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ORIGINAL ARTICLE

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Phase I/II trial of weekly epidoxorubicin and docetaxel (wED) in the neoadjuvant and palliative treatment of patients with breast cancer

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Abstract *Purpose:* Anthracyclines and taxanes are the most active cytotoxic agents in the treatment of breast cancer. Based on observations with weekly administration of paclitaxel which results in better tolerability and higher dose intensity as compared with 3-weekly schedules, we designed a phase I/II trial with weekly epidoxorubicin and docetaxel (wED) for the preoperative and palliative treatment of patients with breast cancer. *Patients and methods:* A group of 33 female patients (20 neoadjuvant and 13 palliative) were treated with weekly epidoxorubicin (25–35 mg/m^2) as a short i.v. infusion followed by docetaxel (25–40 mg/m^2) as a 1-h i.v. infusion once a week for 6 weeks followed by 1 week off therapy, without G-CSF support. Sequential cohorts of patients were treated with epirubicin and docetaxel at the following dose levels: 25/25, 25/30, 30/30, 30/35, 35/35, and 35/40 mg/m^2. *Results:* Patients received a total of 74 courses (median 2, range 1–4 courses) of this therapeutic regimen. The maximum tolerated dose occurred at the dose level combining 35 mg/m^2 of epidoxorubicin and 40 mg/m^2 of docetaxel, with the dose-limiting toxicity being neutropenic fever in two patients at dose level 6. *Conclusions:* The wED regimen is a feasible, safe, and highly active combination chemotherapy for advanced breast cancer. We recommend epidoxorubicin 30 mg/m^2 and docetaxel 35 mg/m^2 for further trials because of the high incidence of neutropenic fever and lymphocytopenia of WHO grade IV at dose levels 5 and 6.

Keywords Breast cancer · Phase I/II study · Epidoxorubicin · Docetaxel · Weekly

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Introduction

Dose optimization is of great importance for the effectiveness of chemotherapy in breast cancer and other solid tumors [6, 8]. Dose intensification can improve objective response rates, and progression-free and overall survival [9, 14]. To date anthracyclines and taxanes are the most active drugs in the treatment of advanced breast cancer and a combination of these is considered to produce the highest response rates in the palliative treatment setting (52–94%) and in the neoadjuvant treatment setting (74–93%) [7, 13, 21, 26]. This combination chemotherapy is also being tested in several ongoing studies in the adjuvant setting for patients at high risk [10].

Weekly administration of chemotherapy agents can possibly result in an increased dose intensity and in a better tolerability profile because of the lower net dose application per week. Clinical trials with paclitaxel and docetaxel have shown a marked reduction in myelosuppression when the drugs are administered on a weekly schedule [2, 19]. Based on observations using weekly administration of paclitaxel and docetaxel monotherapy [2, 19] and of combinations with anthracyclines (doxorubicin or epidoxorubicin) [6, 12, 23, 25], which result in better tolerability and higher dose

intensity, we designed a phase I/II trial with weekly epidoxorubicin and docetaxel (wED) without granulocyte colony-stimulating factor (G-CSF) for the preoperative and palliative treatment of breast cancer. The objective of this study was to determine the maximum tolerated dose (MTD) and the dose-limiting toxicity (DLT) leading to a recommended dose of the wED combination chemotherapy in patients suffering from breast cancer. Another aim of this study was to determine the therapeutic response in the neoadjuvant as well as in the palliative setting.

Patients and methods

Clinical protocol

Eligibility criteria included: histologic proof of primary or metastatic breast cancer; age 19 to 80 years; Karnofsky performance status >70%; a life expectancy of >3 months; adequate hematologic parameters, including white blood cell count >3500/μl (normal range 4200–5800/μ/) and platelet count >100,000/μl (normal range 150,000–350,000/μl); adequate hepatic function [ASAT (normal range 0–15 U/l), ALAT (normal range 0–19 U/l) and alkaline phosphatase (normal range 60–170 U/l) less than twice the upper normal limit, and bilirubin (normal range 0.2–1.0 mg/dl) less than 1.25 times the upper normal limit], renal function [blood urea nitrogen (normal range 6–25 mg/100 ml) or creatinine (normal range 0.5–1.3 mg/100 ml) less than 1.25 times the upper institutional normal limit], and cardiac function (left ventricular ejection fraction >50% as measured by echocardiography); no prior concurrent cytostatic treatment due to another malignancy; and no central nervous system metastases. Patients received neoadjuvant treatment if conventional criteria for breast-conserving surgery would not have been applied (tumor greater than 2 cm, disadvantageous tumor/breast relationship, central tumor site, or inflammatory breast cancer) and none had previously been treated with cytostatic chemotherapy. All metastatic patients received the therapy as first-line palliative treatment. The protocol was approved by the local ethics committee and all patients gave informed consent.

Study design

The study was conducted using a standard phase I design, with sequential cohorts of patients receiving epidoxorubicin and docetaxel at increasing doses, as listed in Table 1. Epidoxorubicin (Farmorubicin; Pharmacia & Upjohn, Peapack, N.J.) was administered as a 30-min intravenous (i.v.) short infusion followed by a 1-h infusion of docetaxel (Taxotere; Aventis, Strasbourg, France). Epidoxorubicin and docetaxel were administered on an outpatient basis without the support of prophylactic G-CSF. Each 7-week cycle comprised 6 weeks of treatment followed by 1 week of rest. Patients were restaged after each cycle. In the neoadjuvant treatment patients had to receive at least one cycle but a maximum of four cycles of wED until best response was achieved. In the palliative setting patients received therapy until progressive disease (PD) was documented on computed tomography (CT), the possibility of surgery for their metastatic lesions was reached, the cumulative dose of epidoxorubicin reached 800 mg/m^2, or implicit patient request to stop treatment. No patient received more than four cycles of weekly epidoxorubicin and docetaxel.

To avoid possible allergic reactions and to prevent the occurrence of docetaxel-induced peripheral fluid retention and anaphylactic reactions, all patients were given a 3-day oral corticosteroid prophylactic concomitantly, starting the day before chemotherapy (dexamethasone 2×4 mg days 0,1 and 2) [4].

Three to five patients were enrolled at each dose level. Five patients were entered at the first two dose levels to improve the chance of detecting DLT. No dose escalation was allowed in an individual patient. After completion of one course (7 weeks) of therapy, the toxicity of therapy was evaluated. Dose-limiting myelosuppression was defined as leukocytopenia WHO grade IV for more than 4 days or resulting in hospitalization for treatment of leukocytopenia and fever, or thrombocytopenia WHO grade IV for more than 4 days or associated with a bleeding episode or requiring platelet transfusion. Any nonhematologic WHO grade III or IV toxicity was also considered a DLT, with the exception of alopecia.

To determine the MTD, the frequency of DLT observed in the first three patients of each cohort was determined. If two hematologic or nonhematologic DLTs were seen among the first three patients, an additional three patients were entered at the same dose level. If four of the first six patients had hematologic or nonhematologic DLTs, further dose escalation was stopped and the previous dose level was defined as the MTD. If hematologic or nonhematologic DLTs occurred in all three patients, then the dose escalation was stopped and the previous dose tested was defined as the MTD.

Monitoring of patients

In the neoadjuvant setting, the tumor status of patients was reevaluated clinically and by mammography, sonography or magnetic resonance imaging, after every 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 and site of the primary tumor after induction chemotherapy. The criteria for breast-conserving surgery after neoadjuvant chemotherapy were identical to those in patients without neoadjuvant chemotherapy. Adjuvant treatment was adjusted according to the stage of the disease. In the palliative setting the tumor status of patients was monitored by CT of the chest and abdomen with additional work-up if indicated every cycle of therapy according to WHO criteria [11].

Toxicity was evaluated according to WHO criteria, and was recorded as the worst episode appearing during every chemotherapy course. Time to progression (TTP), defined as the interval from the first day of wED administration to tumor progression, was documented radiographically in the neoadjuvant and palliative settings. If a patient died without restaging for documenting disease

Table 1. Planned dose levels of epidoxorubicin and docetaxel and treatment administration

Dose level	Epidoxorubicin (mg/m^2)	Docetaxel (mg/m^2)	Number of cycles	
			Total	Median (range)
1 ($n=5$)	25	25	12	2 (2–3)
2 ($n=5$)	25	30	16	3 (3–4)
3 ($n=3$)	30	30	7	2 (2–3)
4 ($n=8$)	30	35	17	2 (1–3)
5 ($n=6$)	35	35	11	2 (1–2)
6 ($n=6$)	35	40	11	2 (2–3)
Total ($n=33$)	–	–	74	2 (1–4)

status, the TTP was taken as the time to the first day of clinical deterioration. Survival time was measured from the first day of wED administration until death. Data were analyzed as of January 31st 2001.

Results

A total of 33 patients (11 premenopausal, 22 postmenopausal) suffering from breast cancer were included in this prospective clinical evaluation between May 1999 and November 2000. Of the 33 patients, 20 (61%) received wED as neoadjuvant treatment and 13 (39%) as palliative first-line therapy. Their median age was 51 years (range 37–71 years), and the median observation time was 17 months (range 3–23+ months). All patients were evaluable for toxicity and response. Patients in both the neoadjuvant and palliative treatment groups were included together in the cohorts because of equal frequency and severity of toxicities in these two treatment groups [26].

Treatment

All patients received at least one course (7 weeks) of treatment. A total of 74 courses (median 2, range 1–4) were administered (Table 1). The following numbers of courses were administered: one course, three patients; two courses, 18 patients; three courses, 11 patients; and four courses, one patient. In all neoadjuvant-treated patients, therapy was stopped because of best possible clinical response. Two (15%) of the palliative-treated patients were removed from treatment for tumor progression. Nine patients (69%) were removed from treatment because of reaching the possibility of surgery for their metastatic lesions (partial response, PR, $n = 5$). One patient (8%) completed four courses of therapy and was withdrawn from treatment having reached a PR and one patient (8%) was removed electively by the treating physicians.

Only nine patients (27%) had doses withheld due to toxicity. The last two patients (6%), who were at dose level 6, required a dose reduction because of leukocytopenia WHO grade IV after 2 weeks of chemotherapy in the first course. After dose reduction, therapy was restarted for the subsequent cycle at the dose level below (dose level 5). Therefore the antitumor response of these two patients, one neoadjuvant and one palliative, were counted to dose level 5.

Toxicity

All 33 patients were assessable for toxicity, and the analysis included all courses with this combination. Neutropenia and its complications were the DLT of this combination. Neutropenia WHO grade III was observed in only eight courses (19%) and only occurred at the three highest dose levels. At these dose levels (4, 5 and 6), the percentages of doses associated with WHO grade III leukopenia were 5%, 12% and 2%, respectively. Leukocytopenia WHO grade IV was not observed at dose levels 1 and 2. At dose levels 3 and 4 leukocytopenia WHO grade IV was observed in one course with 14% and 6% of the doses, respectively. Therefore chemotherapy was stopped on this day and therapy was continued the following week. At dose level 5 leukocytopenia WHO grade IV appeared in two courses in two of six patients (18%) leading to febrile neutropenia and hospitalization in both patients, which was overcome in 5 and 6 days, but required antibiotic treatment. At dose level 6 leukocytopenia WHO grade IV was observed in four of six patients, and two of these patients required dose reduction after 2 weeks of chemotherapy in the first course. After dose reduction, therapy was restarted for the subsequent cycle at the dose level below (dose level 5). The other two patients did not receive this day of the chemotherapy course. No WHO grade III or IV thrombocytopenia or anemia were observed in any patient at any dose level.

One patient showed fever WHO grade III in one chemotherapy course (1%). This patient was included at dose level 4 and, after exclusion of viral and bacterial infection, lymphocytopenia grade IV was observed, evaluated according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC). After retrospective evaluation of the lymphocyte count of all included patients, lymphocytopenia NCI-CTC grade III and IV occurred more often at the highest dose levels and had the potential to complicate treatment.

Only one WHO grade III infection (1%) was observed. Excessive tearing or other WHO grade III or IV nonhematologic toxicities were not observed at any dose level [5]. The nonhematologic toxicities are listed in Table 2. No treatment-related deaths occurred.

Table 2. Toxicities in 74 courses [*n* (%)]

Toxicity	WHO grade			
	I	II	III	IV
Leukocytopenia	14 (19)	12 (16)	10 (14)	6 (8)
Anemia	47 (64)	30 (41)	–	–
Thrombocytopenia	8 (11)	5 (7)	–	–
Lymphocytopenia (NCI-CTC)	1 (1)	1 (1)	45 (61)	10 (14)
Diarrhea	1 (1)	3 (4)	–	–
Allergic reaction	–	–	–	–
Infection	–	–	1 (1)	2 (3)
Fever	–	–	1 (1)	–
Conjunctivitis	5 (7)	3 (4)	–	–
Tearing	12 (16)	6 (8)	–	–
Nausea/vomiting	3 (4)	2 (3)	–	–
Stomatitis	6 (8)	3 (4)	–	–
Peripheral neuropathy	1 (1)	–	–	–
Hand-foot syndrome	–	4 (5)	–	–
Fluid retention	–	–	–	–
Asthenia	50 (68)	10 (14)	–	–
Pulmonary failure	–	–	–	–
Cardiac failure	–	–	–	–
Alopecia	–	–	74 (100)	–

Dose-limiting toxicity

The DLT of the wED combination chemotherapy was leukocytopenia. Four patients treated at epidoxorubicin 35 mg/m^2 and docetaxel 40 mg/m^2 experienced grade IV leukocytopenia, in two patients leading to a severe infection and therefore dose reduction. Another serious complication was lymphocytopenia NCI-CTC grade III and IV, which occurred in 91% and 9% at dose level 5 and in 64% and 45% at dose level 6, respectively. Therefore, by study definition, the MTD was at dose level 6 (epidoxorubicin 35 mg/m^2 with docetaxel 40 mg/m^2). Because of the high incidence of lymphocytopenia at dose levels 5 and 6, the recommended dose for phase II/III studies was established at dose level 4 (30/35 mg/m^2). We included five additional patients at dose level 4 to verify the recommended dose.

Response

All patients were assessable for tumor response. The combination was active in the neoadjuvant as well as in the palliative treatment group at all dose levels.

In the neoadjuvant treatment group a major response (pathologic complete response, pCR) and PR, graded according to the International Union Against Cancer (IUAC), was observed in 18 of 20 patients (90%), with 2 patients (10%) experiencing a pCR of the invasive tumor, and 16 patients (80%) showing a PR. Only 2 patients (10%) presented with stable disease (SD) at dose level 4. Breast-conserving surgery was possible in 17 patients (85%). None of the neoadjuvant-treated patients progressed during therapy at any dose level, and all of these patients were still alive with no recurrent disease at the time of writing. The median observation time for these patients was 16+ months (range: 3+ to 23+ months).

In the palliative treatment group a major response (CR + PR) was achieved in 8 of 13 patients (62%). Four patients (31%) had SD and one patient (7%) had PD after three courses of therapy. Six patients (46%) relapsed between 5 and 16 months, and of these patients, three had previously reached a PR as best response to treatment and two SD. At the time of writing, 17 patients (85%) were still alive and three (15%) had died. The median TTP was 8.5 months (range 5–16 months), and the median survival time from the day of the start of wED treatment was 17.5 months (range 7–21+ months).

Discussion

We performed a single-institution phase I/II study of wED as neoadjuvant as well as palliative first-line chemotherapy in patient suffering from breast cancer. This therapy regimen was administered in an outpatient setting without the support of prophylactic G-CSF.

This phase I/II study established an MTD of 35 mg/m^2 epidoxorubicin and 40 mg/m^2 docetaxel. The DLT was leukocytopenia WHO grade IV which occurred in four patients at this dose level, leading to severe infection and hospitalization in two patients and to dose reduction in the other two patients. Interestingly, another serious complication was observed at the last three dose levels. Lymphocytopenia NCI-CTC grade III and IV occurred in a high proportion of patients at dose levels 5 and 6, and this side effect possibly led to fever WHO grade IV in one patient at dose level 4. The occurrence of lymphocytopenia has not been found in other studies. However, no other nonhematologic WHO grade IV toxicities were observed across the different dose levels and WHO grade III toxicities consisted of infection in one chemotherapy course. Therefore, we recommend dose level 4 (epidoxorubicin 30 mg/m^2, docetaxel 35 mg/m^2 weekly for 6 weeks followed by 1 week rest) for further phase II and III studies.

Myelosuppression has been reported to be minimal with docetaxel or paclitaxel as single agents in a weekly schedule compared with that observed with equal cumulative doses given in an every-3-week schedule [2, 19]. In the weekly schedules the DLT was asthenia, fatigue, or peripheral neuropathy. These toxicities described with single-agent docetaxel were also infrequent and easily manageable in this study [2, 17, 18, 19, 24]. An unexpected toxicity appearing after the first course of weekly docetaxel and epidoxorubicin was tearing and, in some cases mild conjunctivitis or eye irritation. However, formal ophthalmologic examinations revealed no abnormalities. Conjunctivitis has been reported as a side effect of every-3-week docetaxel [16]. In other phase I/II studies of weekly docetaxel conjunctival and tearing problems have been seen in 19–29% of patients [1, 2, 3]. Peripheral fluid retention as well as anaphylactic reactions were prevented by corticosteroid premedication.

Another feared complication of anthracycline-based combination chemotherapies is congestive heart failure, where the chronic appearance is principally dependent on the cumulative anthracycline dose and occurs by definition within 1 year of therapy. Administering epidoxorubicin to a cumulative dose of 800 mg/m^2 instead of doxorubicin and docetaxel instead of paclitaxel results in less cardiotoxicity [11, 15, 19]. Therefore we used epidoxorubicin and docetaxel in our trial, and indeed did not observe any clinical cardiotoxicity.

Although assessment of efficacy was not the primary study end point and our neoadjuvant and palliative patient population was too small to draw a definitive conclusion, the overall response rates were in the range seen with 3-week schedules using a combination chemotherapy of anthracyclines and taxanes [7, 13, 20, 21, 26]. A high level of activity was observed at all dose levels, in particular at the last three dose levels of epidoxorubicin ≥30 mg/m^2 and docetaxel ≥35 mg/m^2. In this trial we achieved an overall response rate of 90% with a pCR rate of 10%, thus leading to a breast conserving surgical procedure in 85% of preoperatively

treated patients. Palliatively treated patients showed an overall response rate of 62%.

In summary, the wED regimen was shown to be a feasible, safe, and highly active combination. This dose-intensified regimen with the recommended dose of epidoxorubicin 30 mg/m^2 together with docetaxel 35 mg/m^2 weekly for 6 out of 7 weeks without prophylactic G-CSF, achieved a comparable toxicity profile to that observed with an every-3-week schedule at 75 mg/m^2 epidoxorubicin and 75 mg/m^2 docetaxel with prophylactic G-CSF which is equivalent to only a 25 mg/m^2 weekly dose of each drug [22]. Our findings suggest that wED is suitable for planned future trials owing to its high efficacy and acceptable toxicity.

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