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Maintaining treatment of locally advanced breast cancer

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ABSTRACT

Locally advanced breast cancer is a specific clinic entity, comprising various degrees of breast cancer local and regional extension. This term is applied to nonmetastatic large primary tumors (including inflammatory breast carcinoma), with or without extensive regional lymph node involvement, with a rapid or slow evolution, and usually with poor prognosis. This clinical presentation of mammary carcinoma is common in developing countries (30% to 60%), but also with a remarkable incidence in developed countries (10% to 20%). During many decades patients were treated with radical surgery or radiation therapy and with their combination, but always with poor results. The inclusion of neoadjuvant chemotherapy in the treatment enabled more favorable treatment results. The mortality from disseminated disease is the main problem in these patients, inducing the question of need for additional postoperative adjuvant systemic therapy. For steroid receptor positive patients hormonotherapy is a convenient choice of maintaining treatment. In endocrine non-responsive tumors, the role of postoperative chemotherapy is doubtful, having in mind preoperative chemotherapy and cumulative toxic effects. New trials including the large number of patients are necessary to obtain the definite answer whether the maintaining chemotherapy is useful, but today it seems that additive postoperative treatment is not more efficient than preoperative alone.

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INTRODUCTION

Locally advanced breast cancer (LABC), as a specific clinic entity, comprises various degrees of breast cancer local and regional extension. To put it simply, this term is applied to nonmetastatic lesions of large size, usually with poor prognosis. Various clinical presentations are characterized by presence of a large primary tumor and/or extensive regional lymph node involvement, but always with the absence of any evidence of distant metastases. Patients can have T3 or T4 tumors with any N stage, or any T category with nodal involvement N2 or N3, and also regional metastatic involvement (M1). Inflammatory breast carcinoma is also included in LABC category (1,2).
The biological behavior of LABC can be very heterogeneous, with a rapid evolution, but also with a long history of slow tumor growth (1).

EPIDEMIOLOGY AND CLINICAL COURSE OF LABC

Locally advanced breast cancer is a common clinical presentation of mammary carcinoma in developing countries (30% to 60%). In developed countries its incidence is also remarkable, in spite of better chances for early diagnosis. The incidence of LABC in USA is between 10% and 20% of all newly diagnosed breast cancers (1).
For a long time LABC represented very unfavorable clinical presentation of the disease, because of limited abilities of local treatments. During many decades patients with LABC were treated with radical surgery or radiation therapy, very often with their combination in different sequences, but always with poor results. The group from Milan analyzed results of such treatment of the large population of 454 patients, and found median survival 2.5 years with only 10% of patients surviving 4 years (3). The inclusion of neoadjuvant chemotherapy in the treatment essentially transformed the management of LABC, enabling more favorable treatment results (1).

COMMON THERAPEUTIC APPROACHES IN LABC

The favorable fact that the breast cancer is hemosensitive and endocrine-dependent tumor enabled good results in treatment of all stages of this neoplasm. Patients with early breast cancer achieve better overall survival and longer disease-free survival due to systemic adjuvant treatment (4,5). A high proportion of patients with disseminated disease respond to measures of systemic treatment, enabling prolonged survival with better quality of life (6). A long period of investigation and numerous randomized clinical trials obtained a huge data pool and enabled assessment of the most favorable approach in treatment of early breast cancer and in metastatic disease.
There are also the official documents, such as Minimal Clinical Recommendations proposed by ESMO, being the practical guidelines for everyday practice, out of clinical trials (7). In Serbia similar recommendations were also officially accepted, obligatory for medical practice (8). The mentioned documents comprise precisely proposed rules for standard treatment, and an oncologist has no doubt how to treat patients with early breast cancer or with disseminated disease. The situation with locally advanced breast cancer has not been cleared up yet. So, there is still a dilemma how optimally to treat each new patient, avoiding both undertreatment and overtreament. This is a result of the fact that LABC is less common in industrialized countries, and the heterogeneity of this disease makes the performance of controlled trials more complex (1). So, the overall knowledge about the best sequential treatment of LABC is still insufficient.
In the mid of the 70s some investigating groups tried to overcome such situation and initiated a new approach based on combined modality treatment, designed with intention to increase local and systemic control of LABC. Such treatment included preoperative (so-called primary or neoadjuvant) combination chemotherapy, followed by local treatments (surgery, radiation, or both), and sometimes followed by adjuvant chemotherapy or hormonotherapy.
The greatest merit for better understanding of this entity belongs to the group

from Houston. Their research begun in1974, and in next twenty years they enrolled near six hundred patients in several studies (1). In early studies they used three cycles of FAC regimen, following by locoregional treatment, and after that further FAC treatment until completing 450 to 500 mg/m2 of doxorubicin. The therapy was continued with CMF regimen until completion of two-year treatment (9). In next studies they confirmed the superiority of anthracycline-containing regimens. Compared to their historical institutional experience, the local control rate, five-year and ten-year disease-free survival, and overall survival were substantially improved (1). Early studies of the Milan group also obtained encouraging results (3). The group from Brussels sequently used radiation, preoperative and postoperative hormonochemotherapy and surgery. They preformed operation two months after beginning of treatment, continued postoperative chemotherapy during next ten months, and also recorded better results (10). One of the biggest studies was EORTC trial, involving 410 patients. Their conclusions were similar (11).

There are also numerous smaller trials; as incidence of LABC is less common in industrialized countries, the most of performed trials included small numbers of patients. Because of that, statistical significance was inevitably low, and sizable differences in outcome could easily have been overlooked (1). Including of taxanes in neoadjuvant chemotherapy of LABC, especially in patients refractory to standard anthracycline-based chemotherapy, offers new chance for better outcome (11).

RATIONALE FOR THE MAINTAINING TREATMENT

The mortality from disseminated disease remains the main problem in patients with LABC. This situation induces the question of need for additional postoperative adjuvant systemic therapy. In case of known steroid receptor status, the majority of medical oncologists should continue treatment in receptor-positive patients as hormonotherapy. In situations when the tumor is not responsive to endocrine therapy, emerges the question of postoperative chemotherapy, doubtfully efficient and undoubtedly toxic.

Possible postoperative chemotherapy has to be individually tailored and based on the knowledge of risks for relapse, e.g. chance for presence of residual tumor cells.

When planning the treatment of patients operated for early breast cancer, well-known prognostic factors to assess the risk of relapse and a need for adjuvant chemotherapy are used. The patients with LABC have the signs of high risk for dissemination (a large primary tumor, extensive nodal involvement) even at the presentation; as a result of that, the mortality from metastatic disease is the greatest problem in this group of patients. From this point they would evidently deserve adjuvant treatment (12).

But this group of breast cancer patients is specific because they are treated with cytostatics before surgery. The question remains, is the preoperative therapy enough to eradicate micrometastatic deposits? In case that residual tumor cells are present in the body, is there a need for further chemotherapy? Even cytological confirmation of the presence of micrometastases does not mean that relapse is inevitable (13). It seems that peripheral blood circulating tumor cells have a little relevance in such assessment (14). Remained cells can be destroyed by body's defense mechanisms; also these cells can be dormant and dorm forever, or at least for some decades, overwhelming the expected life span of the patient. But they can also wake up at once and include themselves in the cell cycle. The removal of the primary tumor is the best-known stimulus for growth of micrometastases.

Experimental data show that its removal stimulates growth of residual tumor tissue, conversing cells from G0 phase into proliferation (15). In animal models it was confirmed that primary tumor removal produces increased proliferation of cells in metastatic foci, and also that chemotherapy applied before operation better suppress cell proliferation than given in days after resection (16). These findings refute the premise that removal of a primary tumor is a local phenomenon with no other biological consequences. They indicate that, following primary tumor resection metastatic behavior may be affected by interplay of growth factor(s) that can influence the outcome of a host to its tumor (17, 18, 19). From this point, preoperative chemotherapy as adjuvant treatment should be a better choice than postoperative. Houston group recognized that extended treatment was not more efficient than shorter one and leaved maintenance chemotherapy used in first trials. They concluded that maximum impact of cytostatics was achieved during the initial six months of chemotherapy (9).

The Amsterdam group proposed an interesting hypothesis that the presence of primary tumor during prolonged neoadjuvant chemotherapy has favorable influence on tumor specific cytotoxic T-cells activation, and on inhibition of angiogenesis in micrometastatic foci. In a trial including relatively small number of patients they found that better end-results are associated with the extended number of preoperative chemotherapy cycles (20). Other authors confirmed enhancement of immune mechanisms by chemotherapy (21), and that the prolonged neoadjuvant chemotherapy for LABC causes better disease-free survival and overall survival (22). The development of metastatic disease many years after the completion of treatment of LABC had been completed proves that some malignant cells survived initial neoadjuvant chemotherapy. Patients treated for early breast cancers can also develop metastatic disease in spite of adjuvant chemotherapy after resection; it must be recognized that the efficiency of such treatment is still limited, making also doubtful additive adjuvant chemotherapy for patients with LBC.

Patients with operable breast cancer, treated with neoadjuvant chemotherapy, and achieving complete abolition of their primary tumor obtain the greatest survival advantage. Relapse-free survival was the best in women whose tumors showed complete pathologic remission, or at least complete clinical remission, compared with those showing partial response or no response. Tumor response to preoperative chemotherapy correlates with outcome and could be used for evaluating the effect of chemotherapy on micrometastases (23). Based on that observation, patients with LABC who showed complete response would not be candidates for additive postoperative chemotherapy, because of excellent response and expected total clearing of malignant cells pool. Should the patients without such response be treated with additive chemotherapy?

In patients with operable breast cancer, the benefits of preoperative approach are not only the increased number of candidates for breast-conserving surgery, but also the therapy tailored to the biological characteristics of the individual tumor. If the patients do not respond to standard, anthracycline-based neoadjuvant regimen, the response could be achieved by switching to taxanes. Long-term outcomes appear similar, regardless of whether chemotherapy is given preoperatively or postoperatively (24). So, the majority of patients with LABC can be successfully treated preoperatively, without the needs of maintaining therapy.

THE CHOICE OF SYSTEMIC MAINTAINING TREATMENT

The problem of choosing proper chemotherapeutics appears in case when postoperative chemotherapy for LABC is necessary. The good response manifested as shrinkage or disappearing of primary tumor confirms that the choice of used drugs was correct, but should the same drugs be used in case of continued cure? Is the chemosensitivity of the cells in the metastatic deposits the same? What to do in situation if the primary chemotherapy had destroyed all sensitive cells and mutant resistant clones remained? In that case, is there indication for a second-line therapy, using the different drugs? Is it possible to predict which combination would be superior (25)? What about the risk of secondary malignancies in patients overtreated by cytostatics, specially the leukemogenic effect of higher cumulative dose of anthracyclines (26, 27)?

So, after primary chemotherapy and consecutive local treatment two approaches remain for patients with high risk of metastatic relapse:

1. Careful follow-up and possible systemic treatment in case of verified dissemination

2. A new, adjuvant chemotherapy as an attempt to prevent the relapse

Nowadays, it is unknown which of these strategies is optimal in term of tumor control. Therefore, well-designed, multicentric randomized clinical trials are needed to determine the optimal strategy. The all mentioned support the need for a prospective randomized trials to address this question (1). Taking in account the achievements obtained due to studies of Early Breast Cancer Trialists' Collaborative Group, we need the multicentric trials including the large number of patients, and conducted by a new "Locally Advanced Breast Cancer Trialists' Collaborative Group".

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