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Primary endocrine therapy of locally advanced breast cancer patients

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ABSTRACT

Primary endocrine therapy has been traditionally reserved for elderly and unfit locally advanced breast cancer patients (LABC patients). In this group, the primary endocrine therapy could not be adequately compared to primary chemotherapy. Rare studies of primary endocrine therapy, and careful subgroup analyses of their results, showed that primary endocrine therapy could achieve at least the similar magnitude of response rate, compared to primary chemotherapy, in selected patients' population. Thus, the primary treatment with tamoxifen in steroid receptor (SR)-positive LABC patients became the standard arm in current studies of primary endocrine therapy. Several questions, concerning the use of endocrine primary treatment in routine clinical practice, should be answered, including the definition of optimum endocrine agents, biomarkers for prediction of response, and patients' selection criteria.

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INTRODUCTION

Primary treatment of breast cancer (BC) is the term determining usually the first systemic treatment used in the management of the disease. When it is used before surgery, appropriate terms are "neoadjuvant" or "preoperative". However, primary treatment of locally advanced breast cancer (LABC) includes also other treatments (surgery and radiotherapy) in various sequences with systemic therapy. In fact, the most investigated primary treatment of LABC has been the chemotherapy. This assumes that the LABC is an aggressive disease, although not disseminated, requiring rapid tumor reduction and subsequent multimodal treatments, including surgery and/or radiotherapy and the adjuvant or maintaining systemic therapy. The endocrine therapy was less investigated as the primary treatment of LABC, mainly due to the fact that its effect is not immediate, allowing the tumor growth during first months. Thus, it was considered mostly in elderly or unfit patients, to whom the chemotherapy could not be safely delivered. So, the main goal of primary endocrine therapy, at least in the earlier studies, differed from the aims of primary chemotherapy: Instead of the decrease of tumor size to allow any surgery, or less radical surgery, its goal was to avoid surgery. However, lessons from the metastatic and adjuvant settings suggested that hormonal therapy could achieve at least the same magnitude of benefit in the selected group of patients, as could the chemotherapy. Thus, the aim of the recent studies becomes - to define the patients' population for whom the endocrine primary therapy could be the treatment of choice. Secondly, the current studies are intended to find out the optimal endocrine agents for primary use, as well as to define the clinically valuable predictive factors.

PRIMARY ENDOCRINE THERAPY INSTEAD OF MULTIMODAL TREATMENT

Tamoxifen (TAM) has been first used as the only treatment of BC, either resectable or locally advanced, for those patients who are frail or unfit for surgery and/or radiotherapy, due to the advanced age or comorbid status. The first studies showed that tamoxifen could be an alternative to surgery or radiotherapy for those patients, who otherwise could not be treated at all. Namely, the objective tumor response rate was relatively high: up to 81%, including 30% of disease stabilization, in the study of Preece et al. (1); or 61% with 27% complete tumor regression in a study of Bradbeer and Kyngdon (2), etc. However, the local recurrences were more frequent, compared to those patients treated with surgery plus tamoxifen (3,4).

In addition, the importance of the clinical response was noted as early as in the study of Preece et al. (1), and in a later reports of these results (5): 5-year survival rate was significantly higher in patients whose response was classified as complete remission, compared to whole group (92% vs. 49.4%). Thus, tamoxifen seemed to be not sufficient for local and/or systemic control of the disease; it may delay definitive treatment, may help in case of contraindications for other multimodal treatments, and may substitute successfully other treatments only in about 30% of BC patients with localized disease. It was recommended to use tamoxifen alone instead of surgery and/or radiotherapy only in patients with LABC, who are frail, elderly or otherwise unfit for other treatments.

Most studies, especially those including the elderly patient population, did not routinely determine and report the estrogen receptor (ER) status, based on the finding that ER was more frequently present in elderly patients. In a study undertaken in Edinburgh, patients with large operable BC were treated with primary tamoxifen, and then with chemotherapy only in case of local failure after three months of treatment. The early results showed the local response in 39% patients, all of them having been ER-positive (6). After this, the study design was changed: endocrine primary treatment was selected only for ER+ patients, and chemotherapy for those who failed to respond to primary endocrine treatment or were ER-negative. Similar results, regarding the relevance of ER status, were reported by others (4,7,8,9).

PRIMARY ENDOCRINE THERAPY vs. OTHER TREATMENT MODALITIES

Tamoxifen vs. surgery + tamoxifen

In Italian study of the Group for Research on Endocrine Therapy in the Elderly (GRETA), significantly higher rate of local progression was found in TAM group of elderly patients with operable BC, compared to the group treated with surgery + TAM. Locally progressive tumors in TAM group were treated with delayed surgery. Since long-term results concerning the disseminated disease and OS were similar, it was concluded that the delayed surgery did not jeopardize the overall results (3).

Tamoxifen vs. radiotherapy

In Nottingham study, tamoxifen primary treatment was compared to radical radiotherapy, but in a dose of 40 Gy, in 143 postmenopausal LABC patients (10). Response rate (OR), including disease stabilization, was similar (78% vs. 89%), as well as median response duration (12 months in both groups). When local failure occurred, patients crossed over the treatment: the OR + SD rate and duration of response was similar. After a median follow-up of 10 years, slightly better progression-free interval was found in favor to tamoxifen, but no difference in survival.

Tamoxifen vs. multimodal treatment

The same group in Nottingham undertook another study in a group of LABC patients, to compare the commonly used multimodal treatment (consisting of neoadjuvant chemotherapy, surgery, postoperative radiotherapy and adjuvant endocrine therapy), to the initial endocrine therapy + further therapy in case of tumor progression. The study was small (56 and 52 consecutive patients), but very informative, because patients were in a good overall condition, suited for standard treatment. The first results reported at 6 months therapy, showed the objective response rate (OR) of 57% to primary chemotherapy, and OR of 36% (plus additional 32% of SD) to tamoxifen (11). Multimodal treatment gave better loco-regional control and longer disease-free interval. However, similar survival rate, similar rate of distant relapse, and very importantly - similar rate of uncontrolled locoregional disease was found. Later report of this study also confirmed that ER-positive patients showed better survival, better locoregional control and lower rate of distant failure (9). This study showed that the use of consecutive therapies instead of initially multimodal, does not compromise the overall outcome and, thus, may avoid numerous unnecessary therapeutic procedures, at least in some patients, especially those with receptor-positive tumors.

PRIMARY ENDOCRINE THERAPY AS A PART OF MULTIMODAL TREATMENT FOR LABC

Since the goal of early studies in elderly was to avoid surgery and/or radiotherapy, the locally advanced and large operable or operable BCs were not exactly discerned. When it was shown that primary endocrine therapy may be equivalent to primary chemotherapy, the need of definition of treatment conditions and response assessment became apparent, as well as definition of some differences, compared to chemotherapy.
At first, it was necessary to confirm the clinical relevance of locoregional disease stabilization for at least 6 months on endocrine therapy; then, to define the necessary treatment duration, and finally to define the selection criteria for primary endocrine therapy.

Static disease

Robertson et al. (12) reported the results of endocrine first- and second-line therapy in 255 metastatic and locoregional BC patients, assessed for response according to UICC criteria. It was shown that patients with complete response (CR), partial response (PR) and static disease (SD) survived significantly longer, than those with progressive tumor (PD) did. The same result was obtained both for first-, and second-line endocrine therapy. Durable SD was confirmed as clinically useful criterion of therapeutic response, either in metastatic or operable BC patients.

Local tumor response and its duration

Italian study showed the CR, PR, Minor response, SD and PD in 10%, 38%, 8%, 36% and 7.5% of patients, respectively. This was dependent on ER status in a subset analysis (4). Overall 5-year response rate duration was found in 31% patients. Similar response rate was obtained in other studies. In the other Edinburgh study, median response duration was 47, 26 and 15.5 months for CR, PR and SD, respectively (13). About 10% of tumors progressed initially. Bergman et al. (14) found 15.3% of initial progression in elderly BC patients with loco-regional disease treated with primary tamoxifen, 25% of later tumor progression in partial responders, 49% subsequent tumor progression in those with static disease, while in complete responders, there were no tumor progression by the closing date of the study.
It seems that the role of the complete tumor regression in elderly patients on primary endocrine treatment is more important than in younger patients, because of their shortest lifetime: it allows the definitive local control, without surgery and radiotherapy.

Time to best response and duration of primary treatment

Median time to best response was found to be 13.5 weeks for CR, and 14 weeks for PR in one study (13). In Italian study, the best overall response to tamoxifen was found in 43% after at least 6 months, and in 57% of patients after 12 months of treatment (4). These results suggested the need for longer duration of primary endocrine therapy, compared to primary chemotherapy.

Overall survival

One of the main goals in neoadjuvant or preoperative systemic treatment is certainly to improve the overall survival. Randomized studies of primary endocrine treatment with tamoxifen, in general, did not find any difference in terms of survival, in comparison to standard treatment modalities (9). There are many reasons why the survival analysis is not simple. First of all, there are no yet meta-analyses of the survival data. Then, primary endocrine therapy is still selected for the elderly population of patients. Earlier clinical studies with the longer follow-up, selected mostly elderly, unfit patients, or those with other chronic diseases. In such studies, the proportion of non-breast cancer-caused mortality must be higher than in general population. Finally, further treatment in failing patients could also be compromised with the same comorbid circumstances. Anyhow, it was found that the factors, which influenced the survival, were tumor response to primary endocrine therapy and ER status, and in surgically treated patients - nodal status and the number of involved nodes (15).
The most important finding from those studies was the fact that delayed surgery, radiotherapy, and even chemotherapy did not compromise significantly the local control of the disease and the overall outcome. Or in other words, by giving the primary endocrine treatment in selected population of patients, we do not expose them to any risk of ineffective treatment modality.

SELECTION CRITERIA

Since the primary chemotherapy is the optimum choice for majority of LABC patients, extremely important became the selection criteria for primary endocrine therapy. Prediction of response to primary endocrine treatment is the key element of the whole treatment efficacy, i.e. of the best patients' and treatment selection. Several biomarkers, beside ER, are currently investigated as predictors of response to neoadjuvant chemotherapy (16), endocrine therapy (17) or both (18). In addition, the selection of optimum endocrine agents remains to be elucidated.

Biomarkers as predictive factors

Biomarker studies in LABC have been, generally, undertaken with the several goals. First of all, the retrospective studies had the goal to determine the ER, or both ER and PR status in patients having been treated with primary endocrine therapy. It was generally accepted that the best response was obtained in ER-positive or ER-rich tumors, better locoregional control, better response to subsequent endocrine treatment, etc. (1,4,7-9,19). Further, several biomarkers are investigated in the aim to improve the selection of ER+ patients for primary endocrine treatment: it is well known that estrogen receptor is clinically relevant, but not ideal predictor of response to endocrine treatment. In that line are the studies of pS2 protein (20), bcl-2, marker of anti-apoptosis, but estrogen-regulated (21), and others. In the first study, it was found that pS2 protein significantly added prognostic information to ER-positivity; the later one suggested that response to tamoxifen might involve changes in proliferation and susceptibility to apoptosis. Finally, the biomarkers are investigated initially and sequentially during the primary endocrine therapy to learn out more about biology and pathology of BC. For example, it was found that several biomarkers indicated differences between tamoxifen and letrozole in changing features of BC cells during neoadjuvant treatment (17). Soubeyran et al. (22) found protein expression modification consistent with clonal selection of tumor cells, rather than phenotype changes. However, most exciting are studies of BC gene expression, promising new insights into the biology of BC, prognosis and resistance to the commonly used treatments (18).

Optimum endocrine agents for primary endocrine therapy

A small phase I/II study of letrozole for 3 months in ER+ LABC patients showed the impressive response rate of 92%, allowing the conservative surgery in most included patients. (23). Thus, the introduction of third-generation aromatase inhibitors in the treatment of LABC initiates a serial of clinical investigations with these potentially more efficacy agents (24). Based on the previous studies, tamoxifen becomes the standard for comparison. In a large international study, it was found that 4-months preoperative treatment with letrozole increased the proportion of the chance for conservative surgery in ER/PR+, postmenopausal LABC patients from 35% on tamoxifen, to 45% (25). Although it was thought that the aromatase inhibitors acted more rapidly than tamoxifen, a recently reported study showed that 8 months might be better than 4 months of pre-operative letrozole treatment, due to the increased percentage of delayed responses (26). Concerning the anastrozole studies, again a small pilot study of Dixon et al., (27) showed a better reduction in tumor volume, suggesting the large studies of Arimidex, in comparison to Tamoxifen in postmenopausal receptor-positive women with LABC or large potentially operable BC.

The pure anti-estrogens and LH-RH analogs for premenopausal patients are also in the focus of currently designed clinical studies.

CONCLUSION

Neoadjuvant or primary endocrine treatment of LABC and operable BC provides the advantages over classical adjuvant studies. According to Ellis (28), it allowed rapid information in the new drug development area. It allowed the sequential tumor sampling for scientific research of cell biology, including the genetic profiling of estrogen (in)dependent BC. Finally, current and future studies will be addressed to compare neoadjuvant chemotherapy with primary endocrine therapy, and to establish its role in the routine clinical practice.

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