

Dose-dense Intensified Sequential *Versus* Conventionally-dosed Anthracycline and Taxane-containing Neoadjuvant Therapy in Patients with Inflammatory Breast Cancer

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Abstract. *Background:* This post-hoc analysis aimed to compare an intense dose-dense sequential chemotherapy (DD-CT) and a conventionally-dosed chemotherapy (CD-CT) in the neoadjuvant AGO-1 study, focusing on the subgroup with inflammatory breast cancer (IBC). *Patients and Methods:* Out of 668 randomised patients, 101 patients presented with IBC. Patients received epirubicin followed by paclitaxel every 2 weeks (DD-CT) or simultaneously every 3 weeks (CD-CT). *Results:* No differences in pathological complete response rates were observed [odds ratio (OR)=1.27, $p=0.33$]. Most patients were scheduled for mastectomy before starting therapy; however, in 21.7% breast-conserving surgery was performed. Disease-free survival rates [Hazard Ratio (HR)=0.65; $p=0.597$] and overall survival rates (HR=1.40; $p=0.327$) were similar for both treatment arms. Patients with breast-conserving surgery had a significantly better outcome than patients

treated with mastectomy (disease-free survival: HR=0.41; $p=0.034$ and overall survival: HR=0.09; $p=0.003$). *Conclusion:* Patients with IBC benefited not from DD-CT but from breast-conserving surgery after neoadjuvant chemotherapy.

Neoadjuvant chemotherapy is well-established as part of the multi-modality management of inflammatory breast cancer (IBC). The latest development in primary chemotherapy was the introduction of anthracyclines and taxanes.

IBC is a distinct, very aggressive, variant of breast cancer. In comparison with non-inflammatory breast cancer, IBC is associated with a higher rate of locoregional recurrence, distant metastasis and lower overall survival (OS) (1). The most common management of the inflammatory disease consists of a multidisciplinary approach to improve local control and overall survival. Primary chemotherapy is considered to be the main component of the treatment (2). The most important prognostic factor for survival after neoadjuvant chemotherapy is pathological complete response (pCR) after primary chemotherapy. Although the survival rate has been improved by the introduction of modern chemotherapy concepts, the outcome is still poor in patients with IBC (3).

Treatment of IBC is similar to treatment of locally-advanced disease, with anthracycline-based chemotherapy

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before surgery. Local control is achieved with surgery and radiation. Further chemotherapy, along with anti-hormonal therapy in hormone receptor-positive disease, can be given adjuvantly (4). However, the best strategy for integrating the different modalities remains controversial (5).

Currently, mastectomy is the gold standard of surgical therapy for IBC. First data, however, justify using preoperative chemotherapy for breast-conserving surgery (BCS) in localized IBC. Clinical observations have shown that BCS can be a useful surgical option in IBC (6).

We investigated a dose-dense, dose-intensified preoperative sequential chemotherapy *versus* a conventional preoperative combination regimen in patients with invasive breast cancer and furthermore in patients with IBC. Treatment arms were compared with regard to pCR as the primary outcome, while surgical outcome, disease-free (DFS) and overall survival (OS), as secondary outcome variables. This report focuses on data of the subgroup analysis including patients diagnosed with IBC.

Materials and Methods

From January 1998 until May 2002 patients were randomized in a multicenter prospective study to compare two epirubicin and paclitaxel-containing regimens given either as dose-dense sequential (DD-CT) with support of filgrastim, at 5 µg/kg, on days 3-10 of each cycle, or as standard combination chemotherapy (CD-CT) in patients with invasive breast cancer (Figure 1). After surgery all patients were treated with three cycles of CMF (cyclophosphamide at 500 mg/m², methotrexate at 40 mg/m² and fluorouracil at 600 mg/m², day 1 and 8 every 4 weeks), radiation and anti-hormonal therapy if indicated. At the time of the study, trastuzumab was not available for patients with early breast cancer.

Inclusion criteria were histologically proven invasive breast cancer, a written consent and imaging methods without suspicion of metastases: chest x-ray, abdominal ultrasound (or computed tomography scan) and bone scan. Further conditions were a normal left ventricular ejection fraction and laboratory values within the normal range.

A total of 668 patients with breast cancer from 55 study centers were randomized, 101 patients had inflammatory disease and 567 patients had a primary tumour ≥3 cm. The primary endpoint was the pCR rate (primary definition: no invasive cancer cells in the breast and axillary nodes in the final histology, after surgery). Secondary endpoints were clinical response rates, side-effects, frequency of BCS, DFS and OS in the two study arms. Age, hormone receptor status, tumour size and clinical axillary lymph node status before chemotherapy, histopathological results after chemotherapy and follow-up data between 2006 and 2008, including local relapse, distant relapse and survival, were collected. Depending on clinical local tumour remission, BCS was performed. If indicated, breast/chest wall radiation was carried out and estrogen-progesterone receptor-positive patients received tamoxifen.

After 6 to 107 months (median=69 months) follow-up time, the rate of relapse of breast cancer (local recurrence and distant metastases) and OS were evaluated for patients in the DD-CT and CD-CT arms separately.

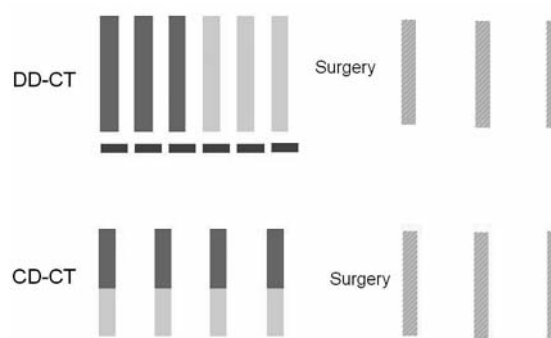


Figure 1. Study design. DD-CT: The red bars represent epirubicin at 150 mg/m² bi-weekly, the orange bars represent paclitaxel at 250 mg/m² bi-weekly. The blue bars represent granulocyte-colony stimulating factor. CD-CT: The combined red and orange bars represent the combination therapy of epirubicin at 90 mg/m² and paclitaxel at 175 mg/m² three-weekly. DD-CT and CD-CT: The striped green bars represent cyclophosphamide at 500 mg/m², methotrexate at 40 mg/m² and fluorouracil at 600 mg/m² at day 1 and 8 every 4 weeks after surgery.

Statistical analyses. For the survey, qualitative data were entered into a database and analysed using the SPSS software (SPSS, Chicago, IL, USA) for Windows (release 17.0). The results in the trial arms were analyzed by Chi-square and Fisher's exact tests, except for survival analyses, performed using the Kaplan Meier method, the log rank test, and the Cox's hazard regression model for covariate adjustment. All reported *p*-values resulted from two-sided testing. *p*-Values <0.05 were considered statistically significant.

Results

Baseline characteristics of patients with IBC by treatment arm, are given in Table I and were well-balanced except for grade. The median age of patients in DD-CT was 53 years (range 33-64 years), 61 % (25/41) were post-menopausal. The median age of the patients in the CD-CT arm was 54 years (range=30-64 years) and 58% were post-menopausal (30/51). The flow of patients throughout the study and the availability of data are shown in Figure 2. Eight patients with IBC had early withdrawal from chemotherapy or refusal of surgical intervention. Five patients (11.9%) of the DD-CT arm and three patients (5.9%) of the CD-CT arm were lost to follow-up, respectively.

Surgery, radiotherapy and anti-hormonal therapy. In 20.6% (19/92) of breast cancer patients who were candidates for mastectomy before chemotherapy, breast conservation was possible after neoadjuvant therapy (Table II); for the DD-CT arm, this means BCS was possible in 14.3% (6/42); 25.5% (13/51) of the patients who underwent the CD-CT regimen were treated with BCS. Some patients with tumours of large

Table I. *Clinical and pathological characteristics at baseline of study patients with inflammatory breast cancer.*

Characteristic	DD-CT (n)	DD-CT (%)	CD-CT (n)	CD-CT (%)
Total number of patients	48	47.5	53	52.5
Number of patients eligible for analysis	42 (42/48)	41.6 (87.5)	51 (51/53)	50.5 (96.2)
Median age, years	53 (range 33-64)	54 (range 30-64)		
Menopausal status	25	61	30	58
cT4	42	100	51	100
Clinical nodal status				
Negative	8	19.0	10	19.6
Positive	33	78.6	39	76.5
Unknown	1	2.4	2	3.9
Grade				
1	0	0	2	3.9
2	8	19.0	20	39.2
3	29	69.0	24	47.1
Unknown	5	12.0	5	9.8
Proposed surgery				
Lumpectomy	2	4.8	3	5.9
Mastectomy	39	92.9	48	94.1
Unknown	1	2.3	0	0
Hormone receptor status				
Positive	20	47.6	27	52.9
Negative	16	38.1	18	35.3
Unknown	6	14.3	6	11.8

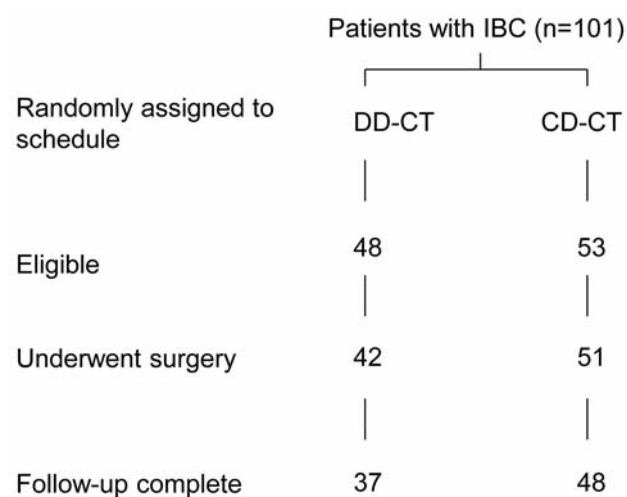


Figure 2. *Consort diagram.*

initial size (up to 7.9 cm) were treated with lumpectomy or quadrantectomy. Three patients needed a secondary resection because of residual disease after first surgery.

After chemotherapy and definitive surgery 65/92 (70.7%) of patients underwent radiation of the breast or chest wall.

Table II. *Final surgery performed versus planned surgery before start of neoadjuvant chemotherapy.*

Performed/ planned	Breast-conserving therapy	Mastectomy	Total
n	5	87	92
Lumpectomy	1 (20%)	12 (14%)	13 (14%)
Quadrantectomy	2 (40%)	8 (9%)	10 (11%)
Mastectomy	2 (40%)	67 (77%)	69 (75%)

Clinical and pathological response. Twelve weeks after the start of chemotherapy, 51/84 (60.7%) patients in both arms showed a clinical response. Ten patients (11%) had a pCR, 12% in the DD-CT and 10% in the CD-CT arm [odds ratio (OR)=1.27, $p=0.33$]. This finding is in contrast to the results of the entire study population, with a significantly higher pCR in the DD-CT arm (18% versus 10%, $p=0.008$) (7, 8).

Recurrent disease. The median follow-up was 69 months (range 6-107 months). For IBC, the recurrence rate was 54.8% (23/42) for the patients treated with the intensified DD-CT regimen and 50.9% (26/51) for patients in the standard arm. Three out of 23 patients developed hepatic, five bone, and three cerebral/meningeal metastases. Four

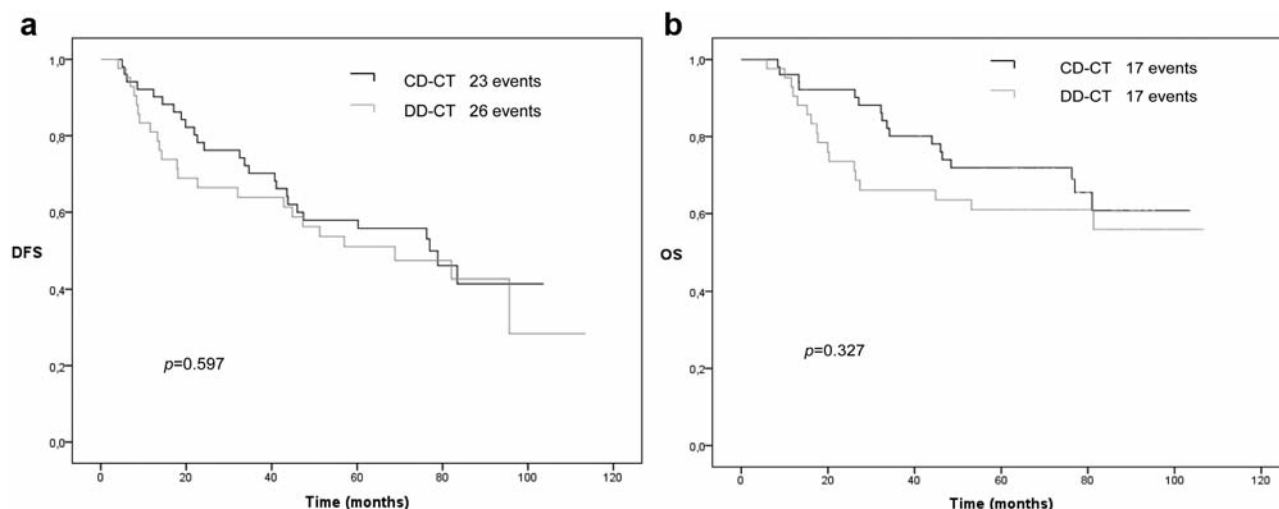


Figure 3. a: Time to relapse by therapy arm [cumulative disease-free survival (DFS)]. The two therapy regimens DD-CT and CD-CT did not differ in DFS. b: Cumulative overall survival (OS) curves by treatment arm. The two therapy regimens DD-CT and CD-CT did not differ in OS.

patients had multiple localizations of metastases. In one patient, infraclavicular lymph nodes were involved. In 26% (6/23) of patients, localization of metastases was not specified. According to the censored data, documented local recurrence occurred in four patients (8.6%).

In 51% (26/51) of patients in the CD-CT arm, recurrence or metastases occurred. Bone metastases appeared most frequently (4/26), followed by cerebral metastases (2/26) and meningeal involvement (1/26). Seven patients had multiple localizations of metastases and as in the DD-CT arm four patients had a local recurrence.

While for the non-IBC group DFS was significantly longer using the DD-CT regimen [Hazard ratio (HR)=0.65, 95% Confidence interval (CI)=0.46-0.92, $p=0.015$] (8), for patients with IBC, DFS did not differ as a function of trial arm (HR=1.16, 95% CI=0.66-2.05; $p=0.597$) (Figure 3a). The result remains virtually unchanged, when adjusted for the baseline grading imbalance (HR=1.31, 95% CI=0.73-2.35). Neither does grading significantly predict DFS, nor do any subgroup analyses show a distinct interaction between grading and therapy. Patients with pCR had no benefit regarding DFS when compared with patients without pCR (HR=0.929, 95% CI=0.45-1.92; $p=0.842$). In terms of surgical therapy a significant benefit in DFS emerged for patients treated with BCS (HR=0.409, 95% CI 0.17-0.96, $p=0.034$). If considered for each therapy arm separately, no benefit of BCS was demonstrated (DD-CT: $p=0.143$, CD-CT: $p=0.116$).

Overall survival rate. In the subgroup analysis of IBC patients, 17/42 (40.5%) patients died in the DD-CT arm and 17 patients (33.3%) in the standard arm. As shown by Untch *et al.* (8) the data of the whole study population

demonstrated a significant benefit for the DD-CT regimen (HR=0.79, 95% CI=0.61-0.94, $p=0.034$). However, this was not proven in this analysis for the IBC cohort (Figure 3b; HR=1.40, 95% CI=0.71-2.75; $p=0.327$). As shown for DFS, adjustment with respect to the significant imbalance in grading between trial arms did not influence OS rate differences either (HR=1.49, 95% CI=0.75-2.97). Patients with IBC and after BCS were demonstrated to have significantly longer survival time compared to patients treated with mastectomy (HR=0.09, 95% CI=0.01-0.65, $p=0.003$). As shown for DFS, there were no differences between the two therapy regimens.

Toxicity. Haematological toxicity included the following: leucopenia, neutropenia, thrombopenia and anaemia. For IBC, data are available from 40/42 patients in the DD-CT arm and from 47/51 patients in the standard arm. Both groups were analysed with regard to frequency and severity of events. Thirty-seven patients in the DD-CT arm had leucopenia (WHO grade 1-4) as did 42 in the standard arm, with WHO-grade 3 being most prevalent ($p=0.0003$). Significant differences were seen for thrombopenia ($p=0.0008$) and anaemia ($p<0.0001$). Neutropenia was not different in the groups. These data are in accordance with the data for the whole patient cohort [Table 5, in (8)].

Reduced appetite, vomiting, dyspnea, infection, alopecia, diarrhea, constipation, pain, stomatitis, allergy, cardiac failure, neuropathy, bleeding, haematuria, fever and skin disorders were summarized as non-haematological toxicities. Significant differences ($p<0.01$) in favour of the standard regimen (lower WHO grade) were demonstrated for reduced appetite, dyspnea, infection, pain, peripheral neuropathy and fever.

Discussion

The IBC subgroup of this study represents one of the largest prospectively randomized neoadjuvant trial populations. pCR rates did not differ significantly between the patients treated with CD-CT compared to DD-CT. The latter was more toxic and less tolerable. Nevertheless, haematological and non-haematological toxicities were manageable with standard supportive measures.

In contrast to the analysis of the total patient cohort of our trial (7, 8) where a significant benefit in pCR was demonstrated for DD-CT (8), this sub-analysis of patients with IBC did not detect statistically significant differences between schedules, but the pathological response rate was slightly higher in the DD-CT arm, yet this did not translate into a better outcome for these patients. In contrast to our findings, previous results show that pCR after neoadjuvant chemotherapy is the strongest prognostic factor for IBC (9, 10). Additionally, our subgroup analysis focused on clinical response rates in patients with IBC, and one aim of applying neoadjuvant chemotherapy to patients with inoperable breast cancer was to increase the possibility for surgery by downsizing the tumour. IBC is generally regarded as a disease with a contraindication for BCS (11, 12). Despite this fact, in about a quarter (25/93, 23.7%) of our patients with IBC, breast conservation was performed after neoadjuvant chemotherapy. Secondary surgery due to involved margins was very low (3.2%). In consideration of the small sample size, the clinical response to chemotherapy and thus the type of surgical therapy seemed to influence the outcome of the patients positively. In summary, for both arms and independent of chemotherapy regimen, patients with IBC and BCS had a better outcome (DFS and OS) than patients treated with mastectomy. This could lead to the assumption for local clinical response being of higher prognostic value than pCR in the case of IBC and in contrast to findings for non-IBC. Most of the results from the literature are retrospective and do not allow any conclusions to be drawn on this issue. One prospective study of Costa *et al.* (13) showed a BCS rate in patients with IBC of 12.9%. These data and our observations suggest that the dogma that IBC always requires mastectomy should be questioned and in IBC, a conservative surgical approach could be allowed. Follow-up data of our patient cohort provides evidence that BCS might be indicated for certain patients with IBC. As shown in this study and according to Shen *et al.* (6), this approach is associated with relatively low locoregional recurrence rates. But it must be summarized that irrespective of the neoadjuvant approach taken and the kind of treatment regimen, patients with IBC had a worse outcome.

In this trial, trastuzumab was not used in patients with HER2/neu-overexpressing tumours because it was not standard practice at that time. The use of trastuzumab can increase the pCR rate as shown in the TECHNO trial (14), in the NOAH trial (15) and in the GeparQuattro trial (16),

with a pCR of 31.7% versus 15.7% in the reference group (HER2/neu-negative after chemotherapy). In a trial of the Southern Italy Cooperative Oncology Group, a pCR of 16% versus 6% was noted for the schedule including cisplatin in combination with epirubicin and paclitaxel weekly versus epirubicin and paclitaxel three-weekly (17). IBC is generally known as a rapidly progressive disease with poor prognosis compared to other types of breast cancer. Our analyses support this. In contrast to the non-IBC patient cohort, the outcome was still poor in both arms, irrespective of the treatment schedule. The small numbers in the subgroups do not allow for definitive conclusions to be drawn. Data from another study of the few prospective neoadjuvant studies for IBC did not demonstrate an advantage of a dose-intensified chemotherapy regimen (18). Most of the published data are from studies with small patient numbers, most of the studies did not evaluate the IBC group separately (14, 19-21).

In conclusion, in the non-IBC group our study demonstrated a significantly higher pCR with better DFS and OS rates after neoadjuvant chemotherapy with dose-dense anthracyclines and taxanes (8). Therefore neoadjuvant DD-CT therapy is a treatment option for high risk primary breast cancer (8). This effect was not evident in the IBC group, although the separate evaluation of the IBC group was not pre-planned. For patients with IBC, the addition of other treatment modalities such as platinum salts for patients with triple-negative or (*BRCA*)-mutated tumours, trastuzumab or other anti-HER2 therapies for patients with HER2/neu overexpression, as well as bevacizumab, (mTOR) inhibitors or (PARP) inhibitors are possible options, as shown in neoadjuvant trials of non-inflammatory breast cancer (22-25). These new and promising compounds are now being included in ongoing prospective randomized neoadjuvant trials (21, 26-30). The addition of new predictive markers from primary tumours before and after surgery, such as HER2/neu status, *BRCA* mutation, (*PTEN*) mutations and, p95 expression, are under evaluation to establish new treatment strategies for IBC in the near future.

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