A phase II study of epirubicin, vinorelbine and cisplatin in advanced breast cancer

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Our objective was to evaluate the activity and safety of the combination of cisplatin, epirubicin and vinorelbine (CEV) in advanced breast cancer patients. Patients with advanced breast cancer, locally advanced or metastatic, received epirubicin 75 mg/m^2 and cisplatin 50 mg/m^2 on day 1, and vinorelbine 25 mg/m^2 on day 8. Cycles were repeated every 3 weeks. A total of 35 patients were treated. Thirty-one patients were evaluated for response. One hundred and fifty-five cycles of chemotherapy were administered overall. The objective response rate (ORR) was 84%, including complete response in 13% of patients. All stage III patients achieved a downstaging, with a pathological complete response in two out of 10 patients. Patients with stage IV disease obtained objective response in 67% of cases. Toxicity was mild to moderate. The most common grade 3–4 adverse event was febrile neutropenia, which occurred in 17% of patients. We conclude that CEV combination represents an effective treatment for patients with previously untreated advanced breast cancer, allowing an important ORR. Moreover this regimen appears to be well tolerated. *Anti-Cancer Drugs* 15:23–27 © 2004 Lippincott Williams & Wilkins.

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Introduction

More than 700 000 new cases of breast cancer are diagnosed worldwide each year and approximately half of these patients will die from the disease [1,2]. The median survival time of metastatic breast cancer ranges from 18 to 24 months, according to the metastatic site [3]. Cytotoxic chemotherapy represents a key element in the treatment of advanced breast cancer and first-line combination chemotherapy with regimens including anthracyclines such as FAC or FEC induces objective response in 50–80% of cases [4,5].

Vinorelbine is generally well tolerated and produces high objective response rates (ORRs) ranging from 41 to 50% in first-line therapy for advanced breast cancer [6–9]. The combination of vinorelbine and anthracyclines (doxorubicin or epirubicin) shows major activity in the treatment of advanced breast cancer with 70–74% ORR [10,11].

Although less widely used, cisplatin too is effective in first-line therapy for advanced breast cancer, with response rates ranging from 47–54% when used as a single agent [12,13].

A randomized phase II trial comparing three four-drug cisplatin-containing combinations [14] in locally advanced breast cancer (LABC) or locally recurrent breast cancer showed high response rates of 84 and 89%, respectively.

A synergistic antitumoral activity was shown with the combination of cisplatin and vinorelbine in animal models [15]. In pretreated breast cancer patients, acceptable tolerance was observed when the two drugs were used in combination [16,17].

Very few data exist on the combination of vinorelbine, epirubicin and cisplatin, although a phase II study of this multidrug regimen was reported in 1999 in LABC, showing an interesting level of activity (ORR 89.2%) [18].

On these premises we performed a phase II study in advanced breast cancer patients with epirubicin and cisplatin administered on day 1, and vinorelbine on day 8 in order to evaluate the response rate and the safety of such combination.

Patients and methods

Patient selection

The study included female patients with cytologically or histologically proven breast carcinoma with advanced disease (stage III or IV) who had received no prior

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chemotherapy for metastatic disease. Patients were required to meet the following criteria: age 18–75 years, life expectancy > 3 months, Eastern Cooperative Oncology Group (ECOG) performance status 0–2, adequate renal, hepatic and bone marrow function, defined as follows: creatinine concentrations < 1.3 mg/dl, total bilirubin ≤ 1.5 times the upper normal limit (UNL), absolute neutrophil count (ANC) ≥ 2000/μl and platelet count ≥ 100 000/μl, and no evidence of symptomatic peripheral neuropathy with grade 2. A negative pregnancy test before study entry was required for women of childbearing potential.

All patients had to have clinically or radiographically uni- or bidimensionally measurable disease. Patients with asymptomatic brain metastases or non-measurable bone metastases were eligible provided they had other measurable sites of disease.

Staging studies to define the extent of disease were performed before therapy initiation, and included full history and physical examination, complete blood cell (CBC) count, platelet count, serum chemistries, chest X-ray, bone scan, mammography, abdominal ultrasound, thoracic and/or abdominal computed tomography (if clinically indicated), and ECG.

Patients were ineligible if they had a history of neoplasm other than breast carcinoma (excepting non-melanoma skin cancer or curatively treated cervical carcinoma in situ), a history of ventricular arrhythmias or congestive heart failure, or other serious illness and medical condition that would hinder study participation.

Patients were excluded from the study if they had received prior therapy for metastatic disease, a cumulative epirubicin dose of more than 360 mg/m^2 or a cumulative doxorubicin dose of more than 240 mg/m^2.

This trial was approved by the Institutional Review Board in 1998.

Written informed consent was obtained from each patient before study entry.

Treatment

Treatment consisted of epirubicin 75 mg/m^2 and cisplatin 50 mg/m^2 on day 1, and vinorelbine 25 mg/m^2 on day 8. Epirubicin was administered by i.v. bolus, cisplatin was administered with vigorous pre- and post-hydration, 2000 ml of normal saline (NS) with KCl and $MgSO_4$; furosemide 10 mg i.v. 20 min prior to cisplatin was also given. Vinorelbine was administered in 50 ml NS over 5–10 min followed by a 200-ml NS bolus to prevent phlebitis. Antiemetic therapy by 5-HT_3 antagonists and dexamethasone was applied on day 1 of the cycle; i.v. dexamethasone and metoclopramide were given on day 8. Cycles were repeated on an outpatient basis every 3 weeks with a white blood cell count ≥ 3000/μl and a platelet count ≥ 100 000/μl. Supportive care including granulocyte colony stimulating factors, erythropoietin, blood products and antibiotics was administered as needed.

Duration of treatment depended on stage (III versus IV) and tumor response. Irrespective of the stage, patients with progressive disease (PD) discontinued the treatment. Patients with stage III disease were treated with 4–6 cycles of chemotherapy before local therapy (surgery and/or radiotherapy). Patients with stage IV disease were treated to a maximum of 8 cycles of chemotherapy.

Response and toxicity assessment

Tumor measurements were assessed every cycle by physical examination (stage III disease) and every 3 cycles by imaging studies (stage III and IV disease), according to WHO criteria [19]. Patients receiving at least three courses of therapy were assessable for response.

The best overall response was defined as the best response recorded from the start of treatment to disease progression. Time to response was defined as the interval between treatment start and the first record of response. A complete response (CR) was defined as the disappearance of all clinical evidence of active tumor. A partial response (PR) was defined as 50% or greater reduction in the sum of the products of bidimensional perpendicular measurements or estimated tumor size. Stable disease (SD) was defined as a less than 50% decrease in tumor size and appearance of no new lesions; and PD was defined as a more than 25% increase in tumor size or the appearance of new lesions.

Time to progression (TTP) was defined as the time from day 1 of treatment to the first evidence of progression. Overall survival (OS) was defined as the time from day 1 of treatment to death.

Physical examination, and a CBC and platelet count were repeated before each cycle.

Toxicity was assessed according to WHO criteria after each cycle of chemotherapy. All patients who received at least one course of therapy were assessable for toxicity.

Statistical considerations

The statistical approach considered here was the optimal two-stage design by Simon [20]. Considering response probability = 0.60 ($p0$) and assuming 'substantial activity' = 0.80 ($p1$), accepting both α and β error at 0.10, the study design requires six responses out of 11 patients

(stage 1) and 26 responses out of 38 patients (stage 2). If both stages were met, the activity of the CEV regimen was considered sufficient to warrant further investigations.

Results

The study was interrupted at 35 enrolled patients because it met in advance the 26 responses requested by the statistical design.

Patient characteristics

From July 1998 to February 2000, 35 patients entered the study. The median age was 57 years (range 40–75) and the majority of patients (88.6%) were asymptomatic (ECOG performance status 0). Patients with LABC or metastatic disease numbered 21 and 14, respectively. Metastatic sites included bone, liver, lung, soft tissues and lymph nodes.

Among patients with metastatic disease, nine out of 14 (64.3%) had disease involvement at more than one metastatic site. Nine patients had received chemotherapy and/or hormonal treatment in the adjuvant setting, but none had received prior anthracyclines.

Table 1 lists the clinical characteristics of the patients in the study.

Treatment compliance

A total of 155 cycles of chemotherapy were administered (94 cycles to stage III and 61 cycles to stage IV patients), with a median of 5 cycles (range 1–6) and 4.5. cycles (range 1–8) for LABC and metastatic patients, respectively. All patients received at least 1 cycle of therapy.

All patients with LABC underwent surgery.

Only one patient with stage IV disease required dose reduction due to grade 3 anemia and grade 2 mucositis. Delayed therapy was recorded in 5 and 6 cycles in stages III and IV, respectively (4 cycles grade 2 leukopenia, 3 cycles personal reasons, 1 cycle flu, 1 cycle phlebitis, 1 cycle talc pleurodesys and 1 cycle pneumothorax). Two patients discontinued the treatment after the second cycle due to early progression.

Table 1 **Patient characteristics**

	No. of patients (%)
Performance status (ECOG)	
0	10 (71.4)
1	4 (28.6)
No. of metastatic sites	
1	5 (35.7)
2	6 (42.9)
>2	3 (21.4)
Site of metastatic disease	
visceral	11 (78.6)
bone	5 (35.7)
soft tissue	8 (57.1)
Previous adjuvant therapy	
none	5 (35.7)
chemotherapy	4 (28.6)
hormonal	3 (21.4)
both	2 (14.3)

Toxicity

All patients who received at least 1 cycle of chemotherapy were evaluable for toxicity. Four patients (11%) discontinued therapy after 1 cycle: three due to treatment-related adverse events (one patient experienced a major drop in LVEF, one paralytic ileum and one patient febrile neutropenia complicated by pneumonia); the last one due to deterioration of performance status.

Apart from alopecia, which occurred in all patients, the most common treatment adverse events were nausea (82.7%) and asthenia (68.4%). Noteworthy, the majority of treatment-related adverse events were mild to moderate. The most common treatment-related adverse events are summarized in Table 2.

The only grade 3/4 adverse event which occurred in more than 10% of patients was febrile neutropenia, which was recorded in 17% of patients (grade IV in two patients), and grade 3 nausea and vomiting in 11.4% of patients.

Response to therapy

Four patients were not evaluable for response because of definitive treatment interruption after one course (two patients with stage III and two patients with stage IV disease, respectively, see Toxicity).

Twenty-six out of 31 evaluable patients obtained an objective response. Twenty-two patients had a PR (71%) and four patients obtained a CR (13%). SD was observed in the remaining three patients (10%), for an ORR of 84% [95% confidence interval (95% CI) 69.9–98.1%]. On 'an intent-to-treat' basis, ORR was 74.3% (95% CI 59.5–88.5%).

Two patients with stage IV disease (6%) experienced early progression after two courses of chemotherapy.

Among the 19 evaluable patients with stage III disease, pre-surgery evaluation revealed an objective response in the whole analyzed population, with an ORR of 100%. Pathological evaluation of the tumors revealed that tumors were downstaged in all patients, with pathologic CR in two patients. An additional patient not evaluable for response because of definitive interruption after one course, with a large breast mass (210 cm^2), experienced paralytic ileum after the first administration of vinorelbine and required hospitalization. Surprisingly, she achieved a dramatic shrinkage of the tumor and was able

Table 2 Clinical adverse events

Adverse event	No. of patients (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Nausea/vomiting	10 (28.5)	15 (42.8)	4 (11.4)	–
Mucositis	10 (28.5)	9 (25.7)	–	–
Asthenia	10 (28.5)	12 (34.2)	2 (5.7)	–
Myalgia	1 (2.8)	–	–	–
Neuropathy–sensory	1 (2.8)	–	–	–
Arthralgia	3 (8.5)	–	1 (2.8)	–
Phlebitis	2 (5.7)	–	–	–
Febrile neutropenia	–	–	4 (11.4)	2 (5.7)
Leukopenia	11 (31.4)	5 (14.2)	–	–
Anemia	11 (31.4)	8 (22.8)	2 (5.7)	–
Thrombocytopenia	–	–	–	–

to undergo surgery after recovery. Moreover, she received adjuvant therapy without any other significant toxicity.

Among the 12 evaluable patients with stage IV disease, CR and PR occurred in two (17%) and six patients (50%), respectively, giving an overall response rate of 67% (95% CI 40.6–93.4). Moreover, disease stabilization was noted in two patients (17%), whereas two other patients experienced early progression after two cycles of chemotherapy.

The median time to response was 2.1 (1.4–3.5) and 1.4 months (range 0.7–3.5) for patients with stage III and IV disease, respectively. At the time of the present analysis, median TTP of stage III disease had not yet been reached (43 + months, range 11–51 +). The median TTP of stage IV patients was 13.5 months (range 3–43 + months). In this latter group, one patient had not yet developed PD. The median OS of stage III patients had not yet been reached (43 + months, range 16–51 +). Median OS for stage IV patients was 18 months (range 5–49). Two patients were still alive. The median duration of follow-up, measured from the first day of therapy to last contact, was 38 + months (range 5–51 + months). At the time of the present analysis, 16 patients had died due to their disease.

Discussion

This trial was designed to assess the activity of the CEV combination. This regimen achieved a satisfactory response rate including four CRs. All patients with locally advanced disease underwent surgery after a median of 5 cycles of chemotherapy. Tumor evaluation prior to surgery demonstrated an objective response in the whole series of patients. Pathological evaluation showed that the tumor was downstaged in 94.7% of patients, with two pathological CRs. It must be stressed that the mean tumor surface of the stage III population was 62 cm^2. Therefore, our series has, in media, larger tumors than those usually seen in the clinical practice. The geographical location of our center, serving people living in remote mountain areas, could explain this finding. Thus, these results, although obtained on a small series of patients, compare favorably to those reported by other authors [14,18,21] given the high response rate obtained in a population with very large tumors.

The responses to CEV (including two CRs) were satisfactory and in line with the literature, even in the metastatic group [5,22].

The CEV regimen did not increase toxicity over that expected by other standard regimens. In particular, no grade 3 and 4 leukopenia, thrombocytopenia and mucositis were recorded. Febrile neutropenia occurred in 17% of patients and only one patient in the metastatic group required dose reduction because of toxicity. No platinum-related toxicities were recorded, such as neuropathy or renal toxicity.

We observed a relatively high number of patients requiring treatment discontinuation after the first course due to adverse events (8%). However, no toxic deaths were recorded and all these patients received further treatments. Noteworthy, one of these patients experienced a dramatic response after this single course of chemotherapy, rendering the tumor suitable for surgery.

Other authors described their experience with the CEV regimen, but all these trials are reported only in abstract form.

Barni *et al.* [18] conducted a phase II study in LABC patients. All drugs were administered on day 1 every 3 weeks. Cisplatin and vinorelbine were administered at the same dose as in our trial, while epirubicin was employed at the dose of 100 mg/m^2. Preliminary results indicate a high activity of the combination; patients had documented downstaging of the tumor in 89.2% of cases [18].

Turpin *et al.* [23] performed a phase II study based on the same triplet, but with a higher dose of platinum (90 mg/m^2) in the metastatic setting. In a series of 14 patients

they reported a 61.5% response rate. Grade III–IV neutropenia occurred in 12 of 13 patients at nadir. The authors concluded that the addition of cisplatin to the epirubicin and vinorelbine association did not increase the response rate, while increasing toxicity.

In our study, the administration of cisplatin did not increase toxicity and, despite the lower dose of platinum, the response rate seems better than that reported by Turpin *et al.* A possible reason of the different behavior could be the dose of platinum. The higher dose could be responsible for the higher level of toxicity and, consequently, for the lower activity due to a poor protocol adherence.

Platinum salts have generated a renewed interest in the oncologist community and many trials have been reported in the past few years. For example, Mustacchi *et al.* [24] tested a combination of cisplatin and vinorelbine in first- and second-line metastatic breast cancer patients, reporting 52.9% ORR. Hsu *et al.* [25] combined paclitaxel and cisplatin in 46 patients with LABC and metastatic disease, reporting similar results (57.1 and 61.1% ORR, respectively). Orlando *et al.* [26] tested a combination of vinorelbine, cisplatin and 5-fluorouracil as a continuous infusion in 26 LABC patients. ORR was 73%, including five complete pathological response (20%). Other studies reported favorable conclusions [16,17].

Platinum rediscovery is based upon multiple factors, including its considerable activity as single-agent chemotherapy of breast cancer [27]; the lack of cross-resistance with major anticancer drugs; the lack of mucosal toxicity, common to many other drugs employed in this disease; and, finally, low costs.

In conclusion, in our study, CEV has reached a sufficient level of activity and safety to warrant further investigations.

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