Cisplatin plus oral etoposide (EoP) combination is more effective than paclitaxel in patients with advanced breast cancer pretreated with anthracyclines: a randomised phase III trial of Turkish Oncology Group

Our objective was to determine whether oral etoposide and cisplatin combination (EoP) is superior to paclitaxel in the treatment of advanced breast cancer (ABC) patients pretreated with anthracyclines. From December 1997 to August 2003, 201 patients were randomised. 100 to EoP and 101 to paclitaxel arms. Four patients in each arm were ineligible. The doses of etoposide and cisplatin were 50 mg p.o. twice a day for 7 days and 70 mg m⁻² intravenously (i.v.) on day 1, respectively, and it was 175 mg m⁻² on day 1 for paclitaxel. Both treatments were repeated every 3 weeks. A median of four cycles of study treatment was given in both arms. The response rate obtained in the EoP arm was significantly higher (36.3 vs 22.2%; P = 0.038). Median response duration was longer for the EoP arm (7 vs 4 months) (P = 0.132). Also, time to progression was significantly in favour of the EoP arm (5.5 vs 3.9 months; P = 0.003). Median overall survival was again significantly longer in the EoP arm (14 vs 9.5 months; P = 0.039). Toxicity profile of both groups was similar. Two patients in each arm were lost due to febrile neutropenia. The observed activity and acceptable toxicity of EoP endorses the employment of this combination in the treatment of ABC following anthracyclines. 

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With the premise that EoP may be more effective than paclitaxel, Turkish Oncology Group (TOG) decided to compare the efficacy of EoP with paclitaxel in anthracycline-pretreated patients with ABC in a phase III randomised trial.

PATIENTS AND METHODS

Patients

After obtaining written informed consent, patients with histologically or cytologically confirmed locally advanced or metastatic breast cancer were randomised if they meet the following criteria: measurable or evaluable disease (metastases to skin, pleura and peritoneum), age 18–70 years, performance status 2 or less according to WHO criteria, pretreatment with anthracyclines, negative hormone receptors or hormone refractory disease, adequate bone marrow reserve measured as neutrophil count $\geq 2 \times 10^9 \text{l}^{-1}$ and platelet count $\geq 100 \times 10^9 \text{l}^{-1}$, normal BUN, serum creatinine and bilirubin levels and AST and ALT levels $<4$ times upper normal limits.

Criteria for exclusion were presence of second primary malignancy or brain metastasis as the only metastatic site. Brain metastasis well controlled with radiotherapy, in addition to other sites of metastasis was not an exclusion criterion.

Patients with disease progression while receiving anthracycline-based CT for ABC, relapse within 6 months following adjuvant anthracycline-based CT and no response after two or more cycles of anthracycline-based CT for ABC, or responded to anthracyclines for ABC or received adjuvant anthracyclines and relapsed after 6 months (total dosage $\geq 360 \text{mg}$ of doxorubicin or $\geq 450 \text{mg}$ of epirubicin) were regarded as anthracycline pretreated.

Study design

This was a prospective randomised nonblinded multicentre phase III study. No stratification was carried out for prognostic factors or centers. Patients were centrally randomised to either paclitaxel or EoP arms. The primary end point was TTP. Secondary end points were tumor response rate, duration of response and overall survival (OS).

Treatment

Chemotherapy doses and schedules were as follows. Paclitaxel 175 mg m$^{-2}$ intravenously (i.v.) on day 1 or etoposide 50 mg b.i.d p.o. daily for 7 days + cisplatin 70 mg m$^{-2}$ i.v. on day 1 with adequate i.v. hydration every 3 weeks. At least two cycles of study treatment was planned for each patient, unless there was clear evidence of progression following the first cycle. Crossover was allowed for patients with progressive disease at any time. Also, patients with stable disease after at least two cycles of study treatment could be crossed over at the discretion of the investigator. Crossover was not mandatory.

Paclitaxel dose was reduced to 135 mg m$^{-2}$ in case of previous RT to pelvis and vertebrae or if ALT and/or AST were more than three times upper normal limits. If grade 3–4 hematological toxicity was observed in the prior cycle of the treatment, paclitaxel was reduced to 135 mg m$^{-2}$ (or 110 mg m$^{-2}$ if prior dose was 135 mg m$^{-2}$). Likewise, etoposide was reduced to 50 mg p.o. twice a day for 5 days and cisplatin to 50 mg m$^{-2}$. Treatment was delayed if there was grade 2 or more toxicity at the scheduled date of study treatment.

Assessment and follow-up

Physical examination, complete blood count, liver and renal function tests, serum CA-15-3, chest X-ray, abdominal ultrasonography (USG) or computerised tomography were carried out before and after every cycle of treatment.

RESULTS

Patient characteristics

Between December 1997 and August 2002, 201 patients from seven Oncology centres in Turkey were enrolled. A total of 100 patients were randomised to EoP arm and 101 to paclitaxel arm. Randomisation was carried out centrally by the data centre of TOG. Four patients in each arm were ineligible because one patient in each arm had poor performance status and were lost before the start of study treatment, three patients in the EoP and two in the paclitaxel arms withdrew their consents and one patient in the paclitaxel arm was injured in a car accident and the treatment could never be started. Thus, there were 96 eligible patients in the EoP arm and 97 in the paclitaxel arm. Patient characteristics including prior treatments are depicted in Table 1. There were no substantial differences between the two arms. There were two evaluable patients, one in paclitaxel and one in EoP arms, who had cytologically proven metastatic disease of pleura with effusion. All other patients had measurable disease. The median number of treatment cycles were 4 (ranges 1–8) for both arms. In total, 68 patients in the EoP and 75 patients in the paclitaxel arm received three to six cycles of treatment. Only four and seven patients in the EoP and paclitaxel arms, respectively, were given one cycle of treatment. Relative dose intensities were 85.17 and 85.74% for the etoposide and cisplatin, respectively, vs 89.27% for the paclitaxel. While paclitaxel dosage was reduced in five patients (5%), EP was...
Efficacy

A total of 91 patients in the EoP arm and 95 in the paclitaxel arm were evaluable for response. One patient was given paclitaxel instead of assigned EoP and was excluded from response evaluation. However, her survival duration was included in the EoP arm on intent-to-treat basis. Two patients in the EoP arm and three in the paclitaxel arm died before any response evaluation. Likewise, two patients in the EoP arm did not come for further treatment following the first cycle. Response to study treatment is shown in Table 2. Total response rates were 36.3 and 22.2% in the EoP and paclitaxel arms, respectively (P = 0.038). Complete response was achieved in three patients in each arm.

Five out of 42 patients (11.9%) crossed over to EoP from paclitaxel vs two out of 30 patients (6.7%) crossed over to paclitaxel achieved a PR. Until July 2003, disease progression was observed in 182 patients and 165 had died.

The duration of response was not significantly different between the two arms (Table 2). Median response duration for patients in the EoP and paclitaxel arms was 7 and 4 months, respectively (P = 0.039) (Figure 2). The 1-year survival rate was also in favour of the EoP arm, although the difference was not statistically significant (55.3 vs 40.7%; P = 0.168).

Although not significant, overall response rates were in favour of EoP arm in patients who had adjuvant anthracyclines more than 6 months ago and those who were resistant to prior anthracyclines for metastatic disease or relapsed within 6 months of adjuvant anthracyclines when compared to paclitaxel arm (36.8 vs 33.3% and 23.3 vs 18.8%, respectively). In patients who responded to prior anthracycline treatment, EoP has yielded a significantly higher response rate (55.6 vs 17.9%; P = 0.005). While there was no significant difference in terms of TTP in patients with adjuvant anthracyclines more than 6 months ago (5.0 ± 1.0 vs 4.6 ± 0.5 months; P = 0.611), it was significantly higher in favour of EoP arm in anthracycline-responsive or -resistant patients (4.5 ± 1 vs 3.0 ± 1.1 months; P = 0.005; 6.0 ± 1 vs 3.5 ± 0.3 months, P = 0.006).

Multivariate analysis including time interval from diagnosis and relapse to study treatment, CT, RDI, number of metastatic sites, age and type of study treatment showed that only type of study treatment had significant impact on survival (P = 0.0281). The only other parameter that was found to have an impact on OS in multivariate analysis close to statistical significance was the number of metastatic sites (P = 0.059).

Table 1  Patient characteristics

|                      | EoP (n = 96) | Paclitaxel (n = 97) | P-value |
|----------------------|-------------|--------------------|---------|
| Median age (years)   | 47 (26–69)  | 49 (24–70)         | 0.377   |
| Performance status   | 0.20        | 17                 |         |
|                      | 1           | 1                  |         |
|                      | 2           | 17                 | 0.401   |
| Site of metastasis   | Locally     | 4                  | 3       |
|                      | advanced    |                    |         |
|                      | Skin        | 47                 | 37      | 0.148   |
|                      | Lymph node  | 22                 | 15      |         |
|                      | Lung        | 47                 | 47      |         |
|                      | Liver       | 35                 | 46      | 0.145   |
|                      | Bone        | 45                 | 39      | 0.385   |
|                      | Brain       | 3                  | 3       |         |
|                      | Peritoneum  | 5                  | 2       |         |
| Number of metastatic | 1           | 29                 | 29      |         |
| sites                | 2           | 33                 | 44      | 0.354   |
|                      | 3 or more   | 34                 | 24      |         |
| Hormone receptor     | ER/PR+      | 29                 | 31      |         |
|                      | ER/PR−      | 15                 | 22      | 0.298   |
|                      | Unknown     | 52                 | 44      |         |
| Oncogene expression  | HER2+       | 11                 | 11      |         |
|                      | HER2−       | 9                  | 13      | 0.763   |
|                      | Unknown     | 76                 | 73      |         |
| TIDTR                | 28.4±5.0    | 28.9±3.9           | 0.350   |
| Prior treatments     | Surgery     | 72                 | 72      | 1.000   |
|                      | Radiotherapy| 17                 | 17      | 0.285   |
|                      | Adjuvant    | 18                 | 11      |         |
|                      | Metastatic  | 10                 | 18      | 0.158   |
|                      | Hormone     | 14                 | 16      |         |
| Prior anthracyclines |             |                    |         |
|                      | 1           | 33                 | 32      | 0.663   |
|                      | 2           | 18                 | 2       |         |
|                      | 3           | 18                 | 4       |         |
|                      | 4           | 43                 | 48      |         |
| Setting of study     | First line  | 18                 | 20      | 0.947   |
| drugs                | Second line | 59                 | 58      |         |
|                      | Third line  | 19                 | 19      |         |

Table 2  Results of the response evaluation and time-related variables

|                      | EoP (n = 91) | T (n = 94) | P-value |
|----------------------|-------------|------------|---------|
| Response type (%)    | OR          | CR         | PR       | Stable   | Progression |
|                      | 33 (36.3)   | 3 (3.3)    | 30 (33.0) | 44 (48.3) | 14 (15.4)   |
|                      | 21 (22.3)   | 3 (3.3)    | 18 (19.1) | 53 (56.4) | 20 (21.3)   |
| Response duration    | 7.0±1.1 (4.9–9.1) | 4.0±0.5 (3.0–4.9) | 0.132 |
| TTP (95% CI)         | 5.5±0.9 (3.7–7.3) | 3.9±0.3 (3.4–4.4) | 0.0035 |
| OS (95% CI)          | 1.0±1.2 (1.17–1.63) | 9.5±0.1 (7.4–11.5) | 0.039 |
| 1-Year survival rate | 55.3±5.1    | 40.7±5.0   | 0.048   |

EoP = etoposideplus cisplatin; TTP = time to progression; CI = confidence interval. OR = overall response; CR = complete response; PR = partial response.
DISCUSSION

This is the first randomised trial comparing the efficacy of paclitaxel with other CT in anthracycline-pretreated patients with breast cancer. In this trial, EoP was found to have higher efficacy in terms of response rates, TTP and OS when compared to paclitaxel.

The additive and synergistic effects of cisplatin and etoposide in experimental models have been reported previously (Burchenal et al., 1979; Mabel and Little, 1981). Although EP has been commonly employed in lung cancer and germ cell tumors, it is not a well-established treatment for patients with breast cancer. Nevertheless, cisplatin was found to be an active drug in breast cancer in 1980s (Sledge and Roth, 1989). However, early trials with single agent i.v. etoposide in previously treated patients with ABC were not promising (Sledge, 1991).

The efficacy of EP was assessed in eight phase 2 trials including 260 patients previously treated for ABC (Athanassiades et al., 1986; Cocconi et al., 1986; Giaccone et al., 1988; Cox et al., 1989; Krook et al., 1990; Icli et al., 1992; Ceci et al., 1995; Remick et al., 1996). A total response rate of 26.8% was obtained by giving etoposide 100 – 130 mg m⁻² i.v. for 3 – 5 days and cisplatin 60 – 100 mg m⁻² i.v. every 3 weeks to these heavily pretreated patients. The highest rate of grade 3 – 4 leukopenia was 31% in one trial, and altogether four toxic deaths were reported in these trials.

Following the emergence of oral etoposide, the role of prolonged oral etoposide in the treatment of breast cancer was investigated in five phase II trials (Calvert et al., 1993; Martin et al., 1994; Palombo et al., 1994; Atienza et al., 1995; Bontenbal et al., 1995). Unlike the results of single agent i.v. etoposide, the overall response rate was 23.8% in 143 patients with ABC, most of whom were pretreated.

Etoposide was utilised 50 – 100 mg p.o. for 14 – 21 days every 3 – 4 weeks in these trials. Myelosuppression, more prominent with 21 days of etoposide, and alopecia were notable toxicities in these trials.

So far, only two phase II trials looked into the role of oral EoP in ABC (Icli and Demirkazik, 1998; Fried et al., 2000). In our phase II trial, we have used the same dosage and schedule of EoP as in the present study. Out of 35 (42.8%) heavily pretreated patients, 15 responded. Median response duration and OS were 6 and 8 months, respectively. Grade 3 leukopenia was observed in 14.3% of the patients and only one patient had grade 4 anaemia.

A lower dosage of cisplatin (50 mg m⁻²) and longer duration of oral etoposide (50 mg m⁻² for 17 days) were utilised in the second trial by Fried et al. In 26 patients previously exposed to anthracyclines, 50% response rate with 7 months of response duration has been reported (Fried et al., 2000). Four patients (15%) required hospitalisation for neutropenic fever in that trial. The response rate achieved in the present randomised study (36.3%) is
close to that obtained in our previous phase 2 trial (42.8%). Likewise, the 22.2% response rate obtained in the paclitaxel arm is comparable with those achieved in previous trials employing 175 mg m$^{-2}$ i.v. paclitaxel every 3 weeks in anthracyclineresistant patients (Abrams et al, 1995). Both results of the past phase 2 trials and present randomised trial are in favour of EoP when compared to paclitaxel. On the other hand, myelotoxicity of EoP was somewhat higher than that of paclitaxel (18 vs 11% grade 3–4 toxicity). Likewise, more patients in the EoP arm had delayed treatment interval due to toxicity. One might argue that the efficacy of paclitaxel could be increased by employing higher and more myelotoxic dosages. However, a randomised trial failed to show any favourable effect of higher than 175 mg m$^{-2}$ of paclitaxel every 3 weeks in ABC, which excludes such an explanation of the lower efficacy of paclitaxel when compared to EoP in our trial (Winer et al, 2004).

Also, it was gratifying to see that both TTP and OS were significantly higher in the EoP arm when compared to paclitaxel arm, which has not been usual for randomised CT trials involving patients with ABC. Both TTP and OS curves show a stable progress in favour of the EoP arm (Figures 1 and 2). Although there were some minor differences in terms of patient characteristics between the two groups, they had no significant impact on TTP and OS in multivariate analysis. Moreover, there were no notable differences between the groups in terms of prior treatments and setting of study treatments, which rule out the role of these factors on the favourable results of EoP arm.

The myelotoxicity, however, was higher in the EoP arm when compared to T. In all, 21 patients in the EoP arm vs only three patients in the paclitaxel arm had at least 7 days of treatment delays due to myelosuppression. Likewise, nausea and asthenia were more common in the EoP arm. Probably more myelotoxicity in each arm would be noted if CBCs were repeated weekly instead of every 3 weeks. Two deaths in each arm following febrile neutropenia also suggest that the grade 4 neutropenia was more common than noticed for both EoP and paclitaxel arms.

Toxicities observed in several phase II as well as in two randomised trials assessing the efficacy of EP in breast cancer have limited the use of this combination in breast cancer (Giaccione et al, 1988; Krook et al, 1990; Cocconi et al, 1991; Remick et al, 1996; Icli et al, 2001). However, the dosage of cisplatin in all these trials was higher when compared to the present trial (100 vs 70 mg m$^{-2}$). A randomised phase 2 study comparing low (60 mg m$^{-2}$) vs high (100 mg m$^{-2}$) doses of cisplatin in the EP combination against breast cancer concluded that the dose of cisplatin had no significant effect in terms of TTP and OS (Ceci et al, 1995). Also, the dose intensity of both cisplatin and etoposide in the present trial was found to have no significant impact on both TTP and OAS in the multivariate analysis. Therefore, it might be premised that similar efficacy could be achieved by lower and less toxic dosages of both cisplatin and oral etoposide in ABC.

In the 1990s, paclitaxel 175 mg m$^{-2}$ i.v. every 3 weeks was considered as the treatment of choice following anthracyclines for patients with ABC (Nabholtz et al, 1996). Our randomised trial of EoP vs paclitaxel proves that EoP is more active in this group of patients. Significantly improved survival in the EoP arm in this trial is a rarely observed phenomenon in randomised trials of ABC treatment. Approximately 10 times lower price of EoP than paclitaxel also favours this treatment, especially in countries with limited sources of health expenditure. However, we should admit that absence of quality of life assessment is the weaknesses of the present trial.

In conclusion, results obtained in the present trial supports the use of EoP in the treatment of ABC. Further randomised trials will enlighten the efficacy of this relatively old treatment when compared to the new active drugs in breast cancer. Likewise, it will be interesting to see the efficacy of this treatment combined with herceptin in HER2-positive patients.

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