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HOW TO IMPROVE ENDOCRINE THERAPY OF BREAST CANCER

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Abstract

The characteristics of endocrine therapy have made it a standard therapy in metastatic breast cancer. Principles for endocrine therapy in the advanced situation are discussed. Recent overviews have shown a definite, although limited effect also in the adjuvant situation. Three possible ways for further improvement of endocrine therapy are discussed. Firstly, the relevance of results with endocrine therapy in advanced disease for the adjuvant situation is challenged. It is suggested that the most meaningful parameter to look for in the metastatic situation might still be the response rate. Secondly, the question is raised of more reliable predictors of effect of endocrine therapy. A possible model for testing in a neoadjuvant setting in operable cancers is suggested. Thirdly, selection criteria for drugs used in endocrine treatment are discussed, in relation to proven efficacy and short-term and long-term toxicity. As endocrine therapy in the future will probably be more frequently used in patients with better prognosis, the aspect of long-term toxicity will be of major concern.

Key words: Breast cancer, endocrine therapy, tamoxifen.

Endocrine therapy is the most important systemic treatment in breast cancer. Adjuvant endocrine therapy has recently been shown to have a definite, although limited effect on 5-year survival (1). Systemic therapy including both endocrine and cytotoxic therapy is not curative in metastatic breast cancer. Furthermore, no overall survival benefit has been shown. With a palliative intention, the systemic treatment should be aimed at an optimalization between effects and side effects. The characteristics of endocrine therapy, a well-documented palliative effect and a beneficial side effect profile, have made it a standard therapy in the metastatic breast cancer situation (2). From the very large experience of endocrine therapy in the metastatic situation and confronted with the still very limited role of cytotoxic therapy in metastatic disease, the following general statements for treatment of patients with metastatic disease could be proposed:

- No major differences in effect can be achieved with available single agent endocrine therapies.
- Side effects of the individual drug is the main determinant of choice.
- Current data give no indication of treatment choice according to disease localization or metastatic pattern.
- Endocrine therapy can often be used successfully in a therapeutic sequence, a new drug being used at relapse or failure after the previous one.

Among many aspects to be explored in order to improve endocrine therapy, the following seems to be of importance: Are results from predicitivity testing and treatment in metastatic disease relevant to the adjuvant situation? At the primary diagnosis, how can prognostic subgroups be better selected, and how can prediction of the effect of endocrine therapy be improved? Which factors are of importance in the selection of endocrine treatment strategy and in the choice of individual drug for adjuvant therapy?

Results from treatment of metastatic disease. Relevant for the adjuvant situation?

Perhaps somewhat unexpectedly, some of the adjuvant tamoxifen trials (3–5) having reached considerable maturity, show survival benefit lasting more than a few years (>5 years). An overview of the adjuvant oophorectomy trials has also shown a survival benefit (6). These results contrast to the results obtained in metastatic disease where the mean duration of objective responses is about a year (7), with very few responses lasting more than 2–3 years.

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However, the survival benefit seen in the adjuvant situation could, at least theoretically, still be a delayed effect, where the difference in time between the adjuvant and the metastatic disease situation could be explained by differences in tumor burden and endocrine sensitivity.

If there is a true, lasting survival benefit in breast cancer patients treated with adjuvant endocrine therapy, not seen in patients with metastatic disease, this implies that the results from the treatment of metastatic disease is not directly applicable in the adjuvant setting. This could again imply that an increase in response rate might still be a meaningful objective in the metastatic situation, so that the results in the adjuvant setting can be further improved. Clinical research undertaken to improve response rates has followed two treatment strategies, either concurrent combination therapy or alternating treatment (8). Some trials from both strategies have resulted in increased response rates, but without any measurable improvement in survival (8). The prospects for alternating therapy have recently been discussed (9). The Norwegian Breast Cancer Group has as first-line endocrine therapy after recurrence randomized receptor positive patients between tamoxifen and an alternating treatment with tamoxifen and medroxyprogesterone acetate, changing between the two drugs every 8 weeks, starting with tamoxifen. The response rate in the tamoxifen arm was 42%, increasing to 65% in the alternating arm (10). Although indicated, no statistically significant survival benefit from the alternating treatment was found.

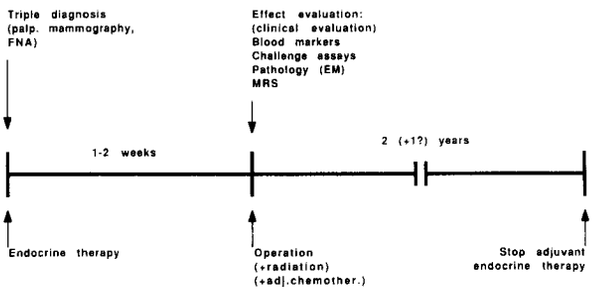

Fig. 1.

will have to await new prospective clinical trials both in the metastatic and adjuvant situation. Another more theoretical proposal for the selection of patients to endocrine therapy is shown in the Figure. After triple diagnosis (palpation, mammography and fine-needle aspiration) endocrine treatment is started before local therapy. The drug/combination of drugs used as endocrine therapy should preferably have fast pharmacokinetics. After 1–2 weeks, operation (plus radiotherapy, if needed) is performed with an effect evaluation and receptor measurements. Possible evaluation parameters are suggested in the Figure. Based on the effect evaluation 3 possible outcomes are predictable. 1) If positive effect, continue treatment with the same drug for 2 (+1?) years. 2) If no effect, but positive receptors, change drug/combination. 3) If no effect, and no receptors, no further endocrine adjuvant therapy.

Can an effect of endocrine therapy more reliably be predicted?

The role of steroid hormone receptors as reliable indicators of endocrine sensitivity in breast cancer tissue has been repeatedly shown (11). However, a discrepancy seems again to exist between the metastatic disease situation and the adjuvant. Steroid receptor presence are powerful predictors of effect of endocrine therapy in metastatic disease (11), while this could not be shown in an overall analysis of the adjuvant tamoxifen trials (1). As some of the individual adjuvant tamoxifen studies clearly show an interaction between treatment and receptor status (12–14), further studies are needed for a conclusion.

As about 50–60% of the receptor positive patients (ER+, PgR+ or both) respond to therapy, there is clearly a need for further improvement in predictivity to successful endocrine therapy. We have measured androgen receptor (AR) in 1 026 breast cancers (852 primary ones) and found it to be present in 85% of the primary tumors (15). About 10% of the primary tumors and 25% of the metastatic tumors were AR+ and ER− and PgR−. This might explain differences in efficacy between progestins, showing androgenic activity, and non-androgenic endocrine treatment. The usefulness of an addition of AR

How do we select drugs for adjuvant endocrine therapy?

The survival benefit shown in both the tamoxifen and oophorectomy overviews (1, 6) will definitively stimulate new research for further improvement. One important aspect will also be to select the best drugs for adjuvant treatment. Important aspects of the drugs in addition to their proven efficacy will relate to acute and long-term side effects. The acute side effects (defined by their appearance during therapy) can be classified according to seriousness and tolerability (which is related to compliance). There is an obvious demand for drugs fulfilling these requirements. The long-term effects (appearing after years) are much more difficult to evaluate. This is partly related to lack of knowledge about long-term effects of drugs used for this purpose, and partly related to the fact that long-term side effects are connected to mechanisms of action and thereby to the effects of the drug. Important long-term effects are consequences of changes in bone mineral and lipid metabolisms, teratogenicity and carcinogenicity. Main aspects to consider when choosing drugs or endocrine treatment strategies are age of patient, i.e. pre- or postmenopausal, overall prognosis for the patient group, status of the endogenous estrogens in the individual patient, all related to the properties of the drug(s) to be used. In a

recently published article an increased risk of endometrial carcinoma was suggested in patients treated with tamoxifen in the adjuvant situation (16). This possibility should be suspected from the estrogenic properties of the drug (17). There is an obvious need for careful long-term follow-up in the ongoing and future studies, also with regard to side effects.

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