Anti-Cancer Drugs 2002, **13,** pp. 67–74

Report

Combined analysis of two phase II trials in patients with primary and advanced breast cancer with epidoxorubicin and docetaxel+granulocyte colony stimulating factor

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Anthracyclines and taxanes are to date the most active cytotoxic agents in the treatment of breast cancer, and a combination of these is therefore considered to result in the highest response rates in the neoadjuvant, as well as in palliative treatment. These two phase II studies aimed to evaluate the feasibility, toxicity and activity of a cytostatic regimen combining epidoxorubicin and docetaxel in outpatient patients suffering from breast cancer. In total, 104 consecutive patients were enrolled in these prospective clinical trials. The chemotherapeutic regimen consisted of epidoxorubicin [75 mg/m^2 body surface area (BSA)] and docetaxel (75 mg/m^2 BSA) on day 1 accompanied by the administration of granulocyte colony stimulating factor on days 3–10, repeated every 3 weeks (ED+G). Sixty-six patients received ED+G as neoadjuvant and 38 patients as palliative treatment, respectively. Patients received a total of 566 cycles (median: 6 cycles, range: 2–11 cycles) of this therapeutic regimen. Outpatient ED+G was well tolerated. A major response to preoperative ED+G could be demonstrated in 54 of 66 patients (82%) and in 22 of 38 palliative treated patients (58%). We conclude that outpatient ED+G is safe in the neoadjuvant and palliative treatment of patients suffering from breast cancer by showing a favorable side effect and activity profile. Thus, this regimen can be considered for further clinical trials. [© 2002 Lippincott Williams & Wilkins.]

Key words: Breast cancer, chemotherapy, docetaxel, epidoxorubicin, neoadjuvant.

Introduction

Breast cancer is one of the leading cancer sites in woman; in North America, approximately 200 000 new cases and 50 000 deaths are reported per year. In Europe, new cases and recorded deaths amount annually to 150 000 and 58 000, respectively.[1]

Preoperative chemotherapy leads to a significant reduction in tumor size (downstaging), and improves both the rate and the cosmetic results of a breast conserving surgery. Another reason to apply chemotherapy preoperatively is that the early use of cytotoxic drugs can possibly avoid resistance and can possibly kill or inhibit clinically undetectable micrometastases to avoid metastatic disease. In the palliative setting the aim of cytostatic treatment is to maintain and improve life quality and prolong overall survival.

The introduction of the combination chemotherapy of the most active cytostatic agents, the anthracyclines (doxorubicin and epidoxorubicin) and taxanes (paclitaxel and docetaxel), was an important step for improving definitive cytostatic treatment in the neoadjuvant, adjuvant, as well as in the palliative setting for breast cancer patients at high risk.[2–9] Before the emergence of taxanes, doxorubicin was considered to be the most active single-agent, showing an overall response rate of 40–50% when given as first-line therapy.[10] Epidoxorubicin, a newer anthracycline with a spectrum of activity similar to that of doxorubicin, has some significant advantages to doxorubicin, including reduced acute and chronic toxicity, especially cardiotoxicity.[11,12] Thus, epirubicin, which is licensed and has been used in Europe for the treatment of breast cancer for 10 years, has replaced doxorubicin in the majority of the European countries. Recently, it has also been approved in the US by the FDA for adjuvant treatment of breast cancer.[13] Yet, objective response rates increased with the introduction of the taxanes.[14–16] With the use of

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combination chemotherapy, it was possible to increase response rates beyond those resulting from single-agent application.[2,5–9,17] Given the single-agent activity and increased response rate of anthracycline/taxane combination therapy alongside the agents' relative non-cross-resistance, partially non-overlapping toxicities and differing mechanisms of action, there is a clear rational for combining them for the treatment of breast cancer.

As a consequence of these data and results, we have initiated two prospective clinical phase II single-institution evaluations to determine the feasibility, the toxicity and the efficacy of combined chemotherapy with outpatient epidoxorubicin and docetaxel plus granulocyte colony stimulating factor (G-CSF) in the neoadjuvant and palliative outpatient treatment of patients suffering from breast cancer. Because of equal frequency and severity of toxicities in these two phase II trials we present the results together in one paper.

Patients and methods

Patients

The protocol passed the local ethical committee. In total, 104 consecutive patients with histological proven breast cancer were accrued in these prospective clinical evaluations between October 1996 and October 1999. Patients received a combination chemotherapy of epidoxorubicin and docetaxel together with G-CSF (ED+G) as neoadjuvant or palliative treatment. Criteria for inclusion were as follows: histologic proof of breast cancer, age 19–80 years, Karnofsky performance status $>70\%$, life expectancy >6 months and informed consent. Patients were not allowed to be under concurrent cytostatic treatment due to another malignancy. Patients with central nervous system (CNS) metastases were excluded too. Other contraindications included pregnant or nursing women and uncontrolled infection. Adequate contraception was mandatory for pre-menopausal women. None of the neoadjuvant patients had previously been treated with cytostatic chemotherapy and in the palliative setting previous treatments with taxane- or anthracycline-containing regimens were considered as exclusion criterion.

If conventional criteria for breast conserving surgery would have been applied in the neoadjuvant setting, all patients would have been treated with modified radical mastectomy in this trial. Sixty-two patients presented with a tumor greater than 2 cm; the remaining four suffered from a disadvantageous tumor/breast relation, a central tumor site or inflammatory breast cancer. In 16 (24%) patients the tumor was clinically classified as T4, in 22 (33%) as T3, in 25 (38%) as T2 and in three (5%) as T1. The clinical lymph node status was negative in 36 (55%) patients and positive in 30 (45%) patients.

In the palliative treatment 14 of the 38 advanced breast cancer patients had metastasis at the time of diagnoses. Out of all advanced breast cancer patients, 18 patients (47%) received this therapy regimen as first-line treatment, 14 patients (37%) as second-line therapy and six patients (16%) as third-line therapy. All patients had at least one neoplastic lesion bidimensionelly measurable by physical examination or instrumental studies. The metastatic sites are listed in Table 1.

Before starting chemotherapy treatment evaluation consisted of a complete history and physical examination, and patients were required to have white blood cell count (WBC) $\geqslant 3500/\mu$l (normal: 4200–5800/μl) and platelet count $\geqslant 100\,000/\mu$l (normal: 150–350 g/l); normal function test for liver [ASAT (normal: 0–15 U/l); ALAT (normal: 0–19 g/l), alkaline phosphatase level (normal: 60–170 U/l) <2 of normal upper limit and bilirubin level below $\leqslant 1.25$ times upper normal limit (normal: 0.2–1.0 mg/dl)] and kidney [blood urea nitrogen (normal: 6–25 mg/100 ml) or creatinine concentration (normal: 0.5–1.3 mg/100 ml) $\leqslant 1.25$ times upper institutional normal]. Due to possible cardiotoxic effects of the anthracycline-containing regimen, patients were required to produce an adequate ECG and an echocardiography [left ventricular ejection fraction $>50\%$] prior to chemotherapy.

In the neoadjuvant setting pathological diagnosis of invasive breast cancer and hormone receptor status was performed in all patients by core biopsy. Tumor size was determined by mammography, sonography or magnetic resonance imaging (MRI). The most suitable radiological method was chosen to monitor the tumor site. To complete the staging examinations in the neoadjuvant and palliative treatment at least a chest X-ray, liver sonography and a bone scan were required. X-ray studies of selected osseous segments were performed when clinically indicated.

Drug administration

The combination chemotherapy consisted of short-time infusion of 75 mg/m^2 epidoxorubicin (Farm-

Table 1. Characteristics of evaluable patients

	Neoadjuvant	Palliative
No. of evaluable patients	66	38
Median age (range)	50 (32–69)	55 (33–77)
Performance status (Karnofsky) (%)	90–100	80–100
Menopausal status		
pre-menopausal	30 (45%)	14 (37%)
post-menopausal	36 (55%)	24 (63%)
Histology		
invasive ductal	56 (85%)	32 (84%)
invasive lobular	10 (15%)	6 (16%)
Hormone receptor status		
ERICA/PRICA+	36 (55%)	16 (42%)
ERICA/PRICA–	30 (45%)	18 (47%)
not evaluable	–	4 (11%)
Previous treatments		
surgery	–	28 (74%)
radiotherapy	–	28 (74%)
adjuvant chemotherapy	–	17 (45%)
adjuvant hormone therapy	–	6 (16%)
Chemotherapy for advanced disease	–	25 (66%)
Disease site		
soft tissue	–	8 (21%)
bone	–	11 (29%)
cutaneous	–	6 (16%)
viscera	–	28 (74%)
bone marrow	–	4 (11%)
Number of metastatic sites		
1	–	22 (58%)
2	–	12 (32%)
3+	–	4 (11%)

orubicin; Pharmacia Upjohn, Peapack, NJ) followed by a 1-h i.v. infusion of 75 mg/m^2 docetaxel (Taxotere; Aventis, Strasbourg, France) both on day 1, accompanied by s.c. administration of G-CSF (Neupogen; Hoffmann-La Roche, Basel, Switzerland, licensed of Amgen, Thousand Oaks, CA) 30 MU from days 3 to 10, repeated every 21 days. Concomitant medication consisted of oral administration of dexamethasone (2×4 mg days 0, 1 and 2) to prevent peripheral fluid retention and anaphylactic reactions.[18] As prophylactic antiemetic therapy, ondansetron 8 mg was administered i.v. before and after treatment and 3×8 mg/day p.o. for the following 3 days.

According to the protocol, the preoperative treated patients had to receive at least 2 cycles until a maximum of 8 cycles (median: 5; range: 3–8) of the ED+G regimen until best response was achieved. In the palliative setting patients received therapy until progressive disease was documented on computed tomography, unmanageable toxicity appeared or the cumulative dose of epidoxorubicin (800 mg/m^2) was reached (median: 6; range: 2–11).

Dose reductions or treatment delays were applied on the basis of hematologic and/or gastrointestinal toxicity, evaluated according to the WHO scoring system for cancer treatment[19] before each chemotherapy course.

In case of bone marrow depression at the planned day of treatment, the antineoplastic treatment was temporarily discontinued until WBC $>3000/\mu$l and platelets $>100\,000/\mu$l.

Evaluations

Monitoring of serum chemistry and blood cell count was performed prior to each cycle of therapy at 3-weekly intervals. In the case of hematotoxicities necessitating a delay of chemotherapy application, blood counts were performed at weekly intervals. Patients were advised to report any adverse event, especially body temperature $\geqslant 37.6^{\circ}$C during treatment cycles. If one of these treated patients had any signs of congestive heart failure (CHF), echosonography was repeated.

Treatment assessment

In the neoadjuvant setting patients were monitored with mammography, sonography or MRI, after every second therapy cycle, until best response was judged. Based on these assessments, either a quadrantectomy with axillary node dissection (QUAD) or a modified radical mastectomy (MRM) was performed, depending on the size of the primary tumor after preoperative chemotherapy. Postoperative treatment consisted of the appropriate number of ED+G cycles in patients who received less than 6 cycles preoperatively in order to reach 6 cycles. Thereafter, treatment was adjusted according to the stage of the disease. Patients who achieved a pCR received 4 cycles of the CMF regimen [cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2) and 5-fluorouracil (600 mg/m^2)], all other patients were treated with 6 cycles of the latter regimen. All patients who experienced a breast conserving surgery received postoperatively local irradiation and in case of positive hormone receptor status patients additionally tamoxifen 20 mg/day orally.

In the palliative setting patients were monitored with the appropriate radiologic method every 3 cycles of therapy.

Therapy response was evaluated using the following criteria. Complete response (CR) was defined as the disappearance of all measurable disease. Partial response (PR) was a $\geqslant$50% decrease in tumor size. Stable disease (SD) was $<$50% decrease and $<$25% increase without the appearance of new lesions. Progressive disease (PD) was a $>$25% increase in tumor size or the appearance of new lesions.

Statistical analysis

Time to progression (TTP), defined as the interval from the first day of ED+G application until tumor progression, was documented radiographically in the neoadjuvant, adjuvant and palliative setting. If a patient died without restaging for documenting disease status, the TTP was measured to the first date of clinical deterioration. Survival time was measured from the first day of ED+G application until death. Data were analyzed as of 31 March 2001. The distributions of TTP and time to death were estimated using the Kaplan–Meier product-limit method.[20] Toxicity was evaluated according to the WHO criteria and was recorded on patients as the worst episode appearing during treatment.

Results

In total, 104 female patients (pre-menopausal/post-menopausal: 44/60) suffering from breast cancer were included in these evaluations. Sixty-six patients received ED+G as neoadjuvant treatment and 38 patients as palliative first- (n=18; 47%), second- (n=14; 37%) or third- (n=6; 14%) line therapy. Table 1 lists the characteristics of the 104 included patients. All patients were evaluable for toxicity and response.

Toxicities

This combination chemotherapy was well tolerated and all patients completed the therapy on an outpatient basis. One hundred and four patients received a total of 566 cycles (neoadjuvant: median: 5, range: 3–8; palliative: median: 6, range: 2–11) ED+G. All appearing toxicities of the 104 patients are shown together in one table (Table 2) because of equal frequency and severity of toxicities in the neoadjuvant and palliative treatment. The most frequent and important toxic effects were leukopenia, anemia, nausea/vomiting, and stomatitis. Only in three (3%) patients was leukocytopenia WHO grade IV observed. Two of these patients, treated in the palliative setting, required hospitalization because of febrile neutropenia. These three patients, who developed leukocytopenia WHO grade IV, were among the first 10 patients included in these studies. Therefore we decided to use prophylactic G-CSF to avoid leukocytopenia WHO grade IV. WHO grade III toxicities consisted of leukocytopenia (5%), nausea/vomiting (1%), stomatitis (2%) and diarrhea (3%). Nausea/vomiting and diarrhea led to inpatient treatment in two patients (2%) due to their reduced physical state. The most common and often reported toxicities of this combined chemotherapy, i.e. edema, nail and pulmonary toxicities, only occurred in a few patients. Cardiac toxicity or allergic reactions were not observed in any of our patients. All patients developed alopecia WHO grade III after the second cycle of ED+G. No toxicitiy-related death occurred.

Response and survival data

In the neoadjuvant treatment, chemotherapy was stopped in 62 (94%) patients because best possible clinical response was achieved and in the other four (6%) patients because of stable disease. Pathological,

Table 2. Toxicity (n=104 patients) in 566 cycles

	WHO grade [n (%)]			
	I	II	III	IV
Leukocytopenia	4 (4)	12 (11)	5 (5)	3 (3)
Thrombocytopenia	5 (5)	2 (2)	–	–
Anemia	37 (36)	16 (15)	–	–
Nausea/vomiting	11 (11)	4 (4)	1 (1)	–
Stomatitis	11 (11)	7 (7)	2 (2)	–
Fever	1 (1)	5 (5)	–	–
Infection	5 (5)	4 (4)	–	–
Diarrhea	1 (1)	4 (4)	3 (3)	–
Obstipation	3 (3)	3 (3)	–	–
PNP	2 (2)	–	–	–
Pulmonary toxicity	1 (1)	–	–	–
Pain	–	3 (3)	–	–
Cardiac toxicity	–	–	–	–
Nail toxicity	–	3 (3)	–	–
Edema	1 (1)	4 (4)	–	–
Allergic reaction	–	–	–	–
Alopecia	–	–	104 (100)	–

a major response (pCR+PR, graded to the International Union Against Cancer) was observed in 54 of 66 patients (82%), with 10 patients (15%) experiencing a pathological CR of the invasive tumor (T0: n=6, DCIS: n=4) and 44 patients (67%) showing a partial response. Only 12 patients (18%) presented with SD. Breast-conserving surgery was possible in 43 patients (65%). None of the neoadjuvant treated patients progressed during therapy, all patients are still alive, median observation time for these patients is 39 months (range: 7–62+ months). Only eight (12%) patients relapsed between 8 and 38 months (median: 20 months) after starting preoperative cytostatic treatment (Figure 1), and four (6%) patients died (Figure 2).

In the palliative treatment we achieved a major response (CR+PR) in 22 of 38 patients (58%). Three (8%) patients had a CR, 19 (50%) patients a PR, 15 (39%) patients a SD and only one (3%) patient, receiving ED+G as third-line treatment, suffered from an early progression of liver metastasis 4 weeks after administering the first cycle of ED+G. Twenty-seven (71%) patients relapsed between 1 and 27 months, whereupon nine of these patients previously had reached a CR or PR as best response to treatment. Twenty-seven (71%) patients are still alive, two (5%) patients are lost to follow-up and 11 (29%) patients died. The median TTP was 16 months (range: 1–47+ months) and the median survival time from the day of start of ED+G treatment is 30.5 months (range: 5–60+ months).

The subgroup analysis for the palliative treated patients receiving this therapy regimen as first-, second- or third-line treatment revealed a major response (CR+PR) in eight (44%) patients (one+seven patients), in nine (64%) patients (two+seven patients) and in five (83%) patients (none+five patients), respectively. A SD was observed in 10 (56%) patients receiving ED+G as first-line and in five (36%) patients as second-line treatment. Median TTP was 16 months (6–38+ months; Figure 3), 17 months (3–47+ months; Figure 3) and 7 months (1–11 months; Figure 3), respectively. Overall survival time is 33+ months (range: 6–60+ months; Figure 4), 24,5 months (range: 12–52+ months; Figure 4) and 14 months (5–35+ months; Figure 4), respectively.

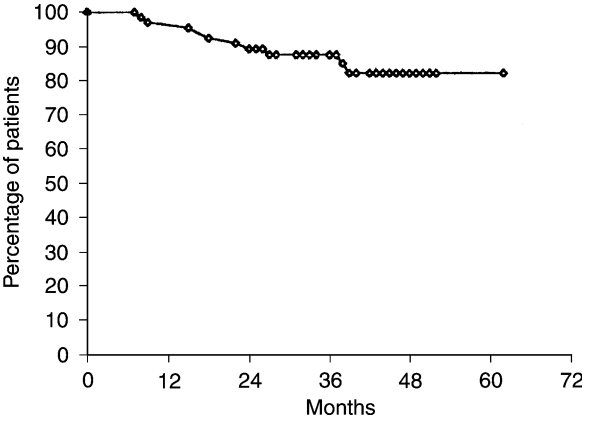

Figure 1. TTP of 66 patients with breast cancer receiving neoadjuvant treatment with epidoxorubicin and docetaxel+G-CSF.

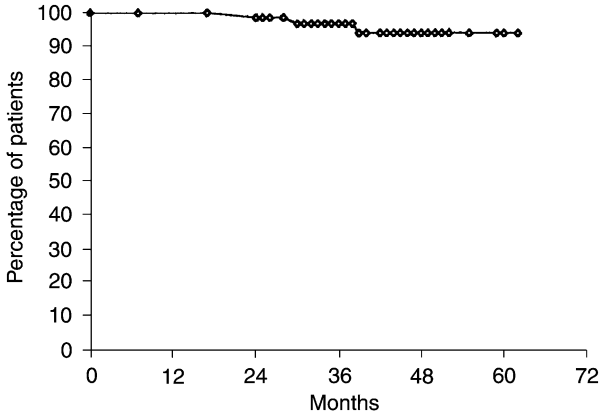

Figure 2. Overall survival of 66 patients with breast cancer receiving neoadjuvant treatment with epidoxorubicin and docetaxel+G-CSF.

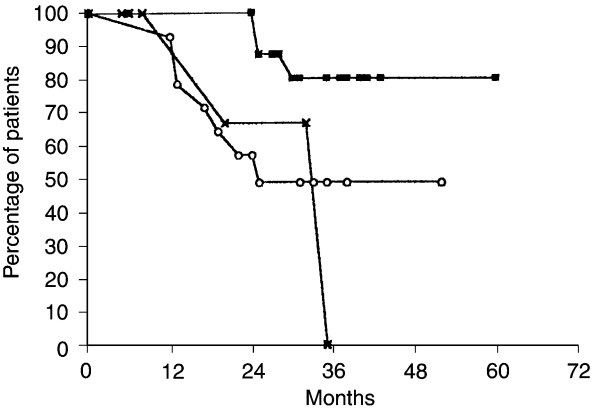

Figure 4. Overall survival of 38 patients with metastatic breast cancer receiving palliative treatment with epidoxorubicin and docetaxel+G-CSF as first- (squares, n=18), second- (circles, n=14) or third- (crosses, n=6) line therapy.

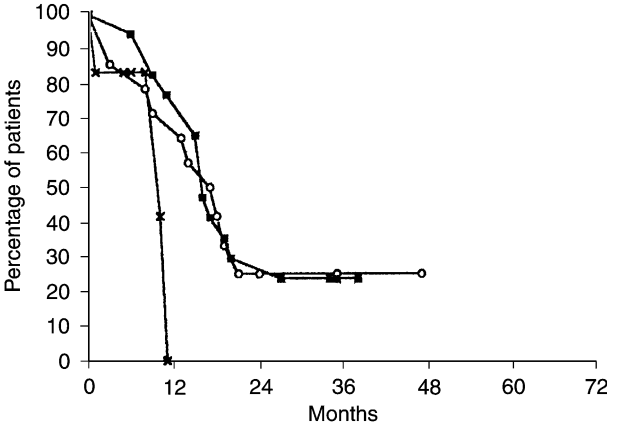

Figure 3. TTP of 38 patients with metastatic breast cancer receiving palliative treatment with epidoxorubicin and docetaxel+G-CSF as first- (squares, n=18), second- (circles, n=14) or third- (crosses, n=6) line therapy.

Discussion

We performed two single-institution prospective clinical trials of a combination chemotherapy consisting of epidoxorubicin and docetaxel+G-CSF in the neoadjuvant and palliative setting of breast cancer to evaluate the efficacy and tolerability of this outpatient regimen.

Reviewing the literature shows that anthracycline-based combination chemotherapies demonstrate overall response rates of 65–80% with pCR rates up to 13% in the neoadjuvant treatment.[21,22] By adding taxanes to anthracycline–based chemotherapies, it might be possible to improve these results.[5] The aim of such studies was to raise the rate of breast conserving surgeries as well as the pCR rates and therefore possibly to prolong survival. In our recent trial we achieved an overall response rate of 82% with a pCR rate of 15%, thus leading to a breast conserving surgical procedure in 43 (65%) preoperatively treated patients. These results confirmed our early data administering the combination chemotherapy with epidoxorubicin and docetaxel preoperatively in 34 patients, leading to an overall response rate of 85%, pCR rate of 11% and quadrantectomy rate of 53%.[23] All these results suggest that preoperative chemotherapy might prevent mastectomy in more than 50% of patients, but further studies are necessary to demonstrate if achieving a pCR after preoperative chemotherapy will correspond to long-term prognosis.

In the palliative setting our study revealed an overall response rate of 58%, including 8% CR. When comparing the overall response rates reached in other studies (48–94%[2,6,17,24,25]), our data are well within range, although we were not able to reproduce the responses of Dombernowsky *et al.*,[24] Gehl *et al.*[17] and Gianni *et al.*[2] This might probably be explained by the pretreatment characteristics of our patient population: 17 out of 38 patients had failed after adjuvant chemotherapy (including anthracycline-based regimens in 12 patients) and six to adjuvant hormonal therapy. Twenty (51%) of the included 38 patients had progressed after first- or second-line palliative treatment. However, our CR rate was also in the range of those reported by other institutions.[2,6,17,24,25] Only the studies of Dombernowsky *et al.*,[24] Gehl *et al.*[17] and Gianni *et al.*[2] showed CR rates between 24 and 41%. Again, in

these three studies, nearly all included patients were chemonaive and only some patients had received prior hormonal therapy, quite in contrast to our patient population. These reasons mentioned above might contribute to the significantly lower response rate observed by us.

ED+G proved to be safe and well tolerated. The WHO grade III and IV toxicities were generally low in all treatment groups in this trial. All patients were able to complete this therapy on an outpatient basis and only two patients required temporary hospitalization because of febrile neutropenia. This is probably the effect of the concomitant medication, especially the consequent use of G-CSF. Study groups not using G-CSF routinely when applying combination chemotherapy consisting of E and D reported WHO grade III and IV leukocytopenia up to 71%.[26] Pagani *et al*.[7] used a combination chemotherapy of epirubicin 90 mg/m^2 and docetaxel 75 mg/m^2 without prophylactic use of G-CSF and reported febrile neutropenia in 12% of the cycles. In addition, dose escalation of E and D increases the WHO grade III and IV toxicities without raising the response rates.[27,28] Higher doses of doxorubicin and paclitaxel, which resulted in higher response rates, also raised the WHO grade III and IV toxicities.[2,17,24] The most feared complication of anthracycline-based combination chemotherapies is CHF, whereby the chronic appearance is principally dependent on the cumulative anthracycline dose and occurs by definition within 1 year of therapy. The combination chemotherapy of doxorubicin and paclitaxel has been investigated in a lot of trials in patients with metastatic breast cancer with differing doses and schedules. The incidence of CHF ranges between 0 and –21% when applying a median cumulative dose of doxorubicin between 240 and 420 mg/m^2.[4] Gennari *et al*.[29] demonstrated that the incidence of CHF after an epidoxorubicin/paclitaxel regimen is low up to cumulative epidoxorubicin doses of 990 mg/m^2. Strategies that result in less cardiotoxicity include substituting epidoxorubicin (the 4′ epimer of doxorubicin) instead of doxorubicin because of its equieffectivity but lower degree of cardiotoxicity than its parent compound[15] or substituting docetaxel instead of paclitaxel.[4] Docetaxel has no significant effect of the plasma disposition of doxorubicin, thus used as an explanation for the decreased cardiotoxicity observed with the doxorubicin/docetaxel combination.[30] In our trial, we therefore used epidoxorubicin until a cumulative dose of 800 mg/m^2 instead of doxorubicin and docetaxel instead of paclitaxel, and indeed we did not observe any cardiotoxicity.

Conclusion

These present studies have shown the combination chemotherapy of 75 mg/m^2 epidoxorubicin and 75 mg/m^2 docetaxel+G-CSF to be a safe and highly effective regimen in the neoadjuvant and palliative setting in patients suffering from breast cancer. It seems possible to reduce hematologic and non-hematologic toxicities by using an appropriate concomitant medication and also to avoid cardiotoxicity by applying epidoxorubicin instead of doxorubicin. Thereby, all patients were able to undergo the therapy on an entirely outpatient basis, leading to obtained and improved quality of life. Our data suggest that ED+G combination chemotherapy is suitable for planned future trials due to its high effectivity and acceptable toxicity.

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(Received 2 October 2001; accepted 16 October 2001)