Cancer Chemother Pharmacol (1999) 44 (Suppl): S26–S28

ORIGINAL ARTICLE

A.Y. Chang · L. Hui · R. Asbury
L. Boros · G. Garrow · J. Rubins

Ifosfamide, carboplatin and etoposide (ICE) in metastatic and refractory breast cancer

Abstract Twenty-five patients with metastatic breast cancer were treated with ICE after failure of previous chemotherapy. Their median age was 50 years (range 36–73). All but 1 patient had multiple sites of metastases. Nineteen (76%) patients had undergone two or more chemotherapy regimens for metastatic disease prior to ICE. The performance status (PS) of the patients was Eastern Cooperative Oncology Group (ECOG) 0:6; 1:12; 2:5; 3:2. Ifosfamide 1.25 g/m^2 over 3 h D1-3 along with mesna, etoposide 80 mg/m^2 D1-3 and carboplatin 300 mg/m^2 D1 were given every 3 weeks. We observed a partial response in 10 patients (40%, 95% confidence interval 21–62%). The response duration ranged from 1 to 15 months with a median duration of 4.5 months. The survival of all 25 patients ranged from 10 days to 25 months, with a median of 9 months. All 25 patients were evaluable for toxicity. Thirteen patients (52%) experienced grade 4 hematological toxicity, which improved after growth factor support. Four patients had leukopenic fever, 1 had gram-negative sepsis, while 2 had Clostridium difficile enterocolitis and another had herpes zoster reactivation. Four patients (16%) experienced grade 3–4 gastrointestinal (G-I) toxicity. No hepatic or renal toxicity was observed (1 patient had microscopic hematuria). One patient died of G-I bleed, and another patient died at home of undetermined cause. We conclude that ICE is an effective salvage regimen in metastatic and refractory breast cancer, even in heavily pretreated patients, and is a tolerable treatment when used with growth factor.

Key words Ifosfamide · Carboplatin · Etoposide · Metastatic breast cancer · Salvage therapy

Introduction

Breast cancer is the most common cancer in women and the second most common cause of cancer death in female patients. While many patients with early localized disease may be cured with surgery or radiation in conjunction with adjuvant therapy, many patients will relapse and ultimately die of metastatic disease. In patients presenting with locally advanced as well as metastatic disease, breast cancer may respond favorably to initial hormonal treatment or chemotherapy. However, the median survival for this group of patients ranges from 18 to 30 months [1].

Anthracycline-containing regimens such as cyclophosphamide, doxorubicin and 5-fluorouracil (CAF), are commonly used in treating patients with metastatic or recurrent breast cancer. Response rates range between 40 and 70%; duration of response is about 6–10 months [1]. Newer chemotherapy regimens such as paclitaxel [2], docetaxel [3], and vinorelbine [4] have been used more commonly now either as first-line or second-line therapy. Again, the response rate is somewhere between 40 and 60% with a response duration of 6–10 months. Once a patient's disease becomes refractory to doxorubicin or taxane-containing regimens, effective treatment choices are limited.

Ifosfamide is an alkylating agent with activity against metastatic breast cancer [5]. Sanchiz and Milla [6] have treated 32 heavily pretreated metastatic breast cancer patients and reported a 36% response rate. In addition, ifosfamide has been used in combination with methotrexate and 5-fluorouracil (IMF) in patients who failed

Work presented at the Satellite Symposium "New Options for Palliative Treatment of Breast Cancer", 29 September 1998, at the First European Breast Cancer Conference, Florence, Italy

A.Y. Chang (✉) · L. Hui · R. Asbury · L. Boros · J. Rubins
Interlakes Oncology and Hematology, P.C.,
211 White Spruce Boulevard,
Rochester, NY 14623,
USA
Tel.: +1-716-350-2300; Fax: +1-716-475-9484

G. Garrow
The Genesee Hospital, Rochester,
NY, USA

first- or second-line chemotherapy, and it has been shown to have a response rate of 17–25% [7, 8].

Cisplatin and etoposide were reported to have a 25–38% response rate in patients with untreated or pretreated metastatic breast cancer [9, 10]. At the same time, carboplatin and etoposide have also been reported to have a response rate of 18.5% in a similar group of patients [11]. Carboplatin by itself is also an active drug in patients with metastatic breast cancer who have not received previous chemotherapy, having an overall response rate of 35% in 34 patients reported by Martin et al. [12].

Carboplatin is a second-generation platinum analog and has a more favorable toxicity profile [13]. Therefore, we chose carboplatin instead of cisplatin in our combination with ifosfamide and etoposide to study in patients with refractory breast cancer, especially in patients who have failed to respond or have become refractory to doxorubicin-containing regimens and paclitaxel-containing regimens.

Materials and methods

Patient selection

Patients must have histologically documented breast cancer with clinical evidence of metastatic disease. They must have failed on at least one anthracycline-containing chemotherapy regimen. However, there was no limit to the number of previous chemotherapy regimens. Entry requirements also included measurable or evaluable disease; Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2; absolute granulocyte $>1{,}500/\mu l$; platelet count $\geq 100{,}000/\mu l$; total bilirubin ≤ 1.5 mg%; and creatinine <1.5 mg/dl. Patients with active peptic ulcer disease, congestive heart failure and random blood sugar >250 mg/dl as well as myocardial infarction within 3 months were excluded from this study as were patients who were pregnant or lactating.

The treatment plan included ifosfamide 1.25 g/m^2 intravenously (i.v.) over 3 h with mesna at the same dose given by i.v. infusion over 6 h. Carboplatin was given 300 mg/m^2 on day 1 in 500 cc D5W over 1 h and etoposide 80 mg/m^2 on days 1–3 in 250 cc normal saline i.v. drip over 30–60 min. Ifosfamide was given at 500 cc D5W, and mesna was prepared also in 500 cc of D5W and piggybacked to the same i.v. lines as the ifosfamide.

Dose modifications were based on the hematological, hepatic and renal toxicities with 25% and 50% dose reduction in subsequent cycles of all three medications for patients with a nadir count WBC 1,000–1,999/μl and $<1{,}000/\mu l$, respectively, or platelet nadirs of 30,000–70,000/μl and $<30{,}000/\mu l$, respectively. Treatment was delayed for serum aspartate transaminase increase >2.5 times normal or bilirubin >1.5 mg/dl as well as creatinine >2.0 mg%. In addition, the dose of ifosfamide was reduced by 25% if patients developed a grade 2 central nervous system (CNS) toxicity and by 50% if they developed a grade 3 or worse CNS toxicity.

Patients were treated until disease progression or unacceptable toxicities judged by the patient and/or the investigator. In the first 19-patient cohort, no granulocyte-colony stimulating factors (G-CSF) or granulocyte macrophage-colony stimulating factors (GM-CSF) were used. For subsequent patients, we used G-CSF along with ICE chemotherapy. This was initiated after 1 patient had sepsis with grade 4 neutropenia after the first cycle of chemotherapy.

Patients received repeated cycles every 3 weeks, and their tumor response was evaluated every 3 cycles according to ECOG response criteria [14]. Toxicity was evaluated every cycle according to the Common Toxicity Criteria from the National Cancer Institute. In addition, complete blood counts were done weekly and clinical chemistry tests were done every 3 weeks.

Results

From September 1993 to January 1997 we entered 25 patients in the phase II trial. Two patients were ineligible because of a performance status of 3 and no prior doxorubicin in 1 of 2; 2 other patients were unevaluable owing to early death. However, all the patients were included in this report. The above 4 patients were deemed treatment failures. The patients' characteristics are shown in Table 1. The typical patient had a performance status of 1 and had received at least 3 prior chemotherapy regimens, and ICE therapy is used as a salvage treatment. All but 1 patient had refractory disease to anthracycline-containing regimen before ICE. We have observed 10 partial responses in this group of patients (40%, 95% confidence interval 21–62%). Responses were seen in all disease sites and also in patients previously treated with paclitaxel (2/7) and vinorelbine (1/4). The median duration of response was 4.5 months (range 1–15). The survival in all 25 patients ranged from 10 days to 25 months, with a median survival of 9 months.

All 25 patients were evaluable for toxicities, and the most common toxicity was myelosuppression with grade 4 neutropenia observed in 13 patients (52%) and grade 4 thrombocytopenia in 8 patients (32%). Four patients had leukopenic fever and 1 had gram-negative sepsis. In addition, 2 patients had Clostridium difficile entercolitis, and the other patient had herpes zoster reactivation. Four patients experienced grade 3 nausea/vomiting before the use of 5-HT$_3$ agonist. No hepatic or CNS toxicity was observed. Only 1 patient had microscopic hematuria. One patient died of G-I bleeding; the other patient died of undetermined cause. The remainder of the patients died from progressive metastatic breast cancer.

Table 1 Patient characteristics

	Patients (*n*)
Total	25
Mean age (range), years	50 (36–73)
Performance status	
0	6
1	12
2	5
3	2
Prior chemotherapy for metastatic disease	
Anthracycline-containing regimen	24
Paclitaxel-containing regimen	7
Vinorelbine	4
Number of prior chemotherapy regimens	
1	3
2	4
>2	18
Number of metastatic sites	
1	5
2	7
>2	13

Discussion

ICE combination chemotherapy has not commonly been used in the salvage treatment for metastatic breast cancer. As a single agent only, ifosfamide has been shown to have a response rate of about 15–20%; carboplatin or etoposide had dismal response rates by themselves when used in the refractory disease.

We observed a 40% (10/25) partial response rate in 25 heavily pretreated patients, suggesting a clinical synergistic interaction between the 3 agents as suggested in preclinical evaluations. Fields et al., however, reported a 20% response rate in 93 patients with metastatic and refractory breast cancer [15]. The reasons for this difference are uncertain, except that Fields et al. gave patients a continuous infusion of etoposide and used a lower dose of ifosfamide (only 1 g/m^2 per day for 2 cycles).

Myelosuppression was the most common toxicity which was dose-limiting. We noted 52% grade 4 leukopenia and 32% grade 4 thrombocytopenia. Most of these occurred in the first 19 patients when G-CSF was not used routinely from cycle 1 of treatment. In this group of heavily pretreated patients, we feel justified in using colony-stimulating growth factor, although we had only 4 patients with leukopenic fever and 1 patient with sepsis. (An additional patients who died at home with grade 4 leukopenia could also have had sepsis.) All 5 cases occurred before the routine use of G-CSF (in the first 19 patients). Four patients experienced grade 3 or 4 G-I toxicity in the form of nausea and/or vomiting without the use of 5-HT_3 agonist as antiemetics. Once we started the ondansetron, no patients reported grade 3 or worse nausea/vomiting.

In conclusion, ICE chemotherapy is an effective salvage regimen for refractory breast cancer with manageable and tolerable toxicities. It may be useful in young patients with good performance status and adequate organ function who have exhausted most of the commonly used regimens. It may also be worth considering for use in adjuvant therapy as a non-cross resistant regimen to doxorubicin-containing regimen.

Acknowledgement This study was supported by a grant from Bristol-Myers Squibb.

References

1. Harris JR, Morrow M, Norton L (1997) Malignant tumors of the breast. In: Devita VT, Hellman S, Rosenberg SA (eds) Cancer. Principles and practice of oncology. Lippincott, Philadelphia, pp 1557–1616
2. Hortobagyi GN (1997) Paclitaxel-based combination chemotherapy for breast cancer. Oncology 11 [Suppl 2]: 29–37
3. Ravdin PM (1995) Taxoids: effective agents in anthracycline-resistant breast cancer. Semin Oncol 22 [Suppl 13]: 229–234
4. Livingston RB, Ellis GK, Gralow JR, Williams MA, White R, McGuirt C, Adamkiewicz BB, Long CA (1997) Dose-intensive vinorelbine with concurrent granulocyte colony-stimulating factor support in paclitaxel-refractory metastatic breast cancer. J Clin Oncol 15: 1395–1400
5. Hortobagyi GN (1992) Activity of ifosfamide in breast cancer. Semin Oncol 19 [Suppl 12]: 36–42
6. Sanchiz F, Milla A (1990) High-dose ifosfamide and mesna in advanced breast cancer: a phase II study. Cancer Chemother Pharmacol 26: 991–992
7. Becher R, Höfeler H, Kloke O, May D, Wandl U, Niederle N, Richter R, Scheulen ME, Schmidt CG (1991) Ifosfamide, methotrexate and 5-fluorouracil for pretreated advanced breast cancer. Oncology 48: 459–463
8. Gad-el-Mawla N, Hamza MR, Zikri ZK, Elserafi M, El-Khodari A, Khaled H, Gafaar R (1990) Ifosfamide, methotrexate, and 5-fluorouracil: effective combination in resistant breast cancer. Cancer Chemother Pharmacol 26: 85–86
9. Cox EB, Burton GV, Olsen GA, Vugrin D (1989) Cisplatin and etoposide: an effective treatment for refractory breast carcinoma. Am J Clin Oncol 12: 53–56
10. Krook JE, Loprinzi CL, Schaid DJ, Kardinal CG, Mailliard JA, Pfeifle DN, Ellison NM, Reuter NF, Nelimark RA (1990) Evaluation of the continuous infusion of etoposide plus cisplatin in metastatic breast cancer. A collaborative North Central Cancer Treatment Group/Mayo Clinic phase II study. Cancer 65: 418–421
11. Vinolas N, Daniels M, Estape J, Grau JJ, Palombo H, Sola C (1992) Phase II trial of carboplatin and etoposide activity in pretreated breast cancer patients. Am J Clin Oncol 15: 160–162
12. Martin M, Diaz-Rubio E, Casado A, Santabarbara P, Vega JML, Adroves E, Lenaz (1992) Carboplatin: an active drug in metastatic breast cancer. J Clin Oncol 10: 433–437
13. Von Hoff DD (1987) Whither carboplatin? – a replacement or an alternative to cisplatin. J Clin Oncol 5: 169–170
14. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 5: 649–655
15. Fields KK, Zorsky P, Hiemenz JW, Kronish LE (1994) Ifosfamide, carboplatin, and etoposide: a new regimen with a broad spectrum of activity. J Clin Oncol 12: 544–552