Accelerated versus standard cyclophosphamide, epirubicin and 5-fluorouracil or cyclophosphamide, methotrexate and 5-fluorouracil: a randomized phase III trial in locally advanced breast cancer

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Background: The purpose of this study was to evaluate the impact of a dose-dense primary chemotherapy on pathological response rate (pCR) in patients with locally advanced breast cancer (LABC) treated with combined modality therapy.

Patients and methods: Stage IIIA/IIIB patients received three courses of induction chemotherapy (ICT) with cyclophosphamide, epirubicin and 5-fluorouracil (CEF) followed by local therapy (total mastectomy or segmental mastectomy with axillary nodes dissection) and adjuvant chemotherapy (ACT) with three courses of CEF alternated with three courses of cyclophosphamide, methotrexate, 5-fluorouracil (CMF). Patients were randomized to receive ICT and ACT every 3 weeks (arm A, ‘standard treatment’) or every 2 weeks with granulocyte–macrophage colony-stimulating factor (GM-CSF) support (arm B, ‘dose-dense treatment’). In both arms radiotherapy was administered after the end of chemotherapy (in selected cases) and patients with hormonal receptor-positive tumors received tamoxifen for 5 years.

Results: A total of 150 patients were randomized (77 arm A and 73 arm B) and demographics were well balanced between the two arms. Compliance to treatment was excellent: 95% and 93% of patients in arms A and B, respectively, completed the treatment program with no modification or delay. Median duration of treatment (ICT+local+ACT) was 183 days (range 0–265) in arm A and 139 days (0–226) in arm B. The average relative dose intensity (ARDI) of chemotherapy was 1.3 with a 30% increase in the dose intensity in arm B in comparison with arm A. No difference in clinical [62%; 95% confidence interval (CI) 49% to 73.2%] and pathological response rates to ICT was observed between the two arms. Median follow-up was 5 years (range 1–96 months); median disease-free survivals were 4.8 years in arm A and 4.5 years in arm B. Median overall survival was 7.8 years in standard therapy: this figure has not yet been reached in the dose-dense treatment.

Conclusions: In LABC a dose-dense regimen, while allowing a 30% increase in the dose intensity of chemotherapy, did not provide significant improvement in pathological response rates. However, accelerated chemotherapy reduced the duration of the combined-modality program (6.1 versus 4.6 months) with no additional toxicities.

Key words: dose-dense chemotherapy, locally advanced breast cancer, randomised trial

Introduction

Locally advanced breast cancer (LABC) represents 10–20% of newly diagnosed breast cancers. After surgery and/or radiotherapy the prognosis is very poor [1], while the introduction of primary chemotherapy has significantly improved the outcome of these patients [2, 3]. In particular, in the case of inflammatory carcinoma, 5-year survival rates were 1.9–2.4% with local treatment alone and rose to 23–74% with a multimodality approach [4]. Primary chemotherapy represents an ‘in vivo’ chemosensitivity test allowing the identification of subgroups of patients with different prognosis. In fact, several authors have demonstrated that the achievement of a pathological complete remission is an excellent predictor of long-term survival both in locally advanced and operable breast cancer [5–7]. Unfortunately, in patients with LABC, a pathological complete response (pCR) is very rare: pCR rates with standard anthracycline-based regimes range from 3.5% to 12% [2, 3, 6, 8].

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Retrospective analyses and a few prospective trials have suggested that dose intensity (DI) can be an important determinant of successful chemotherapy [9–11]. In particular, an increase in DI can be achieved by shortening the interval between courses, usually maintaining unchanged the dose per course and the cumulative dose (accelerated or dose-dense chemotherapy) [12]. There are very few available data on the role of a dose-dense chemotherapy in LABC patients treated with a multimodality approach. The present study was designed to evaluate the relationship between accelerated primary CT and pCR rate in LABC. Granulocyte–macrophage colony-stimulating factor (GM-CSF) was primarily chosen, for dose-densification support, because of its potential immunostimulatory effects [13]. In the adjuvant setting, an alternated cyclophosphamide, epirubicin and 5-fluorouracil (CEF)/cyclophosphamide, methotrexate, 5-fluorouracil (CMF) was administered in order to reduce the cumulative dose of epirubicin and minimize the cardiotoxicity of the treatment where stage IIIIB patients also received extended field radiation therapy.

This multimodality approach has already proven its cardiac safety in LABC patients [14]. The secondary end-point of the present trial was to study the perturbations induced by primary chemotherapy on tumor cell growth. The biological data have already been published [15]; in the present paper, we report the clinical part of the study after a median follow-up of 5 years.

Patients and methods

Patients

Eligibility criteria were as follows: histologically documented stage IIIA/B breast cancer [ipsilateral supraclavicular metastases were admitted according to the American Joint Committee on Cancer (AJCC) staging 1983], no distant disease, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and normal baseline organ functions (serum creatinine <1.5 mg/dl; bilirubin <2 mg/dl; hemoglobin >11 g/dl, WBC >4000/µl and platelets count ≥100 000/µl). Before chemotherapy patients underwent a complete staging procedure including clinical history, physical examination, mammography, chest X-ray, abdominal ultrasound, bone scan or skeletal X-ray, and ECG. Each patient was evaluated before and after induction chemotherapy by a multidisciplinary team including a radiation oncologist, a surgeon, a medical oncologist and a breast radiologist. Written informed consent was obtained from all patients; the study was approved by the local IRB/ethical committee of participating institutions.

Treatment plan

Patients were randomized to arm A (standard treatment) and arm B (dose-dense treatment):

Arm A (standard treatment). Both primary and adjuvant chemotherapy were given at 3-week intervals. Patients received three courses of primary CEF (cyclophosphamide 600 mg/m², epirubicin 60 mg/m² and 5-fluorouracil 600 mg/m², day 1), followed by local therapy (surgery or radiotherapy) and subsequent adjuvant chemotherapy consisting in one course of CEF alternated with one course of CMF (cyclophosphamide 600 mg/m², methotrexate 40 mg/m², 5-fluorouracil 600 mg/m², day 1) for a total of six courses.

Arm B (dose-dense treatment). Both primary and adjuvant chemotherapy were given at 2-week intervals. Patients received three courses of primary CEF plus GM-CSF (300 µg total dose subcutaneously days 4–13), followed by local therapy and subsequent adjuvant chemotherapy consisting in one course of CEF plus GM-CSF alternated with one course of CMF plus GM-CSF for a total of six courses. Doses of drugs were the same in both arms.

The acceleration of chemotherapy (induction and adjuvant) was planned to lead to a 30% increase in the DI of the treatment. Dose intensity of each drug as well as cumulative average relative dose intensity (ARDI) was calculated according to Hrynui and Bush [16].

In cases of clinical remission or stable disease, with technically operable lesions, patients underwent surgery (radical mastectomy or segmental mastectomy with axillary node dissection) within 3 weeks after the completion of induction chemotherapy (ICT). Inoperable cases or patients refusing surgery (with no evidence of distant metastasis) received radiotherapy.

At the end of adjuvant chemotherapy (ACT), in both arms, patients with T4 tumors received radiotherapy for a total dose of 50–60 Gy to the breast or chest wall, internal mammary lymph nodes and supraclavicular fossa. Patients with hormonal receptor-positive tumors received tamoxifen for 5 years.

Response evaluation

Response to ICT was determined by physical examination and mammography. Clinical complete response (cCR), complete disappearance of the tumor mass and adenopathy; partial response (PR), >50% reduction in the product of the two largest perpendicular diameters of the breast mass and adenopathy; stable disease (SD), <50% reduction in the product of the two largest perpendicular dimensions of the breast mass and adenopathy. A >25% increase in the sum of the products of the two perpendicular diameters of all measurable lesions, or the appearance of new lesions or distant metastases were considered as progressive disease (PD). A pathological complete response (pCR) was defined as no residual invasive tumor in the breast and axillary nodes. Patients with in situ carcinoma only and negative axillary nodes were coded as having a pCR; patients with no residual invasive tumor in the breast and positive axillary nodes were not considered pCRs.

Definition of end-points

The primary end-point of the study was the percentage of pCRs in the breast and axillary nodes in the two treatment arms. The percentage of pCRs was chosen as the primary end-point because it is a validated and objective assessment with demonstrated prognostic significance [5, 6]. Secondary end-points were as follows: (i) the changes in tumor cell proliferative activity induced by ICT (previously published, [16]); (ii) disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS) in the two arms. Overall survival was calculated from the date of randomization to death or last observation; PFS was calculated from the date of randomization to evidence of relapse or last observation/death and DFS from the date of complete response (whether this was achieved with chemotherapy or surgery) to first relapse or last observation/death [17].

Statistical analysis and sample size calculation

In our previous experience with primary ‘standard’ 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) in LABC the pCR rate was 3.5% [8]. To detect an increase in pCR rates from 4% to 20% with α = 0.05 (two-sided) and a power of 80% a sample size of 150 total patients was estimated. The Kaplan–Meier method was used to calculate OS, PFS and DFS [18]. Difference between curves was tested using the log-rank test [19]. Toxicity was reported according to World Health Organization (WHO) recommendations. Response rates and toxicities were compared using the chi-square test. To
investigate the prognostic significance of age, stage, receptor status, axillary node involvement and treatment (standard or experimental) on DFS, PFS and OS a univariate and Cox-regression analyses were performed on the whole population [20].

Randomization procedures

Centralized randomization was performed by calling the clinical trial office at the National Institute for Cancer Research in Genoa. Randomization was stratified by participating institutions; randomization lists were balanced using random permuted blocks of varying size within strata.

Results

From June 1992 to March 1997, 150 patients were randomized: 77 received standard therapy (arm A) while 73 received dose-dense treatment (arm B). The two populations were well balanced in terms of clinical and pathological features (Table 1). Four of 150 patients were ineligible: one in arm A (metastatic disease) and three in arm B (two metastatic disease and one stage IIB).

Chemotherapy-related toxicities were mild and superimposable in the two arms. No episode of febrile neutropenia was reported, no patient was admitted for treatment-related toxicity. In the dose-dense arm, 37 patients (52.9%) received GM-CSF as planned, while 33 (47.1%) interrupted GM-CSF and switched to G-CSF (300 µg total dose subcutaneously) because of WHO grade 2 myalgias, arthralgyas, bone pain and skin rush (Table 2).

In both arms the median number of primary chemotherapy courses was three (range 0–6); 19 patients (11 in arm A and eight in arm B) with inoperable disease after three courses, received three additional neoadjuvant CEF then local therapy and three adjuvant CMF. Median duration of treatment (ICT plus local plus adjuvant chemotherapy) was 183 days (range 0–265) in the standard arm and 139 days (range 0–226) in the experimental arm. The ARDI of the regimens and each single drug was 1.3 with a 30% increase in the DI of chemotherapy in the experimental arm compared with the standard arm.

The overall response rate to primary CEF was 62.3% [95% confidence interval (CI) 51% to 73%] in arm A and 61.6% (95% CI 49% to 73%) in arm B; two cCRs were obtained in arm A and one in arm B. Twenty-six (33.8%) and 24 (32.9%) stabilizations were reported in arms A and B, respectively. Seven patients were not evaluable for response: two patients were missing data and one was ineligible in arm A; one patient was missing data and three were ineligible in arm B. No patient progressed during induction chemotherapy. Local treatments were as follows: radical mastectomy, 65 (84.4%) patients in arm A and 60 (82.2%) patients in arm B; conservative surgery, five (6.5%) patients in arm A and seven (9.6%) patients in arm B; radiotherapy alone, six (7.8%) and five (6.8%) patients in arms A and B, respectively. Two pCRs (2.6%) (95% CI 0.32% to 9.07%) were observed in arm A and three (4.1%) (95% CI 0.86% to 11.5%) in arm B (P = 0.95); three additional patients in arm B achieved a primary tumor pCR only (no invasive breast tumor with positive axillary nodes).

After primary CEF and loco-regional therapy 137 of 150 patients (91%) were disease-free: subsequent adjuvant treatment was completed, as planned, for 63 patients (81.8%) in arm A and 60 patients (82.1%) in arm B. Main reasons for earlier discontinuation was patient refusal (arm A, 12 patients and arm B, nine patients). The median number of adjuvant chemotherapy courses administered was five (range 0–6) in both arms.

All patients were considered for survival analysis. At a median follow-up of 5 years (range 1–96 months), 66 patients (44%) relapsed (37 in arm A and 29 in arm B) and 46 (30.7%) died. Relapses included five cases of second primary in the contralateral breast (four in arm A and one in arm B) and ineligible

<table>
<thead>
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<th>Table 1. Patients characteristics at diagnosis</th>
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<tr>
<td>Arm A, n (%)</td>
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<td>----------------</td>
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<tr>
<td>Total patients</td>
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<tr>
<td>Median age, years (range)</td>
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<td>Premenopausal</td>
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<td>Postmenopausal</td>
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<td>Stage</td>
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<td>Estrogen receptor</td>
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<td>Positive</td>
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<td>Negative</td>
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<td>Unknown</td>
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<td>Progesterone receptor</td>
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<td>Negative</td>
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IBC, inflammatory breast cancer.

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<th>Table 2. Worst toxicities per patient (%)</th>
<th>induction chemotherapy (ICT)</th>
<th>plus adjuvant chemotherapy (ACT)</th>
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<tr>
<td>WHO grade</td>
<td>Arm A (n = 76)*</td>
<td>Arm B (n = 70)*</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>13.5</td>
<td>5.4</td>
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<tr>
<td>Thrombocytopenia</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Anemia</td>
<td>2.7</td>
<td>–</td>
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<tr>
<td>Mucosistis</td>
<td>17.8</td>
<td>–</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>28.4</td>
<td>10.8</td>
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<tr>
<td>Alopecia</td>
<td>12.2</td>
<td>82.4</td>
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<tr>
<td>Myalgia</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Arthralgia</td>
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<td>Bone pain</td>
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<td>Skin rush</td>
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*Ineligible patients were excluded.
WHO, World Health Organization.

ACT) was 183 days (range 0–265) in the standard arm and 139 days (range 0–226) in the experimental arm. The ARDI of the regimens and each single drug was 1.3 with a 30% increase in the DI of chemotherapy in the experimental arm compared with the standard arm.
patients. First site of recurrence was loco-regional alone (six patients in each arm), distant alone (18 and 16 patients in arms A and B, respectively) and both loco-regional and distant in four patients in the standard and three in the experimental arm. Five-year disease-free survival rates were 48% and 60% in arms A and B, respectively (\( P = 0.18 \)) (Figure 1); 5-year progression-free survivals were 52% in the standard arm and 56% in the experimental arm (\( P = 0.3 \)) (Figure 2) while 5-year overall survival rates were 52% and 54% in arms A and B, respectively (\( P = 0.64 \)) (Figure 3).

At univariate analysis, stage of disease, in particular inflammatory breast cancer (IBC), significantly affected DFS (\( P = 0.03 \)), while a trend towards a better DFS was observed for patients with negative axillary nodes at surgery (\( P = 0.09 \)). Stage and nodal status did not significantly impact on PFS. Estrogen receptor positivity significantly affected OS (\( P = 0.01 \)). Cox-regression analysis showed that the stage of disease (particularly IBC) significantly influences DFS [hazard ratio (HR) = 2.21 (95% CI 1.09–4.47); \( P = 0.03 \)] and PFS [HR = 2.19 (95% CI 1.10–4.35); \( P = 0.04 \)] but not OS [HR = 1.94 (95% CI 0.41–1.38); \( P = 0.17 \)]. Estrogen receptor positivity maintained prognostic significance on OS [HR = 3.57 (95% CI 1.49–8.57); \( P = 0.02 \)]; a trend toward a better OS was reported for patients with negative axillary nodes [HR = 2.74 (95% CI 0.83–9.04); \( P = 0.09 \)]. Type of treatment had no influence on outcome either at univariate or at multivariate analysis.

Discussion

Several randomized trials have tested the dose-intensification of chemotherapy in metastatic breast cancer with disappointing results: an increase of the response rate has been reported, but this does not translate into survival benefit [21–23]. An increase in DI with accelerated chemotherapy was tested by Fountzilas et al. [24] in metastatic breast cancer: patients were randomized to

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Figure 1. Disease-free survival (from complete response).

Figure 2. Progression-free survival.
receive epirubicin 110 mg/m$^2$ every 4 weeks, or the same drug administered every 2 weeks with G-CSF support. The authors reported a significant difference in CR rates favoring accelerated chemotherapy over the standard approach (17% versus 5%); however, after a median follow-up of 25 months, no advantage in time to progression and OS emerged between the two arms. These data are in agreement with those published by Del Mastro et al. [25] who tested an accelerated and intensified CEF (with G-CSF) versus a standard CEF in 151 women with metastatic breast cancer. The authors showed that acceleration and escalation of drugs allowed an 80% increase in the DI of chemotherapy: however, no difference in activity and efficacy was observed between the two arms. In addition, the experimental approach was significantly more toxic than the standard one.

There are limited experiences regarding DI manipulation in locally advanced breast cancer. Dhingra et al. [26] preliminarily reported the results of a randomized trial in which 112 LABC patients received either standard FAC every 3 weeks or escalated and accelerated FAC every 18 days with G-CSF support. A significantly higher response rate was reported for the experimental arm compared with the standard arm (98% versus 76%; $P = 0.002$), but no difference in pCRs was observed; moreover, the escalation of drugs beyond the standard level induced more severe toxicities [26]. The European Organisation for Research and Treatment of Cancer (EORTC), the National Cancer Institute of Canada and the Swiss Group for Clinical Cancer Research carried out a phase III trial in which LABC patients (including IBC) were randomized to CEF (5-FU 500 mg/m$^2$ i.v. days 1, 8; epirubicin 60 mg/m$^2$ i.v. days 1, 8; cyclophosphamide 75 mg/m$^2$ o.s. days 1–14) every 28 days for six courses or to a dose-intensified and accelerated EC (epirubicin 120 mg/m$^2$ i.v. day 1; cyclophosphamide 830 mg/m$^2$ i.v. day 1) with G-CSF support every 14 days. Preliminary data showed a more than 2:1 DI ratio favoring the experimental arm; however, at a median follow-up of 27 months no difference in PFS was reported [27].

The present randomized study was aimed at evaluating the impact of a dose-dense primary chemotherapy on pCR rate in LABC. Despite a 30% increase in the DI only three patients in the dose-dense arm achieved a pCR versus two patients in the standard arm, for an overall pCR rate of 3.3%. In our study a high percentage of patients had T3 or T4 (including IBC) primary tumors (92% and 89% in arms A and B, respectively); patients with a large primary are significantly less likely to obtain a pCR [6]. More courses of primary chemotherapy are required to induce a higher rate of pCR in LABC. Kuerer et al. [6] reported a 12% pCR rate with four courses of primary FAC rate in LABC patients; however, this large series did not include IBC. Merajver et al. [28] obtained a 28% pCR rate in LABC patients treated with nine courses of chemo-hormonal induction therapy with CAMF-PT (cyclophosphamide, doxorubicin, methotrexate and 5-fluourouracil plus premarin and tamoxifen).

In the present trial, after primary chemotherapy and local treatment, most patients (91%) were rendered disease-free and received, on average, five additional courses of adjuvant chemotherapy with alternating regimens (CEF/CMF), every 3 or 2 weeks according to the randomization arm. Therefore, the 30% increase in DI achieved in the neoadjuvant setting was maintained throughout the entire therapeutic program. Recently Hryniuk et al. [29] have introduced the concept of summation dose intensity (SDI): SDI can be used to predict activity and efficacy of dose-intensive treatments in breast cancer. In our study, by calculating SDI of adjuvant therapy a difference of 0.64 was obtained, indicating a potentially positive study in terms of DFS in favor of the accelerated arm. At a median follow-up of 5 years, a trend towards a better DFS was observed for dose-dense treated patients (60% versus 48%) (Figure 1). At the time of this report only 42% of patients have relapsed; a longer follow-up and more events are required to detect a possibly significant difference between the two arms.

Despite the low pCR rate, the overall efficacy figures of our negatively selected population compare favorably with those reported by other authors [6, 30]. The low rate of locoregional failures (8% as first site of relapse) we obtained with radical
mastectomy plus radiotherapy, in cases of T4 primary tumors, contributed to the satisfactory clinical results.

In conclusion, the present study suggests that, in LABC, a dose-dense chemotherapy is feasible, without additional toxicities, and the treatment can be completed in a shorter period of time (6.1 versus 4.6 months). However, three courses of dose-dense CEF did not increase the pCR rate; more courses are probably needed and a longer follow-up is required to detect possible long-term outcome differences.

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References