A Phase II Study of Primary Dose-dense Sequential Doxorubicin Plus Cyclophosphamide and Docetaxel in cT4 Breast Cancer

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Abstract. *Background: Dose-dense chemotherapy with anthracyclines and taxanes has improved either disease free survival or overall survival in high risk patients with early breast cancer. Patients and Methods: The activity and safety of a dose-dense schedule (q14 days) of adriamycin 60 mg/sqm and cyclophosphamide 600 mg/sqm (AC) x 4 cycles followed by docetaxel 75 mg/sqm for 4 cycles with hematopoietic support in patients with stage IIIB breast cancer was explored. Patients with ER ≥10% tumors received concomitant endocrine therapy with 3-month triptorelin and letrozole. Results: Fifteen patients with histologically proven cT4b (three patients) and cT4d (twelve patients) M0 breast cancer were enrolled. Median age was 48 years (range 25-66). Eight clinical responses including one pathological complete remission (pCR), three stable disease (including minor responses) and four progression of disease, one during AC and three during taxotere, were observed. Four patients had grade 3-4 non hematological toxicities and all except one discontinued treatment. Conclusion: Due to the high rate of progressive disease, this schedule should not represent a standard option in cT4 breast cancer.*

Pre-operative treatment is indicated for patients with locally advanced disease or those needing a reduction of primary tumor size to undergo conservative breast surgery (1). The sequential administration of anthracycline-based regimens and taxanes has allowed higher rates of pathological complete remissions (pCRs) to be achieved and one study has suggested an improved overall survival (OS) for patients with no residual tumor in the surgical specimen (2-4).

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Key Words: Cyclophosphamide, docetaxel, doxorubicin, preoperative therapy, breast cancer.

Chemotherapy schedules with reduced intervals between successive doses (dose-dense chemotherapy) are hypothesized to decrease the chance of tumor re-growth between treatment courses and, therefore, improve therapeutic results (5). The CALBCG trial 9741 showed an improved disease free survival (DFS) and OS in high risk breast cancer women treated with a dose-dense AC→ paclitaxel sequential regimen as adjuvant therapy (6). A recently published trial of dose-dense *vs.* standard FEC failed to show a clear advantage for the accelerated schedule (7). Dose-dense pre-operative chemotherapy regimens containing docetaxel following anthracyclines have not been extensively investigated as primary therapy.

The activity of a dose dense regimen including anthracyclines and docetaxel in women with T4 breast cancer, a subpopulation of patients which, due to the poor prognosis, deserves a more aggressive approach was investigated in this study.

Patients and Methods

Patients with stage IIIB breast cancer (cT4 a-d, N0-2, M0), consecutively admitted at the Department of Medicine of the European Institute of Oncology from October 2004 to September 2005 were enrolled in this study. A punch biopsy or a trucut was performed for diagnosis and for assessment of biological characteristics of the tumor and an instrumental work up was performed to exclude the presence of distant metastases.

All patients received standard AC (doxorubicin at a dose of 60 mg/sqm plus cyclophosphamide at a dose of 600 mg/sqm through intravenous (*i.v.*) infusion every two weeks for four courses followed by four courses of docetaxel at a dose of 75 mg/sqm *i.v.* over 1 h every two weeks. Filgrastim at a dose of 5 μg/kg was given by subcutaneous injection on days 4-10 of each 14-day course. Patients with ER and/or PgR ≥10% (HR+ve) tumors received concomitant endocrine therapy with 3-month triptorelin and letrozole 2.5 mg/day at achievement of post-menopausal estradiol levels.

Definitive surgery, (radical modified mastectomy with complete axillary lymph node dissection) was performed approximately four weeks after the fourth course of docetaxel. Locoregional radiotherapy was prescribed to complete local treatment.

Table I. *Patient characteristics at baseline and at surgery.*

	Baseline	Surgery
No. of patients	15	11
Evaluable for response/toxicity	15/15	
Median age (range)	48 years (25-66)	
Clinical stage		
T4 (b/d)	3/12	–
N-ve/N+ve	0/15	
Pathological stage		
T0/Tis		1
T1/T2/T3/T4	–	2/3/5/0
N-ve/N+ve		2/9
HR+ve/HR-ve	7/8	7/3
c-erbB-2		
3+/ absent- 2+*	4/11	5/5

HR+ve ER ≥10% of the cells; H-ve ER <10% of the cells.
IHC Her-2/neu 2+ was further tested as FISH negative

Table II. *Responses and toxicity.*

Response (%)	
CR+PR	8 (53%)
SD	3 (20%)
PD	4 (27%)
pCR	1 (7%)*
Toxicity (%)	
Grade 3-4	4 (27%)
Withdrawal (%)	
PD	3 (20%)
Toxicity	3 (20%)

CR=complete response; PR=partial response;
SD=stable disease; PD=progressive disease;
pCR=pathological complete remission.
*The patient achieving pCR obtained also a complete clinical response.

At baseline, at the end of the four cycles with AC and at the end of the four cycles of taxotere patients were submitted to instrumental evaluation with breast ultrasound and to mammography, when feasible. Clinical response was defined according to WHO criteria , as ≥50% reduction of the product of the two largest diameters of the tumor, when measurable, at physical and instrumental evaluation and the disappearance of erythema, edema and decreased swelling of the breast in cancers without measurable nodules. pCR was defined as absence of invasive tumor in the surgical specimen, according to Sataloff *et al*. (8).

This is a two stage phase II clinical trial, taking into account both toxicity and treatment response, according to the methodology described by Bryant and Day (9). A pCR rate of 0.1 was considered as unacceptable activity, and a pCR rate of 0.3 as acceptable; 40% of patients with grade 3-4 toxicity as unacceptable toxicity, and 20% of patients with grade 3-4 side effects as acceptable. Significance levels of 10% for treatment and 15% for toxic effects and a 90% power were adopted.

After testing the regimen on 15 patients in the first stage, the trial would be terminated for poor activity if none or only one achieved pCR, and would be terminated for toxicity if nine or fewer patients were spared grade 3-4 toxic effects. If the trial proceeds to the second stage, a total of 33 patients should be studied. If the total number responding is less than or equal to 5, or if the total number without grade 3-4 toxicity is less than or equal to 22, the regimen should be rejected.

Results

Fifteen patients were enrolled in this study. Major patient characteristics are shown in Table I. Median age was 48 years (range 25-66 years). Eight patients were pre-menopausal and 7 were post-menopausal. Among the pre-menopausal patients six out of eight had HR+ve tumors (3 T4b and 3 T4d) and received endocrine therapy, while six out of seven of the post-menopausal patients had ER and PgR <10% (HR-ve) tumors. Only four patients had her-2/neu 3+ tumors.

Tumor characteristics at surgery are reported in Table I. Four out of 15 patients were not submitted to surgery at the end of the study treatment, three because of progressive disease, while one patient stopped treatment because of grade 3 cutaneous toxicity. All these patients were treated with different chemotherapeutic regimens: one patient with her-2/neu overexpressing breast cancer received weekly trastuzumab + paclitaxel attained stable disease and was submitted to surgery, and the remaining three received continuous 5-fluorouracil (5-FU) infusion containing regimens (ViFuP or ECF), with one positive response followed by surgery, while the other two patients have not been submitted to surgery yet.

Clinical and pathological responses are summarized in Table II. Among responding patients 50% obtained or improved the response with taxotere, while the remaining four patients showed the best response after AC. One patient progressed at the end of AC and received taxotere with minor response, while 3 patients progressed during or at the end of taxotere administration and received trastuzumab + paclitaxel (1) and continuous 5-FU infusion containing regimens (2) (see above). One patient was withdrawn after AC because of occurrence of two episodes of grade 3 sopraventricular parossistic arythmia. Two patients were withdrawn because of grade 3 and 4 cutaneous toxicity after the first cycle of taxotere, while two patients with grade 2 unresolved toxicity required a dose reduction of up to 50% to complete treatment. One patient had grade

3 biochemical toxicity and required dose reduction for subsequent courses. According to the two-stage design (9), patient recruitment was discontinued after the first stage, based on the rate of progressive disease and grade 3-4 toxicity.

Discussion

Inoperable stage IIIB breast cancer, and particularly inflammatory breast cancer, represents a subset of tumors with poor long term prognosis (10). No standard treatment is established although anthracycline based chemotherapy followed by surgery and radiotherapy are recommended (11). Since dose-dense chemotherapy has been shown to be beneficial in high-risk patients (6), the activity of the accelerated administration of a regimen which had been shown very active in pre-operative therapy was investigated in patients with T4 tumors (2). Our results do not support an advantage for this accelerated regimen due to the unexpected high rate of progressions and grade 3-4 toxicities. The results achieved compared unfavorably with results we previously obtained in patients with locally advanced disease (T4) treated with a regimen containing vinorelbine, cisplatin and 5-FU as continuous infusion (ViFuP regimen) (12). In the previous study eleven patients (43%) had inflammatory breast cancer. Objective response was observed in 19 out of the 26 evaluable patients (73%; 95% CI: 52-88%), five had complete pathological response (20%; 95% CI: 7-41%), while no disease progression under treatment occurred and side effects were mild. We have also shown, in a large series of 399 patients with T2-T4 breast cancer treated pre-operatively with various regimens, that infusional 5-FU containing regimens significantly correlated with a greater rate of pCR and of nodal negative status at surgery (13). Moreover, in this series the rate of progressive disease was only 1.5%. The high percentage of progressive disease observed in the present study cannot be explained simply by the selection of high risk patients (12 out of 15 patients had T4d disease). In fact, in a recent review the rate of progressive disease during induction chemotherapy for inflammatory breast cancer was reported to be up to 6% (10).

A phase II study evaluating the role of dose-dense sequential doxorubicin and docetaxel for patients with advanced operable and inoperable breast cancer was recently reported (14). An overall response rate of 92% was reported including 13 (33%) complete responses, 23 (59%) partial responses and 4 (10%) pCR. However, two out of the nine patients with inflammatory breast cancer progressed during docetaxel (27%), a figure which is comparable with our series. The regimen was defined as well tolerated, but despite a protocol change requiring 3 weeks between doxorubicin and docetaxel, overall 5 out of 39 patients were unable to complete all cycles of docetaxel and eight patients required dose reduction of docetaxel (due to development of grade 3-4 mucositis and hand-foot syndrome).

Other studies have shown that the dose-dense administration of taxotere might be associated with a high incidence of grade 3-4 cutaneous toxicity (42%), although in this study an increased rate of both clinical and pCR was observed (15). Conversely, an improvement in pCR rate from prolonging duration of treatment rather than shortening treatment intervals was shown in the GEPARDUO trial (16) and no advantage in the response rate was reported in two recent trials with the use of dose-dense anthracyclines (9).

In conclusion, in our experience dose-dense docetaxel chemotherapy correlates with significant toxicity, in particular and with a high rate of disease progression (20%) in locally advanced disease. However, these data together with other published evidence, indicate that further studies on locally advanced disease are needed in order to optimize dose and schedule of pre-operative dose-dense docetaxel-containing chemotherapy before widespread introduction in current clinical routine. Other treatment options , including regimens containing infusional 5-FU, should be evaluated.

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Received May 3, 2006
Accepted June 19, 2006