Journal of BUON **8:** 317-320, 2003

REVIEW ARTICLE

Simultaneous or sequential chemotherapy for locally advanced breast cancer

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Summary

Chemotherapy of breast cancer is still an area of intensive research. Based on mathematical model of tumor cell growth kinetics, a novel concept of chemotherapy in breast cancer was launched which implies dose-densification of chemotherapy through the use of sequential non cross-resistant single agents or regimens. The relative infrequency of locally advanced breast cancer (LABC) has limited the speed of clinical progress in this area. The introduction of primary (neoadjuvant) systemic chemotherapy (PSCT), however, improved the outcome of patients with LABC. The first data concerning neoadjuvant sequential chemotherapy were related to primary operable breast cancer. Many studies, using the two most active classes of cytotoxic drugs, anthracyclines and taxanes, in primary breast cancer, showed that sequential PSCT was superior to simultaneous combination chemotherapy in terms of enhancing the rates of patients rendering suitable for breast-conserving (BC) treatment. There are few trials dealing with sequential PSCT in LABC. In the majority of them sequential dose-dense PSCT was administered because the rapid delivery of the most active cytotoxic drugs (anthracyclines and taxanes) is necessary to achieve reduction of the size of the primary tumor, to increase the possibility of BC treatment and to eliminate occult distant micrometastases, contributing thus to possible prolongation of survival. This article summarises recent data concerning sequential PSCT in LABC in order to evaluate its possible use in clinical practice.

Key words: locally advanced breast cancer, primary systemic treatment, sequential chemotherapy

Chemotherapy of breast cancer is still an area of intensive research. The development in this area followed a path similar to chemotherapy in other solid tumors and hematologic malignancies. Before 1970, almost all trials were based on the use of single-agent chemotherapy. Thanks to these studies the single-agent activity of active drugs was defined [1]. After the early successes of combination chemotherapy in hematologic malignances, multidrug regimes were developed for breast cancer as well. In the pre-taxanes era reviewed randomized clinical trials of metastatic breast cancer showed an increase in overall survival favoring combination chemotherapy over single agent chemotherapy [2]. Norton and Day have analyzed the clinical data from multiple adjuvant studies and from available studies of untreated patients with localized disease [3]. In each clinical study, the Gompertzian model precisely fitted the growth curves of these tumors [4]. Based on this mathematical model of tumor cell growth kinetics, first reported by Norton, a novel concept of chemotherapy in breast cancer was launched, which implies dose-densification of chemotherapy through the use of sequential non cross-resistant single agents or regimens [5]. The importance of sequential chemotherapy was especially increased with the introduction of taxanes.

LABC is relatively uncommon, accounting for 10-20% of newly diagnosed breast cancer cases. Maybe this relative infrequency of LABC has limited the speed of clinical progress in this area. Also the

Received 30-06-2003; Accepted 23-07-2003

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definition of LABC itself is variable. It encompasses a heterogeneous group of patients, including those with neglected, slow-growing tumors, as well as those with biologically aggressive disease. The majority of the investigators include patients with T4b N1-2 M0, i.e. clinical stage IIIB. Patients with LABC treated using surgery and radiotherapy (RT) showed very poor survival [6]. The introduction of primary chemotherapy, however, significantly improved the outcome of these patients [7,8]. Primary chemotherapy in LABC, apart from reducing the distant failure rate and the extent of the operative procedure needed to render a patient grossly free of disease, it also represents an *in vivo* chemosensitivity assay.

Because of the relative infrequency of LABC, the first data concerning sequential primary chemotherapy were related to primary operable breast cancer. Administration of the two most active classes of cytotoxic drugs in primary breast cancer, anthracyclines and taxanes, was more frequently used than other drugs. Referring to primary endpoint analysis of the GEPARDUO study, which compared dose-dense with sequential adriamycin/docetaxel (AT) combination as preoperative chemotherapy in 913 operable breast cancer patients, Loehr et al. concluded that sequential adriamycin/cyclophosphamide (AC)-T is superior to the shorter dose-dense AT schedule in terms of pathological (p) complete response (CR) (breast+axilla), clinical (c) response rate (RR) and breast conservation rates [9]. In the European Cooperative Trial (ECTO) study, PSCT in operable breast cancer patients with sequential AT and cyclophosphamide, methotrexate and 5-fluorouracil (CMF) produced cCR in 52% of the patients (27% after AT and 25% more after CMF), with pCR in 23% of them. Conservative surgery was possible in 71% of the patients and the frequency of pathologically negative lymph nodes was 61%, as reported by Gianni et al. (38th ASCO meeting, 2002) [10]. In the same meeting, the preliminary results of the Arbeitsgemeinschaft Gynakologische Onkologie (AGO) study were also presented. In this study patients with locally advanced primary tumors or inflammatory carcinoma of the breast were randomly assigned to receive epirubicin (E) and paclitaxel (T), either as dose-dense sequential chemotherapy or simultaneously. Data from 475 patients demonstrated statistically significant differences favoring sequential over simultaneous chemotherapy in terms of higher frequency of BC surgery, pCR and negative axillary lymph nodes at surgery [11].

Combination *versus* sequential doxorubicin and docetaxel as PSCT for breast cancer, stage II or non-inflammatory stage III, was addressed in a randomized pilot trial conducted by the Hoosier Oncology Group [12]. Sequential chemotherapy with doxorubicin 75 mg/m^2 every 2 weeks for 3 cycles followed by docetaxel 100 mg/m^2 every 2 weeks also for 3 cycles were compared with combination chemotherapy with doxorubicin 56 mg/m^2 plus docetaxel 75 mg/m^2 every 3 weeks for 4 cycles in 40 randomly assigned patients. The cumulative dose of both drugs was identical, but the dose intensity was 50% less in the combination as compared with the sequential schedule. Although clinical responses were similar in both groups (ORR-87%, cCR-20%, pCR-13%), the patients who received sequential chemotherapy had significantly less positive lymph nodes. Myelosuppression was severe in both groups, but hand-foot syndrome was more common after sequential chemotherapy. The encouraging results of this study should be interpreted cautiously due to the small number of patients.

There are few trials dealing with sequential PSCT in LABC. In the majority of them sequential dose-dense PSCT was used [13] because the rapid delivery of most active cytotoxic drugs (anthracyclines and taxanes) is necessary to achieve reduction of the size of the primary tumor, to increase the possibility of BC treatment and to eliminate occult distant micrometastases, contributing thus to possible prolongation of survival. The results of the prospective randomized AGO trial showed that dose-dense sequential PSCT with paclitaxel and epirubicin resulted in significantly higher BC treatment rates, even in advanced cases [14], confirming that sequential dose-dense PSCT produced better results than simultaneous administration of the same drugs. During the 39th ASCO meeting O'Regan et al. also reported that docetaxel (D) given simultaneously with doxorubicin and cyclophosphamide (AC) does not appear to be as effective as sequential AC followed by D in the preoperative setting in stage III breast cancer [15]. In the same meeting, Ezzat et al. reported the results of the study in which 3 cycles of doxorubicin (A) were followed by 3 cycles of paclitaxel (T) and 3 cycles of cyclophosphamide (C) in 2-week intervals, as PSCT to patients with LABC [16]. The clinical response reached 100% (cCR 73%) and pCR was confirmed in 41% of the patients. This result is very important since pCR is a good indicator for the overall disease outcome and a very strong predictor of survival. Another study, conducted by Ambulkaar et al., evaluated the clinical efficacy of sequential PSCT with 3 cycles of docetaxel followed by 3 cycles of combination of epirubicin and cyclophosphamide (EC), at conventional 3-week intervals, in patients with large or LABC [17]. Assessing the response after every 3

cycles, the authors were able to evaluate the *in vivo* chemosensitivity to docetaxel and EC as PSCT separately, and found that the overall clinical response rate to docetaxel was 92.5% and to EC 86.95%. Besides this very important *in vivo* assessment of chemosensitivity of the primary tumor, BC treatment was possible in 84.61% of the patients and pCR was confirmed in 15.38%. The results of this study should be interpreted cautiously due to the small number (40) of patients. Fernandez Morales et al. also reported the results of a small pilot study with 26 patients with LABC, in whom they obtained similar results with sequential PSCT consisting of 4 cycles of EC given at 3-week intervals, followed by 6-8 weekly administration of docetaxel [18]. Two more trials from the USA and UK also documented that sequential PSCT in patients with LABC enabled downstaging of nodal disease and high rate of BC treatment [19,20]. In the trial from the UK, Davidson et al. observed that patients with pCR could be managed without breast surgery with no impact on local recurrence rate [20].

In a recent study for metastatic breast cancer, sequential chemotherapy displayed a safer hematological toxicity profile than simultaneous treatment [21]. But in sequential dose-dense regimens, even with G-CSF support, grade III/IV neutropenia was seen in half, and febrile neutropenia in one third of the patients [16]. No cardiotoxicity was noted in sequential dose-dense regimens with anthracyclines and taxanes [22,23], but more than one third of the patients experienced sensorial peripheral neuropathy [16].

In conclusion, it can be said that the role of sequential primary systemic chemotherapy in locally advanced breast cancer deserves further evaluation in larger prospective randomized trials.

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