ABSTRACT

In an International Breast Cancer Study Group phase I/II program, 70 patients with advanced breast cancer received up to eight courses of 75 mg/m² doxorubicin combined with 90 mg/m² epirubicin, every 3 weeks. G-CSF was not administered prophylactically. Grade 4 neutropenia occurred in 88% of cycles that were not supported by G-CSF. However, febrile neutropenia affected only 24% of cycles. It occurred after the first cycle in 56% of cases and was managed by oral antibiotics in 52% of cases. When supportive G-CSF was administered, the incidence of febrile neutropenia fell to 3% and grade 4 neutropenia to 41%. Only 6% of patients experienced a greater than 20% reduction in left ventricular ejection fraction and no severe, irreversible cardiotoxicity was observed. The overall response rate (RR) was 66% and median time to progression was 4.5 months. The RR was similar in patients with prior adjuvant chemotherapy and patients with predominantly visceral disease. These data and those of comparable series suggest that the combination of epirubicin and docetaxel is tolerable and active, and that it should be further developed clinically.

Several institutions have conducted phase I dose-finding trials with the docetaxel/epirubicin combination [17-21]. Under the auspices of the International Breast Cancer Study Group (IBCSG), six centers (two in Italy and four in Switzerland) took part in studies of the docetaxel/epirubicin combination. An initial dose-finding study sought to identify the maximum tolerated doses (MTD) of the two agents when used in combination q 3 weeks [22, 23]. It also aimed to determine whether safe use of the combination required prophylactic G-CSF. This study was followed by a phase II trial to define the antitumor activity and toxicity of the combination used in a larger number of patients at the doses recommended in the dose-finding trial.

Dose-Finding

The dose escalation used, number of patients treated and cycles administered, together with the incidence of febrile neutropenia, are shown in Table 1 [22, 23]. Epirubicin was administered as a 15-minute infusion and followed 1 hour later by the 1-hour infusion of doxorubicin. Steroids (dexamethasone p.o. 8 mg bid) were administered on the day before chemotherapy and for 2 days afterwards. Eligible patients had advanced breast cancer with no prior exposure to anthracyclines and had a maximum of four cycles of the combination was administered.

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The starting doses of docetaxel and epirubicin were chosen on the basis of previous experience with the combination of docetaxel and doxorubicin. It was intended that the dose of epirubicin should be escalated to a greater extent than that of docetaxel. The MTD was defined as the one administered during first cycle where more than two of three or three of six patients suffered a dose-limiting toxicity (DLT). Definition of the MTD was based mainly on neutropenia, with DLT defined as the absolute neutrophil count (ANC) less than $0.5 \times 10^9/l$ for more than 7 days or febrile neutropenia.

Without G-CSF, the MTD determined by the study was 75 mg/m$^2$ docetaxel plus 90 mg/m$^2$ epirubicin. At this dose level 16% of the 62 cycles administered were complicated by febrile neutropenia, and grade 3 or 4 neutropenia occurred in 87% of cycles. With the addition of G-CSF, it proved possible to increase the dose of epirubicin to 120 mg/m$^2$ without unacceptable myelosuppression. However, increasing the dose of docetaxel to 85 mg/m$^2$ resulted in an unacceptably high incidence of febrile neutropenia (which affected 20% of cycles) with one toxic death due to typhlitis. The MTD without G-CSF (75 mg/m$^2$ docetaxel plus 90 mg/m$^2$ epirubicin) was chosen for further development.

**Phase II Study of Docetaxel Plus Epirubicin**

The phase II study involved 50 patients. Women with prior exposure to anthracyclines were eligible provided that the cumulative dose had not exceeded 240 mg/m$^2$ doxorubicin or 430 mg/m$^2$ epirubicin, and provided that neoadjuvant or adjuvant chemotherapy had been completed at least 12 months previously. All patients had to have a left ventricular ejection fraction (LVEF) of 50% or greater. Epirubicin was given at a dose of 90 mg/m$^2$ followed by docetaxel 75 mg/m$^2$ q 3 weeks. The standard 3-day course of steroids pre- and post-medication was used.

G-CSF was given only if febrile neutropenia had developed on the previous cycle. On the contrary, the dose of epirubicin had to be reduced in two cases of grade 3 non-hematological toxicity. Patients received a maximum of eight cycles of treatment and were not allowed to exceed a total cumulative epirubicin exposure of 970 mg/m$^2$.

**Combined Series**

Including the 20 patients treated in the dose-finding study and 50 in the phase II trial, a total of 70 patients received the combination of 75 mg/m$^2$ docetaxel and 90 mg/m$^2$ epirubicin [22, 23]. The dominant site of disease was visceral in 38 patients (54%). Forty had two or more sites of disease, and 29 had received adjuvant chemotherapy (which had contained anthracyclines in seven cases). In short, the population studied was typical of patients with metastatic breast cancer who would be considered for treatment with a taxane/anthracycline combination as first-line therapy.

**Myelosuppression**

A total of 326 cycles were evaluable for hematological toxicity, i.e., they were administered at full dose, and patients were followed up with weekly blood counts. In the 161 cycles administered without G-CSF, the median ANC nadir was $0.16 \times 10^9/l$. Twenty-four percent of cycles were affected by febrile neutropenia, which was managed with oral outpatient treatment in 52% of cases, and grade 4 neutropenia occurred in 88%. This incidence of neutropenia was acceptable.

A total of more than 70 courses of G-CSF were administered to the 47 patients who at some stage required growth factor support. In the 165 evaluable cycles given with G-CSF, the median ANC nadir was $0.66 \times 10^9/l$. With G-CSF support, only 3% of cycles were complicated by febrile neutropenia, and toxicity was grade 4 in only 41%.

**Cardiotoxicity**

The median dose of epirubicin administered to the 70 patients included in the safety analysis was 495 mg/m$^2$ (range 270-1,020 mg/m$^2$). In total, only 6% of patients experienced a greater than 20% fall in LVEF, which was reversible in all cases. One patient developed a greater than 35% fall in LVEF 6 months after the end of treatment. This patient had received prior epirubicin in the adjuvant setting for a total cumulative epirubicin dose of 870 mg/m$^2$ and had prior radiotherapy to the left chest wall.

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**Table 1. Docetaxel in combination with epirubicin: doses and hematological toxicity [22, 23]**

<table>
<thead>
<tr>
<th>Dose (mg/m$^2$)</th>
<th>+ G-CSF</th>
<th>Patients</th>
<th>Cycles</th>
<th>% Cycles with neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>Epirubicin</td>
<td>No</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>75</td>
<td>75</td>
<td>No</td>
<td>6</td>
<td>24</td>
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<tr>
<td>75</td>
<td>120</td>
<td>Yes</td>
<td>7</td>
<td>34</td>
</tr>
<tr>
<td>85</td>
<td>120</td>
<td>Yes</td>
<td>9</td>
<td>39</td>
</tr>
</tbody>
</table>

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Activity

The antitumor activity observed in this series was comparable with that seen in other studies of taxane/anthracycline combinations. The ORR was 66% (95% confidence interval: 54%-73%), the median response duration 8 months (range: 3-16 months), and median time to progression 4.5 months. The overall 2-year survival was 60%.

Looking at the efficacy data in greater detail, there were three complete responses among the 49 evaluable patients in the phase II series, and 31 partial responses (ORR 69%). Among the 68 evaluable patients in the combined phase I/II series, 29 had received prior adjuvant chemotherapy. The RR in this subgroup was 76%. A small number (seven patients) had had prior adjuvant treatment that included anthracyclines, and in this group the RR was 71%. RRs were comparable in different disease sites: 64% in the case of lung metastases, 76% with liver metastases, and 58% in the primary tumor. In patients treated with neoadjuvant intent, the RR was 58% (a median of five cycles was administered).

Responses appeared reasonably rapidly: the degree of response increased after four cycles in only 20% of responders. This suggests that there would not be substantial clinical benefit in continuing combination therapy beyond the maximum of eight cycles used in the phase II trial.

Discussion

The major purpose of the IBCSG program outlined here was to determine the safety of combining docetaxel with epirubicin in patients with advanced breast cancer treated in a multi-institutional setting. The degree of myelosuppression seen with the 75 mg/m² /90 mg/m² regimen was acceptable and relatively easily managed clinically. It does not appear necessary to administer G-CSF routinely to patients treated, although such support may be needed subsequently in individual cases. However, patients should be monitored at least weekly, and dose modification may be required to prevent complications. Nonhematological toxicity, in particular mucositis, was limited. Particularly important for the future development of the combination is the fact that no severe and irreversible cardiotoxicity was seen in this series after a median cumulative dose of epirubicin of 495 mg/m² (range: 270-1,020 mg/m²).

Recently, several studies of docetaxel and epirubicin in the first-line treatment of advanced breast cancer have been reported (Table 2). Milla-Santos et al. treated 32 patients with 100 mg/m² docetaxel plus 130 mg/m² epirubicin [24]. G-CSF was administered prophylactically. In this series, the RR was 88%, and 15% of cycles were affected by grade 3-4 neutropenia. Astone et al. also used growth factor support when treating 26 patients with 80 mg/m² docetaxel plus 80 mg/m² epirubicin [25]. The RR was 65%, and 27% of cycles were followed by neutropenia. In a further study without G-CSF, 75 mg/m² docetaxel were given to 28 patients in combination with 90 mg/m² epirubicin [26]. The RR was 65%, with a 77% rate of grade 3-4 neutropenia.

These results are comparable with those seen in the IBCSG series reviewed here and provide supportive evidence that the combination of docetaxel with epirubicin is both tolerable and active. Given the relative lack of mucositis with docetaxel and epirubicin, the addition of fluoropyrimidines appears possible. Recent experience suggests that the addition of continuous infusion 5-fluorouracil or capecitabine to docetaxel/epirubicin is feasible [27-29]. Investigation of the docetaxel/epirubicin combination in the earlier treatment of breast cancer has been initiated with a weekly schedule in the neoadjuvant setting [30].

References

5. Nabholtz J-M, Tonkin K, Smylie M et al. Chemotherapy of breast cancer: are the taxanes going to change the natural
28 Grafeo R, Longhi S, Pagani O et al. Dose-finding study of day 1, 8 Taxotere (T), epirubicin (E), and continuous infusion 5-FU (Fci) as first line treatment in advanced breast cancer (ABC). Proc European Society Medical Oncology—Ann Oncol 2000;28(suppl 4):5-11.