Tailoring endocrine therapy in early breast cancer

Valorisation

Breast cancer is the leading cause of death among women worldwide.[1] During the last three decades the prognosis of women with breast cancer has improved significantly, but since the risk of recurrence remains high for at least 20 years after diagnosis, especially in case of hormone receptor positive breast cancer, it seemed logical to explore the possibilities for extending endocrine therapy beyond the standard of 5 years. Therefore, the DATA trial was designed, a phase III randomised controlled trial, investigating the efficacy and safety of 6 vs 3 years of adjuvant anastrozole in the setting of postmenopausal women with hormone receptor positive breast cancer, who received prior treatment with tamoxifen for 2-3 years. This thesis includes several analyses of the DATA trial. We aimed to guide treatment decisions in adjuvant endocrine therapy for patients with hormone receptor positive breast cancer, focussing on the optimal duration and its potential drawbacks.

The first part concentrates on the optimal duration of endocrine therapy in postmenopausal women including aromatase inhibitors. The results of the DATA trial did not show a benefit of extended endocrine therapy with aromatase inhibitors on disease free survival for postmenopausal breast cancer patients.[2] Nevertheless, we found a possible benefit in the group at high-risk of recurrence (positive lymph nodes, tumour size > 5cm). These results were in line with those of the NSABP B42 trial, and the MA.17 trial which had a similar design.[3,4] The IDEAL and ABCSG-16 trials had a different design, comparing two extended regimens (10 vs 7 years) showing no statistically significant difference on disease-free survival.[5,6]

After the publication of these trials in 2018, the guideline of the American Society of Clinical Oncology (ASCO) was updated, recommending that extended endocrine therapy with an aromatase inhibitor should be considered in postmenopausal breast cancer patients with node positive disease for a maximum of 10 years.[7] The 2018 Dutch national guideline on breast cancer recommends that extended endocrine therapy with aromatase inhibitors should be considered in the node positive subgroup, but only if patients tolerate treatment well.[8] We hope that the long-term follow-up results of these trials will provide more information on the optimal duration and answer the question if extended adjuvant endocrine therapy will result in an overall survival benefit. Currently, health care costs are a hot topic of debate. The financial consequences of extending adjuvant endocrine therapy are small. In the Netherlands, the generic anastrozole tablets cost 15,12 euro per year[9] thereby, creating higher chances of breast cancer curation.

The second part of this thesis focusses on the subgroup op women with chemotherapy induced ovarian function failure (CIOFF). This is of interest because for a long time it was unknown if these women should be treated as premenopausal breast cancer patients, with only tamoxifen, or as postmenopausal breast cancer patients with a treatment regimen including an aromatase

inhibitor. We showed that women with CIOFF, who were between the age of 45 and 52 and who had not undergone ovariectomy / used LHRH agonists, had a 12.4% chance of ovarian function recovery (OFR) during the treatment with aromatase inhibitors.[10] Moreover, the women who experienced OFR had significantly higher oestradiol levels during the treatment before OFR was established, which probably led to a worse distant recurrence-free survival and overall survival.[11] We can conclude from these results that treatment with aromatase inhibitors without ovarian function suppression or ovariectomy in women with CIOFF is not safe, even if the oestradiol and FSH levels are checked regularly and treatment is adjusted if OFR is noted. The results of these trials were also referred to in the 2018 Dutch national guideline on breast cancer, thereby warning medical professionals about the risk of OFR.[8]

The third part considers bone-health during endocrine therapy in breast cancer patients. A decrease of the bone mineral density (BMD) is a well-known side effect of aromatase inhibitors, but it was unknown into which extent. We observed that the BMD decreased during the use of anastrozole, but that the decrease was modest and partially reversible if bisphosphonates were prescribed. Moreover, the BMD recovered after the aromatase inhibitors were discontinued. At 7 years after randomization, the incidence of osteoporosis was not higher in the patients who received extended aromatase inhibitor treatment. Therefore, we believe osteoporosis should not be a major reason for disregarding extended endocrine therapy with aromatase inhibitors. Moreover, we showed that of the women with a normal BMD at the start of endocrine therapy none developed osteoporosis. This might implicate that BMD measurements could be performed less often in this subgroup of women than the currently advised in the (inter)national guidelines, with consequently lower health care costs and a lower radiation load.

We believe this research has contributed to a better care for breast cancer patients because it examines the possibilities of endocrine therapy and the precautions needed during its use, which is essential for treatment optimization and the identification of the patients who benefit most. Since millions of women worldwide are on endocrine therapy, this is also important as is research on new cancer drugs.

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