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ORIGINAL ARTICLE

Tailored preoperative treatment of locally advanced triple negative (hormone receptor negative and HER2 negative) breast cancer with epirubicin, cisplatin, and infusional fluorouracil followed by weekly paclitaxel

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Abstract
Background No specific treatment guidelines are available for triple-negative breast cancers, defined by a lack of expression of estrogen (ER), progesterone (PgR), and HER2 receptors.
Patients and methods We investigated in patients with T2–T3 N0-3 ER, PgR <10% and HER2 negative breast cancers the activity both in terms of pathological (pCR) and objective responses of four courses of cisplatin containing chemotherapy (ECF, epirubicin, cisplatin, and fluorouracil as continuous infusion) followed by three courses of weekly paclitaxel. Adjuvant metronomic chemotherapy including cyclophosphamide and methotrexate for 4–6 months was administered.
Results Thirty patients are evaluable. Median age was 41 years (28–64 years). Twenty-three of 25 evaluable tumors stained positively for epidermal growth factor receptor. An objective response, either complete and partial, was observed in 26 patients (86, 95% CI 69.3–96.2%). and a pCR was obtained in 12 patients (40, 95% CI 22.7–59.4%). Two patients progressed during paclitaxel. Negative axillary nodes were found in 80% (95% CI 61.4–92.3%) of patients at surgery. Twenty-six patients (86, 95% CI 61.4–92.3%) underwent breast conserving surgery. Grade >2 non-hematological toxicity was observed in three and two patients during ECF and paclitaxel, respectively. The 2-year disease free survival (DFS) was 87.5% (95% CI 74.7–100%). No significant correlation was observed between EGFR staining and either pCR or DFS.
Conclusions Preoperative cisplatin containing chemotherapy followed by paclitaxel induced an high pCR rate in a population of triple-negative breast cancer. The impact of this schedule on long-term outcome should be investigated in larger series.

Keywords Breast cancer · Preoperative chemotherapy · Triple negative tumors · Platinum based chemotherapy

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Introduction

Polychemotherapy including anthracyclines and taxanes has improved clinical outcome in terms of disease free survival (DFS) and of pathological complete remission (pCR) when administered post-operatively and as primary therapy, respectively [1–3]. The sequential administration of

anthracyclines and taxanes appears to be superior to the concurrent schedule, possibly due to the prolonged duration of treatment [4, 5] although the optimal schedule has not been defined yet.

Hormone receptors negative (HR-ve) breast tumors are more likely to benefit from these more intense chemotherapeutic regimens as compared to hormone receptor positive (HR+ve) tumors [1, 6–7]. However, the long-term outcome of patients with HR-ve tumors remains worse, even in those experiencing a complete disappearance of the tumor after primary chemotherapy prompting the search of improved therapeutic strategies in this subset of patients [6].

Triple negative breast cancer is a recent definition and refers to cancers that do not express estrogen (ER), progesterone (PgR), and HER-2 (HER2) receptors, while often staining positively for epidermal growth factor receptor (EGFR) [8] Triple-negative breast cancers are characterised by an aggressive clinical history with poor DFS and OS [9, 10]. Preoperative anthracycline and taxane containing chemotherapy seems effective on terms of pCR rate but new therapeutic approaches are indicated [11].

The combination of epirubicin, cisplatin, and infusional fluorouracil (ECF) has been proven to be highly active in the preoperative setting [6, 12], yielding a similar rate of pCR and showing a not significant trend toward improved survival as compared to AC in a phase III trial [12].

In order to ameliorate these results in the present study we decided to investigate the combination of this highly active infusional regimen with weekly administration of paclitaxel. The latter schedule was shown to improve either pCR rate and time to progression as compared with the 3-week administration [13, 14]. We thus investigated the pCR rate of a schedule providing a prolonged duration of treatment and including both anthracyclines and taxanes in addition with infusional fluorouracil and cisplatin in patients with steroid hormone receptors and HER2 negative breast cancer, who are more likely to benefit from a prolonged chemotherapy. Considering the poor results in terms of DFS and the role of alkylating agents in triple negative breast cancer, a tailored adjuvant program including metronomic chemotherapy with cyclophosphamide and methotrexate, whose role after completion of standard adjuvant chemotherapy is currently under investigation in a phase III trial, was administered. The results in terms of DFS were also reported in the present manuscript.

Patients and methods

Patients with stage II-IIIA (cT2-3, N0-3, M0), ER, PgR <10% and HER2 negative breast cancer consecutively admitted at the Department of Medicine of the European Institute of Oncology (EIO) from October 2004 to March 2006 were enrolled into this study. A trucut was performed for diagnosis and for assessment of biological characteristics of the tumor. Investigations (chest X-ray, abdomen ultrasound and bone scan) were performed to exclude distant metastasis and blood tests were performed to assess bone marrow, renal, and hepatic function.

Estrogen receptor and PgR status, assessment of the proliferative activity (% of Ki-67 stained cells) and overexpression of HER2 and of EGFR were determined on core biopsies obtained for diagnosis, as previously described [6]. Tumors were defined ER and PgR negative if <10% of neoplastic nuclei stained positively. HER2 status was defined at immunohistochemistry (IHC) as negative (faint and partial staining in >10% of cells = 1+); and equivocal (faint and complete staining in >10% of cells = 2+). In the latter cases fluorescence in situ hybridization (FISH) was performed to assess the amplification of the HER2 gene. Since no definite cut off has been established for EGFR, samples containing any percentage of distinct membranous stained cells were considered positive.

All patients were treated with the ECF regimen containing epirubicin 25 mg/sqm i.v. dd 1,2 cisplatin 60 mg/sqm i.v. d1 and fluoruracil 200 mg/sqm as a continuous infusion from day 1 through 21 for four courses. Cycles were repeated every 21 days. Paclitaxel was administered at the dose of 90 mg/sqm dd 1,8,15 every 28 days for three courses.

Patients were assessed at each course for clinical response, by physical examination with a caliper, and at baseline and at the end of the fourth cycle of ECF and after the completion of chemotherapy with paclitaxel for instrumental response with breast ultrasound and mammography. A 28-day GnRH analogue, was offered to premenopausal patients for ovarian function preservation and was started in combination with chemotherapy and continued till the end of the adjuvant treatment.

Clinical responses were evaluated according to both radiological (breast ultrasound or mammography) and clinical evaluation, by measuring the largest diameters of the tumor and were graded according to standard RECIST criteria [15].

Pathological complete remissions (pCR) were evaluated according to Kuerer et al. [16]. A pCR was defined as a total disappearance of invasive tumor either in the breast and in the axilla. The presence of intraductal carcinoma qualified for pCR.

Toxicity was recorded and classified according to the NCITC-CTG Criteria. The treatment was post-poned by 1 week if the blood count on day 21 showed a neutrophil count <1,000/mm3 and/or platelet count <100,000 mm3. In case of febrile neutropenia, or anemia, mucositis, hand & foot syndrome, gastrointestinal, biochemical and neurological toxicity ≥grade 2, dose reduction by 25% of the related drug was performed.

Surgery was performed ~28 days after the last paclitaxel administration to allow recovery from toxicity.

Written informed consent was obtained from all patients. The protocol was notified to the Ethical Committee.

This is a single institution study. All included patients had pathological evaluation performed at the EIO. Surgical specimens were extensively sampled for the evaluation of residual tumor as previously described [6].

Immunostaining experiments for the localization of ER and PgR, HER2 protein and Ki-67 antigen were performed on consecutive tissue sections of the tru-cut biopsies obtained before primary treatment, as previously reported [6]. The following primary antibodies were used: the monoclonal antibody (MAb) to ER (Dako, at 1/100 diluition), the Mab to PgR (Dako, 1/800), the MIB-1 Mab to the Ki-67 antigen (Immunotech, Marseille, France, 1/1200), the polyclonal antiserum (Dako, 1/3200) to the HER2 protein and the antibody 31G7 (Zymed Laboratories, San Francisco, CA, USA, pronase, 1:20) to HER1.

The immunostained slides were evaluated independently by two of the authors. Only nuclear reactivity was taken into account for ER, PgR, and Ki-67 antigen, whereas only an intense and complete membrane staining >10% of the tumor cells was taken as evidence of HER2 over-expression (3+). For EGFR only distinct membranous staining was defined as positive.

We adopted an optimal two-stage design [17], with a target rate of pCR $\geq$30% deemed acceptable, and a pCR $\leq$10% considered unacceptable. For a 0.05 type I error and a 0.2 type II error probabilities, ten patients are needed in the first stage and if 0 or 1 achieve a pCR the study is closed for insufficient activity. If two or more pCR are observed among these initial patients, an additional 19 assessable patients would be entered. If five or more pCR were observed among 29 assessable patients, the treatment would be considered worthy of further consideration.

The primary endpoint was rate of pCR. The secondary endpoints were clinical responses either complete and partial.

The predictive value for pCR of EGFR and Ki-67, considered as continuous variables, was assessed by logistic regression univariate analyses, using the likelihood ratio test to assess significance. $P < 0.05$ are considered significant.

Results

Thirty-one patients entered the study: one patient was not considered eligible due to expression of ER > 10% of the cells and thirty patients were evaluable on an intention-to-treat basis. One patient had bilateral triple negative cancer and one patient had cytologically positive nodes in the contralateral axilla which were attributed to an occult contralateral primary breast cancer. One patient received cyclophosphamide instead of cisplatin in association with epirubicin and infusional fluorouracile due to hypoacusia but was evaluated for response.

Baseline characteristics of patients and tumors are reported in Table 1. Twenty-two patients (73%) had clinically positive nodes assessed by physical examination, ultrasound, and fine needle aspiration (three patients).

Twenty-eight patients had hormone receptor absent tumors, while in two patients ER stained positively in 2% of tumor cells. HER2 was negative at IHC in all but two patients who had IHC 2+ tumors. In both cases FISH did not show gene amplification. EGFR was determined by IHC in 25 samples of 30. Twenty-three tumors (92%) were positive for EGFR with a median percentage of stained cells of 40% (range 3–90%).

Six patients obtained a clinical complete response (20%) and a partial response was observed in 20 patients (66%) reaching an overall response rate of 86% (95% CI 69.3–96.2%). Two patients had stable disease, one of whom after a partial response to ECF, and two patients progressed during paclitaxel, one of whom after a partial response to ECF. Breast conservative surgery was feasible in 26 patients (86%). Biopsy of sentinel node with no further clearance of the axilla was performed in ten cases (33%), while axillary dissection was performed in 20 cases (67%). Radiotherapy was performed in all patients submitted to breast conserving surgery.

Table 1 Baseline and tumor characteristics

Eligible	30
Not eligible (ER > 10%)	1
Evaluable for response	30
Evaluable for toxicity to ECF/Paclitaxel	30/26
Median age (range)	41 (28–64)
Menopausal status	
Pre	20 (66%)
Post	7 (23%)
Peri	3 (1%)
T stage	
2	26 (87%)
3	4 (13%)
N stage	
0	8 (27%)
1	20 (67%)
2	1 (3%)
3	1 (3%)
Type of surgery	
Quadrantectomy	26 (86%)
Mastectomy	4 (13%)
Sentinel node biopsy only	10 (33%)
Axillary clearance	20 (67%)

Pathological complete remission was observed in 12 patients of 30 (40, 95% CI 22.7–59.4%) Another pCR was observed in one breast in the patient with bilateral breast cancer for a pCR rate of 43% when considering tumors. In two further patients only <2 mm residual tumor were observed and in one patient only embolic neoplastic cells were detected. Negative axillary nodes were found in 80% (95% CI 61.4–92.3%) of patients at surgery.

Responses according to chemotherapeutic regimen are reported in Table 2. Four patients who achieved a partial response after ECF had a local progression upon paclitaxel (in three cases documented only at breast ultrasound according to RECIST criteria) and one patient who did not respond to ECF developed distant disease upon paclitaxel. One patient showed no imaging response to both schedules but turned out to have only a <2 mm residual tumor at surgery. Among the patients who achieved their better response after ECF without progression on paclitaxel, four patients achieved a pCR.

The GnRH analogue was administered to 12 of 20 premenopausal patients and six of them achieved a pCR.

Adjuvant chemotherapy with metronomic oral cyclophosphamide (50 mg/day) and methotrexate (5 mg/twice a week) for 4–6 months was administered in 27 patients; one patient received AC for four courses, one patient did not receive further therapy and one patient developed metastastic disease upon paclitaxel and received treatment for advanced disease.

Median follow up was 17 months (range 6–28 months). Three patients have developed distant disease and two patients are dead. Two of them progressed during paclitaxel and the third had an increase in tumor size during paclitaxel after a partial response upon ECF. Two-year DFS is 87.5% (95% CI 74.7–100%).

Table 2 Clinical responses overall and according to chemotherapeutic regimen

Overall response *N* (%)		Response after ECF *N* (%)		Response after Paclitaxel *N* (%)	
CR	***6 (20%)***[a]	**CR**	4 (13%)	→ **CR**	4 (13%)
				CR	2 (7%)
				PR	10 (33%)
PR	***20 (66%)***[b]	**PR**	21 (70%)	→ SD	4 (13%)
				PD	4 (13%)
				NE	1 (3%)
				PR	3 (10%)
SD	2 (7%)	SD	5 (17%)	→ SD	1 (3%)
				PD	1 (3%)
PD	2 (7%)				

[a] 5 pCR

[b] 7 pCR

Main toxicities are reported in Table 3. ECF was administered for four courses in all patients. Nine patients (30%) required dose reduction of at least one drug because of grade ≥ 2 hand &foot syndrome (one patient), gastrointestinal (one patient), mucosal (two patients) and haematological (five patients) toxicity. Two patients experienced a thrombosis of the vein where the port-a-cath was inserted, which required discontinuation of 5-FU infusion but completely resolved after treatment with subcutaneous low-molecular weight heparin.

Paclitaxel was early discontinued in three patients, because of grade 2 neurological or biochemical toxicity (two patients), or because of no response (one patient). Paclitaxel was administered at reduced dosage in six patients because of transaminitis (two patients), neurological, haematological and mucosal (one patient each) toxicity.

Univariate logistic regression failed to show any predictive value of EGFR, either for pCR (OR = 0.98 $P = 0.19$) and for DFS, while a trend toward a statistical significance was observed for Ki-67 (OR = 1.03, $P = 0.08$) in predicting pCR.

Discussion

Hormone receptor negative breast tumors generally experience a worse outcome as compared to the cohort of patients with hormone receptor positive tumors. While the availability

Table 3 Main toxicities according to the chemotherapeutic regimen

	ECF (*N* = 30)				Paclitaxel (*N* = 26)[a]			
	Grade 2		Grade 3/4		Grade 2		Grade 3[b]	
	N	%	*N*	%	*N*	%	*N*	%
Leukopenia	11	37	2	6	0	(–)	0	(–)
Neutropenia	4	13	12[c]	40	1	4	0	(–)
Nausea	15	50	0	(–)	3	12	0	(–)
Vomiting	8	27	0	(–)	0	(–)	0	(–)
Diarrhea	0	(–)	0	(–)	0	(–)	0	(–)
Stipsis	3	10	0	(–)	2	8	0	(–)
Mucositis	5	17	0	(–)	1	4	0	(–)
Transaminitis	0	(–)	0	(–)	5	19	2	8
Neurological	0	(–)	0	(–)	6	23	0	(–)
Myalgia	0	(–)	0	(–)	1	4	0	(–)
Asthenia	1	3	1	3	2	8	0	(–)
Epigastralgya	1	3	0	(–)	0	(–)	0	(–)
Hand-foot syndrome	1	3	0	(–)	1	4	0	(–)
TVP	0	(–)	2	6	0	(–)	0	(–)

[a] Four points were not evaluable for toxicity

[b] No grade 4 toxicity was reported

[c] Only two patients experienced G4 neutropenia 1 of whom had febrile neutropenia

of trastuzumab has improved the clinical outcome of patients with HER2 positive tumors, irrespective of hormone receptor status, the prognosis of hormone receptor and HER2 negative tumors, the so called triple negative tumors, remains hominous.

This subpopulation, identified at IHC also by the expression of basal cytokeratins and EGFR [18], is associated with a more aggressive clinical behavior independent of tumor size and nodal status if compared with luminal subtypes which include hormone receptor positive tumors [8–10]. A reduced sensitivity to common chemotherapeutic agents, namely anthracyclines and taxanes, has been called in question to explain the poor prognosis associated with this subgroup [19]. However, triple negative tumors have been shown to achieve a higher rate of pCR after preoperative anthracycline containing regimens as compared to luminal subtypes [11, 20].

New chemotherapeutic strategies are required to improve the long-term outcome of patients with triple negative tumors. The BRCA1 gene plays a critical role in double-strand DNA repair. There is mounting evidence of the existence of a link between BRCA1 deficiency and the basal-like phenotype in that BRCA1 associated breast cancers share many molecular features with sporadic triple-negative tumors. Preclinical studies have shown that the loss of BRCA1 function increased sensitivity to DNA-damaging agents as cisplatin or alkylating agents [21].

A combination of weekly paclitaxel, cisplatin, and epirubicin has yielded an high pCR rate (66%) in hormone receptor negative tumors [22] and single agent cisplatin has shown significant activity in a phase II study in a selected series of triple negative tumors both in terms of clinical response and pCR rate [23].

In the present study we investigated the activity in terms of pCR and clinical responses of a schedule including the sequential admnistration of anthracyclines and weekly taxanes in addition with infusional 5-FU and cisplatin in a homogeneous series of triple negative tumors.

Our results showed a 86% of imaging confirmed clinical responses and a 40% of pCR, using a stringent definition which includes the disappearance of invasive tumor either in the breast and in the axilla. In two further patients only < 2 mm residual tumor were observed and in one patient only embolic neoplastic cells were detected. This pCR rate is higher than that we have previously reported using the same definition of pCR with six courses of ECF [24] and is comparable with that reported by Green et al. with paclitaxel for 12 weeks followed by the combination of FAC for four courses [13]. Interestingly, a recent retrospective analysis of the MD Anderson trials with the Paclitaxel/FAC regimen a 30% pCR rate was reported in triple negative tumors [25].

The rate of pathological nodal negative disease (80%) also is impressive as compared to our and others previous studies [13, 22, 24], although about 2/3 of patients had clinically positive nodes at baseline. Both pCR and pN0 have been independently associated with improved disease free and overall survival [26, 27]. Treatment was well tolerated and no grade 3 neurological toxicity was observed as previously reported with longer duration of weekly paclitaxel [13].

We observed some 16% of patients progressing on paclitaxel, a rate which is quite higher than that previously reported. In particular, in the NSAPB B-27 trial only 1.8% of patients progressed during taxotere [3]. Since the increased tumor size was detected at ultrasound in three of five patients, while other studies evaluated responses only by physical examination, differences in the assessment of response may in part account for the higher rate of progression observed in this study. Similarly, in a previous study of dose dense AC followed by docetaxel in patients with inflammatory breast cancer the accrual was prematurely closed due to the high rate of progressive disease during taxotere [28]. These results and the preclinical data supporting lower responsiveness to taxanes if compared with cisplatin in BRCA1 defective breast cancer support further studies on the use of paclitaxel in these patients [21].

Interestingly, we observed a high prevalence of EGFR positivity, even greater than that previously reported in basal-like tumors (57–72%) [18, 29]. No data are available on the predictive and/or prognostic role of the degree of EGFR expression. We did not find any correlation between the percentage of EGFR stained cells and either response to preoperative therapy and clinical outcome, although the small sample size might account for this finding. However, our data strongly support that EGFR targeting agents containing regimens should be usefully exploited in this population.

In addition, with the aim of designing a targeted strategy for triple negative tumors, we proposed a metronomic post-operative treatment including an alkylating agent as cyclophosphamide. Noticeably, 2-year DFS was 87.5%. Although the median follow up is relatively short, considering that the recurrence risk of this population is greater in the first 3 years, this rate is appreciable [9, 10]. The choice of a post-operative treatment with an alkylating agent as cyclophosphamide, although still under investigation, may have concurred to this result.

In conclusion, our schedule containing both anthracyclines and taxanes in addition to cisplatin and infusional 5-FU proved to be active both in terms of pCR and pathological negative nodes which are considered surrogates of clinical outcome other than in terms of breast conserving surgery. Given the poor prognosis of patients with triple negative tumors, the true impact of this combination on long-term outcome merits further investigations in larger series.

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