Short Communication

Is epirubicin effective in first-line chemotherapy of metastatic breast cancer (MBC) after an epirubicin-containing adjuvant treatment? A single centre phase III trial

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The aim of the study was to demonstrate the superiority of docetaxel and epirubicin vs docetaxel alone as first-line therapy in metastatic breast cancer patients pretreated with adjuvant or neoadjuvant epirubicin. We compared single agent docetaxel vs docetaxel alone vs docetaxel 100 mg m$^{-2}$ (D) with the combination of docetaxel 80 mg m$^{-2}$ and epirubicin 75 mg m$^{-2}$ (ED). The response rate (72 vs 79%), the progression-free survival (median 9 vs 11 months) and the overall survival (median 18 vs 21 months) were not significantly different between the ED (n = 26) and D arms (n = 25), respectively. Leucopenia, nausea and stomatitis were significantly worse with ED. In conclusion, epirubicin should not be administered in combination with taxanes in metastatic breast cancer patients relapsed after an anthracycline-based adjuvant or neoadjuvant therapy.

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Anthracyclines are among the most active agents in the treatment of metastatic and adjuvant breast cancer (Fossati et al, 1998; EBCTCG, 2004). Docetaxel is the only agent that has demonstrated survival benefits in anthracycline-resistant patients (Nabholtz et al, 1999) and superior activity over doxorubicin as first-line chemotherapy in patients previously treated with alkylating agents (Chan et al, 1999). Owing to its activity and to the lack of cross-resistance with anthracyclines, there is a strong rationale for combining docetaxel with anthracyclines. The anthracycline-taxane regimens can now be considered the most effective regimens in metastatic breast cancer (MBC) and a first-line therapy of choice in this set of patients (Valero and Hortobagyi, 2003). In particular, many reports have described the combined use of docetaxel and epirubicin, an anthracyline less cardiotoxic than doxorubicin, with the objective to find the safest and most efficient way to integrate these classes of drugs (Mavroudis et al, 2000; Pagani et al, 2000). However, whether an anthracycline-taxane regimen is worthy as first-line treatment for MBC patients pretreated with adjuvant or neoadjuvant anthracyclines is an open question, not definitely assessed by appropriate prospective trials. Therefore, we planned a randomised phase III trial to compare epirubicin and docetaxel vs docetaxel alone for efficacy and safety as first-line chemotherapy of MBC patients pretreated with epirubicin in adjuvant or neoadjuvant setting.

MATERIALS AND METHODS

Eligibility criteria were: women with MBC ≤65 years; no previous chemotherapy for metastatic disease; measurable disease; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; previous adjuvant or neoadjuvant chemotherapy with anthracyclines, up to a total dose of doxorubicin ≤250 mg m$^{-2}$ or epirubicin ≤500 mg m$^{-2}$, completed at least 12 months before enrollment; absence of brain metastases; adequate bone marrow, renal and liver function; left ventricular ejection fraction (LVEF) ≥50%. Previous adjuvant endocrine therapy as well as endocrine therapy for metastatic disease were allowed. Patients were excluded if they had received taxanes as adjuvant chemotherapy or had history of serious medical conditions potentially compromising study participation. Pregnant or lactating women were ineligible. All patients were required to provide written informed consent and the protocol was approved by the Independent Ethical Committee of the National Cancer Institute of Naples.

Patients were randomly assigned to docetaxel 100 mg m$^{-2}$ (Arm D) or to epirubicin 75 mg m$^{-2}$ and docetaxel 80 mg m$^{-2}$ (Arm ED) on day 1, every 3 weeks for six cycles of chemotherapy, unless disease progression or unacceptable toxicity. Prednisone and a prophylactic antiemetic regimen with 5-HT3 antagonists were given from the first infusion. No dose reduction of chemotherapy was planned by protocol. Treatment was delayed for 1 week for grade ≥2 neutropenia and/or grade ≥1 thrombocytopenia.
Granulocyte colony-stimulating factor (G-CSF) was administered at 5 mcg kg day$^{-1}$ subcutaneously in case of grade 4 neutropenia until neutrophil count $>2000$ mm$^{-3}$.

Pretreatment evaluation, performed within 1 month before randomisation, included physical examination, laboratory studies, ECG, echocardiography with LVEF, brain, chest and abdomen computed tomography, bone scan, skeletal radiographs (if required). Echocardiography and evaluation of tumour response, according to Response evaluation criteria in solid tumor (RECIST) guidelines, were performed every three cycles.

Toxicity was evaluated according to National Cancer Institute Common Toxicity Criteria version 2.0. For each type of toxicity, the worst degree experienced throughout the treatment was computed for each patient.

The study was designed as a single centre randomised phase III study with response rate as primary end point. Stratification factors were: performance status (0 vs 1 vs 2), disease-free survival (<24 months vs >24 months) and type of dominant metastatic site (soft tissue vs bone vs viscera). Primary objective was to evaluate the objective response rate (ORR) of docetaxel and epirubicin compared with docetaxel alone. Secondary end points included toxicity, progression-free survival (PFS) and overall survival. Calculation of sample size was based on a 40% expected response rate, a 5% of risk of false positive result, and a one-tailed $\alpha$ of false negative and a 5% of risk of false positive result, and a one-tailed $\alpha$ of false negative and a 5% of risk of false positive result.

RESULTS

From May 2000 to October 2003, 51 patients were enrolled. The recruitment was slower than expected, due to the restrictive inclusion criteria of the protocol and prompted us to stop the study, after 3.5 years, because time needed to reach the planned sample size would have been too long. Baseline characteristics of the patients were well balanced between the two arms (Table 1).

The median number of administered cycles was six (range 2–6); 81 and 76% of patients received all the planned therapy (six cycles) in the ED and D treatment arms, respectively. Median average relative dose intensity of treatment was similar in the two groups, while G-CSF was used far more frequently in ED group; 77% of ED patients, indeed, used G-CSF in at least one cycle compared with 56% of D patients ($P = 0.0582$).

All the responses were independently validated. Both therapeutic regimens showed similar antitumour activity (Table 2). The

| Table 2 | Outcomes |
|----------|---------|
| Variable | Overall (N = 51) | ED (N = 26) | D (N = 25) | $P^*$ |
| Objective response analysis, n (%) | | | | |
| Not eligible | 2 (4) | 1 (4) | 1 (4) | |
| Eligible | 49 (96) | 25 (96) | 24 (96) | |
| Best response, n (%) | | | | |
| Complete | 10 (20) | 4 (16) | 6 (25) | |
| Partial | 27 (55) | 14 (56) | 13 (54) | |
| Stable disease | 7 (14) | 4 (16) | 3 (12) | |
| Progressive disease, | 4 (8) | 3 (12) | 1 (4) | |
| Not assessed | 1 (2) | 1 (4) | | |
| Objective response rate, % (95% exact CI) | 76 (61–87) | 72 (51–88) | 79 (58–93) | 0.8196* |
| Time to progression (TTP), Events, n (%) | 45 (88) | 22 (85) | 23 (92) | 0.6998* |
| Median (95% confidence interval) TTP, (months) | 10 (8–12) | 9 (7–13) | 11 (9–15) | |
| Overall survival | 30 | 15 | 15 | 0.6406* |
| Events, n (%) | | | | |
| Median (95% confidence interval) overall survival, (months) | 20 (17-na) | 18 (15-na) | 21 (18-na) | |

*One-tailed P-values. *From Fisher exact test. *From Log-rank test.
ORR was 72% (18 patients; 95% exact CI: 51–88) in the ED arm and 79% (19 patients; 95% exact CI: 58–93) in the D arm (one-tailed \( P = 0.8196 \)). Based on these results, the probability that the response rate of the ED group would be significantly better than that of the D group, if the trial were brought to its completion, is equal to 0.0334.

After 45 (88%) events, the median progression-free survival was 9 months in the ED and 11 months in the D arm (one-tailed \( P = 0.6998 \)). With regard to overall survival, 30 events (15 in each arm) were reported after a 30 months median follow-up of alive patients. The median overall survival was 18 months in the ED and 21 months in the D arm (one-tailed \( P = 0.6406 \)). Progression-free and overall survival curves are reported in Figure 1.

Haematological and nonhaematological toxicities are summarised in Table 3. Leucopaenia, the most frequent haematological toxicity, was significantly more severe in the ED arm (\( P = 0.0290 \)). Among nonhaematological toxicities, nausea and stomatitis were significantly worse in the ED arm (\( P = 0.0210 \) and \( P = 0.0499 \), respectively). No significant differences between the arms were found in other nonhaematological toxicities. Grade 1 cardiac toxicity was reported in 19 and 16% of patients, with ED and D, respectively (\( P = 0.9999 \)).

**DISCUSSION**

Our phase III study indicates that the addition of epirubicin to docetaxel did not improve outcomes as compared to single-agent docetaxel, in the first-line treatment of metastatic breast cancer patients, who already had received adjuvant epirubicin. Both therapeutic regimens showed similar antitumour activity, and no significant differences were found between the two treatments in progression-free survival and overall survival. Of course, we are aware that the small sample size and the fact that enrollment was stopped before than planned are major limitations of our study. However, our results are strengthened by the finding that the Bayesian predictive probability that the study hypothesis (that ED could increase by a 20% the response rate as compared with D alone) could be eventually demonstrated if the study had reached the planned sample size is definitely low (only 3.3%). To the best of our knowledge, there is no randomised study addressing the role of anthracyclines in the treatment of patients relapsing...
after anthracycline-based adjuvant chemotherapy. Retrospective studies, indirectly addressing this issue, have produced conflicting results. Chauvin et al (1990) demonstrated a low activity of the CEF regimen in patients previously treated with anthracycline-based adjuvant chemotherapy. Other authors (Venturini et al, 1996; Pierga et al, 2001) found that previous adjuvant chemotherapy could adversely affect the prognosis of MBC patients treated with an anthracycline-based first-line chemotherapy, but this effect was independent of whether adjuvant chemotherapy was CMF- or anthracycline-based. On the contrary, other studies (Buzdar et al, 1981; Valagussa et al, 1986; Kardinal et al, 1988; Gennari et al, 2004) did not demonstrate a poorer outcome in metastatic breast cancer patients previously treated with adjuvant chemotherapy. Namely, Gennari et al (2004) did not find any negative influence of adjuvant anthracyclines on the activity of first-line epirubicin and paclitaxel, confirming that modern chemotherapy regimens, including anthracyclines and taxanes, provide satisfactory results in metastatic breast cancer patients, regardless of previous adjuvant chemotherapy.

In conclusion, the results of our trial support that epirubicin should not be included in taxanes-containing regimens for breast cancer patients relapsed after an anthracycline-based adjuvant or neoadjuvant therapy, also taking into account the availability for these patients of new active, non-cross-resistant drugs.

CONFLICT OF INTEREST

We declare no conflicts of interest.

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Appendix A1

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