven on diagnosis, four on local and locoregional treatment, two on systemic treatment and four on staging, counselling, follow-up and rehabilitation. In this way, the above mentioned quality indicators require that registration is being done, and that the results hereof can be used during audit meetings regarding quality of care, and to provide more insight in differences in patterns of care between regions and countries.

Side effects

Along with the introduction of new treatments and the optimalisation of standard therapies nationwide and internationally to improve survival, new risks and side effects of therapies do arise which have to be addressed. Where at the start of the TEAM trial endocrine therapy was given for five years, the current insight is to prolong the time period of adjuvant endocrine therapy up to ten years for a large part of breast cancer patients. Additionally, there is a common perception of physicians that endocrine treatment is well tolerated and less toxic compared with for instance chemotherapy, and therefore this is a not always adequately addressed during follow-up. However, it appears that up to 60% of patients discontinue their endocrine therapy and that the main reasons for non-adherence are side effects reducing patients' quality of life.[11-14] In fact, this has also been seen in the TEAM trial, with 43% of patients discontinuing their treatment within five years. Importantly, 31% of these patients stopped therapy due to side effects.[15] It also has been reported that early discontinuation of adjuvant endocrine therapy is associated with an increased mortality.[16] Moreover, there is evidence that several specific side effects are associated with superior survival outcome.[17-20] These observations together emphasize that therapy adherence is important and that this and the experienced side effects have to be given more attention. Therefore, identifying the

proper patients who benefit from endocrine therapy and preventing side-effects are very important in the treatment and support of hormone sensitive early breast cancer patients.

The differences in efficacy between tamoxifen and AIs are small and, consequently, the side effects will become more important in treatment decisions regarding the type and duration of therapy. In the TEAM trial, no differences were seen in disease free survival and overall survival at five years between both trial arms.[15] However, postmenopausal bleeding, endometrial abnormalities, and venous thrombosis were reported more often in the sequential treatment than in the exemestane treatment group. In contrast, exemestane monotherapy was associated with significantly higher incidences of musculoskeletal adverse events, osteoporosis and fractures compared to the sequential treatment. The incidence of hypertension, hyperlipidaemia and cardiac failure was also higher with exemestane alone compared with sequential therapy. Therefore, in different chapters of this thesis, (side) effects of adjuvant endocrine therapy were examined in postmenopausal, hormone sensitive breast cancer patients included in the TEAM trial.

The effect of postoperative endocrine therapy on bone health was examined in American, Belgian, Dutch and German TEAM patients using bone mineral density (BMD) and bone turnover markers. Patients using tamoxifen had an increase in lumbar spine BMD and a decrease in bone turnover markers. The opposite result was found for patients using exemestane, meaning that exemestane had a small negative and tamoxifen a positive impact on bone metabolism. These findings are consistent with data of bone studies of other AI trials.[21, 22] In general, postmenopausal women are at risk of osteoporosis. However, the changes found in our and other studies appeared to stabilise after initial treatment and bone loss is not life threatening and can be managed. Therefore, the data from our and other studies indicate that postmenopausal patients should be properly informed about these effects when prescribing an AI, and that BMD should be monitored.

The effect of endocrine therapy on breast density was examined in Dutch TEAM patients using analogue mammograms. In these postmenopausal early breast cancer patients, the baseline breast density was low and did not substantially change over time, nor for patients using tamoxifen, nor for patients using exemestane. In other AI-studies, no differences or only a small percentage breast density reduction was found.[23-25] It is possible that AIs, contrary to tamoxifen, are not associated with a change in breast density over time, especially in postmenopausal women in whom the initial breast density score is low.

As side effects can influence quality of life, the effect of endocrine therapy was investigated in Dutch TEAM patients using questionnaires of the European Organisation of Research and Treatment of Cancer (EORTC), namely the EORTC QLQ-C30 and the breast cancer module, the EORTC QLQ-BR23 at one years and after two years after start of endocrine therapy. In general, the scores for the various items did not differ significantly between patients using tamoxifen and patients using exemestane. The only clinically relevant and statistically significant difference between the two treatment types concerned insomnia, which more commonly was reported by exemestane users. Over time, quality of life scores improved, what can be attributed to habituation.

One of the problems of side effect analyses is that, in clinical practice, many side effects are underestimated and underreported, even being the case in phase III trials. The quality of life study in the context of the TEAM trial is exemplary for this, as it appeared from the questionnaires of this study that patients reported more and different side effects compared to the adverse events recorded by the physicians and health care workers on the CRFs. Another problem is that not all reported side effects are caused by the administered endocrine therapy. In the MA-17 trial, where postmenopausal early breast cancer patients were randomised between the AI letrozole or placebo after five years of adjuvant tamoxifen therapy, 16-43% of patients randomised to placebo were experiencing complaints (hot flashes, night sweats, altered sexual desire, aching muscles) which one also could attribute to the use of letrozole.[26] This phenomenon was also reported in the IBIS-II study, a breast cancer prevention trial, randomising healthy postmenopausal women between the AI anastrozole

or placebo.[27] Overall, complaints were frequently reported, also by women using placebo. Musculoskeletal side events were reported significantly more often by women taking anastrozole versus placebo, but musculoskeletal symptoms were observed by 58% of the women from the placebo group. It is important that involved clinicians recognize this, and potentially future research should address this phenomenon.

Quality of life is influenced by physical activity, and this has been investigated in Dutch TEAM patients. Questionnaires concerning quality of life and lifestyle were filled out one and two years after the start of endocrine therapy, including a pre-diagnosis lifestyle assessment. Patients who managed to maintain high pre-diagnosis physical activity levels (about ten hours an week) and a healthy body weight had a clinically relevant advantage with respect to quality of life. Unfortunately, the number of women who increased their level of physical activity after breast cancer diagnosis was insufficient to draw conclusions hereon. The results of this study however, suggest that patients themselves can influence their quality of life after breast cancer diagnosis.

In conclusion, physicians and health care workers should inform patients properly about the side effects of endocrine therapy before and during treatment. Besides, patients should be informed that not all experienced symptoms are caused by the drug taken. Moreover, (maintaining) a high physical activity level and a normal body weight should be stimulated. We think that this would increase quality of life, adherence to therapy and, as a result, efficacy of the treatment.

Biomarkers

Prognostic and predictive factors are used to categorise patients into risk groups and to identify those who really will benefit from systemic therapy. Prognostic factors estimate the patient's risk of relapse in the absence of adjuvant systemic therapy and include, amongst others, age at diagnosis, tumour size and grade, and lymph node status. Predictive factors estimate the responsiveness of a tumour to a specific treatment. Only two predictive factors are currently routinely used in clinical practice: hormone receptor content (oestrogen receptor (ER) or progesterone receptor (PgR)) for response to endocrine therapy, and overexpression of human epidermal growth factor receptor 2 (HER2) for the response to trastuzumab. The current guideline in the Netherlands recommends postoperative systemic therapy for all patients with lymph node positive disease and for patients with unfavourable lymph node negative disease (www.oncoline.nl). This means that the vast majority of patients with early breast cancer will receive systemic therapy. However, not all these patients are at sufficiently high risk of disease relapse and will regretfully be overtreated with, consequently, exposition to possible unneeded, but hindering side-effects. Therefore novel markers or novel combinations of markers are needed to further subcategorise patients into various risk groups aiming at better tailoring of particular systemic treatments in different patient subgroups.

In our study populations, we investigated the role of several potential biomarkers.

(1) Change in mammographic breast density has been suggested to be a predictive biomarker for efficacy in patients using tamoxifen whereas the effect of exemestane hereon is insufficiently unknown. In a subgroup of Dutch TEAM patients, we investigated alterations of breast density during endocrine therapy. In our population, breast density was not a prognostic marker for locoregional recurrences, contralateral breast cancer or disease free survival.

(2) The impact of COX2 expressions as potential biomarker was investigated in a consecutive series of women with early breast cancer being operated in the Leiden University Medical Centre between 1985 and 1994. COX2 expression was examined by immunohistochemistry and was scored using a weighted histoscore. In multivariable analysis, increased COX2 expression was not an independent prognostic marker for an increased risk of relapse and/or death. However, a correlation was found with COX2 expression and response to endocrine therapy.

(3) SNAIL, SLUG and TWIST are transcription factors and regulators of E-cadherin, which plays a critical role in epithelial mesenchymal transition (EMT). Accumulating evidence suggests that EMT plays a critical role in the development of inva-

siveness and metastatic potential of cancer. Using immunohistochemistry, expression of SNAIL, SLUG and TWIST were assessed in the same patient population as described for the COX2 study. The expression levels of these factors were statistically significantly associated. None of these factors were prognostic in univariate analyses. However, in ER positive tumours, SNAIL and TWIST were associated with a worse prognosis. The combination of high SNAIL and high TWIST expression was an independent prognostic factor for recurrence free period.

It should be stated that both analyses (COX2 and response to endocrine therapy and the combination of SNAIL and TWIST in hormone sensitive tumour) were subanalyses and therefore hypothesis generating analyses.

Concluding remarks

In conclusion, in this thesis various clinical aspects of mainly postmenopausal women with early endocrine sensitive breast cancer have been studied. Firstly, differences in patterns of care do exist and will probably continue to exist. This should not be an issue as long as treatment decisions are made by a breast cancer team considering the available knowledge and valid standards. Secondly, endocrine therapy is associated with various side effects becoming increasingly important as adjuvant endocrine therapy is given for extended periods of time. Patients should be informed about these side effects before and during treatment to increase adherence to therapy and eventually efficacy of this treatment. Thirdly, a countless number of prognostic markers does exists, however, only a few are used in clinical practice. The biomarker analyses we performed were hypothesis generating and further research is necessary.

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