Cancer Chemother Pharmacol (1990) 26 (Suppl): S 81–S 84

Cancer Chemotherapy and Pharmacology

Ifosfamide + mitoxantrone in advanced breast cancer previously treated with anthracyclines*

Joaquin Bellmunt, Serafin Morales, Matilde Navarro, and Luis-Alfonso Solé

Department of Medical Oncology, Hospital Valle Hebron, E-08035 Barcelona, Spain

Summary. We treated 19 patients previously exposed to anthracyclines (progression during therapy or after discontinuation of therapy) with ifosfamide (IFO) 2 g/m^2 i.v. in a 1-h infusion daily for 3 days with mesna uroprotection and mitoxantrone (MZT) 12 mg/m^2 on day 1 of every 3-week cycle. The response rate was assessed after two cycles. A response to treatment was observed in 6 of 15 evaluable patients (40%), with no complete remission and 6 partial remissions. The median duration of response was 6+ months (3+ to 12+). The toxicity was acceptable, with three episodes of grade 3–4 myelosuppression (8%) and one case of congestive heart failure resulting from a fluid overload that responded to medical treatment. The IFO-MZT combination is an effective second-line regimen in advanced breast cancer previously treated with anthracyclines.

Introduction

Different combination chemotherapy regimens with drugs normally used in the treatment of advanced breast carcinoma [Adriamycin (ADR) cyclophosphamide (CYC), methotrexate (MTX), 5-fluorouracil (5-FU), mitomycin-C (MMC), and vinca alkaloids] in previously untreated patients can yield an overall response rate of 50–70%, with a median duration of response of 8–15 months [12].

Since virtually all patients who respond eventually relapse, the search for effective second-line chemotherapy has been vigorous, but so far the results have been disappointing, with responses limited to a rate of 30–40%, almost never complete and, as a rule, of short duration. With third-line chemotherapy responses are rarely seen, and if they are present, they are probably of slight or limited usefulness to the patients [11, 19].

In patients who have previously received ADR as induction treatment, the selection of the second-line treatment is limited to different types of CMF chemotherapies or combinations containing vinca alkaloids or MMC [14, 18, 23, 26]. In a previous study from our unit, we reported the results of a combination regimen including vinblastine-MMC as a second-line therapy in advanced breast cancer resistant to standard combinations. We obtained an overall response rate of 32% with a median duration of response of 6 months [21].

The introduction of new active drug analogues, such as ifosfamide (IFO), for the treatment of advanced breast carcinoma and of drugs with lower toxicity and without absolute cross resistance to anthracyclines, such as mitoxantrone (MZT), justifies the study of new therapeutic combinations with both these drugs.

Patients and methods

Patients

A total of 15 evaluable patients from a group of 19 with metastatic breast cancer previously treated with anthracyclines, received at least two cycles of IFO/MZT combination chemotherapy. The mean Karnofsky status was 80% (range 60–100%) and mean age was 53 years (range 29–71). At the time of diagnosis, 7 patients were premenopausal or perimenopausal, and 12 patients were postmenopausal. The relapse-free interval after diagnosis of the primary tumor was <2 years in 10 patients and >2 years in 9 patients.

All patients had been pretreated with anthracyclines up to maximum tolerated doses or until progression, 4 with THP-ADR and 15 with ADR at the time of metastatic disease. The median dose of anthracyclines received previously was 390 mg/m^2 (range 290–550 mg/m^2). The maximum responses to prior chemotherapy were complete remission (CR) in 4, partial remission (PR) in 4, no change (NC) in 5, and progressive disease (PD) in 6.

* Presented at the Satellite Symposium "Ifosfamide in Gynecological Tumors" of the 5th European Conference on Clinical Oncology and Cancer Nursing, London, September 3–7, 1989

Offprint requests to: Joaquin Bellmunt, Department of Medical Oncology, Hospital Valle Hebrón, P. Valle de Hebrón s/n, E-Barcelona 08035, Spain

Table 1. Patient characteristics

No. of patients	19
Evaluable patients	15
Age (years)	29–71 (median, 53)
Menopausal status	
Pre-perimenopausal	7
Postmenopausal	12
Relapse-free interval (years)	
<2	10
>2	9
Site of metastases	
Soft tissue	10
Lung	9
Pleura	4
Bone	3
Liver	2
Mediastinum	1
Response to previous treatment	
Complete remission (CR)	4 (21%)
Partial remission (PR)	4 (21%)
No change (NC)	5 (26%)
Progressive disease (PD)	6 (32%)
Duration of response (months)	6+ (3+ to 12+)

Table 2. Response to ifosfamide + mitoxantrone (IFO/MTZ)

Response	Patients	
	n	%
CR	0	0
PR	6	40
NC	6	40
PD	3	20

Table 3. Toxicity observed in the applied courses ($n = 57$)

Toxicity	ECOG grade				
	0	1	2	3	4
Alopecia	0	14	43	0	0
Emesis	16	21	15	5	0
Neurologic	55	1	0	1	0
Urotoxicity	54	3	0	0	0
Cardiac	56	0	0	1	0
Leukocytes	34	9	11	2	1
Platelets	43	9	5	0	0
Hemoglobin	39	17	1	0	0

Ten patients had only a single metastatic site and 9 had more than one site. Soft tissue lesions were present in 10 patients, lung lesions in 9, pleural lesions in 4, bone lesions in 3, liver lesions in 2 and mediastinum involvement in 1. The patients with only one site of metastasis had metastasis to soft tissues (4 cases), lung (4 cases) or pleura (2 cases).

Treatment

The treatment schedule consisted of ifosfamide (IFO), 2 g/m^2 i. v. in a 1-h infusion each day for 3 days and MZT 12 mg/m^2 on day 1 of each 3-week cycle. One hour before IFO administration, immediately before IFO administration and 4 h and 8 h after, patients received mesna as uroprotection, at a dosage of 20% of the IFO dose i. v. or 40% of the IFO dose p. o. The treatment schedule was repeated every 3 weeks until tumor progression or unacceptable toxicity. Nine patients were treated as outpatients.

Evaluation

The response rate was assessed after two cycles. CR was defined as disappearance of all measurable lesions for at least 1 month and PR as a greater than 50% reduction in size and the absence of any new lesion for at least 1 month. NC was defined as stabilization, or a reduction of less than 50% without progression of other lesions for at least 2 months. PD was defined as an increase of more than 25% in the volume of any of the metastatic lesions, based on the maximum response observed. Duration of response was calculated from the start of treatment.

Results

Of 19 patients, 4 could not be evaluated for response: 2 died of their metastases early in the trial, 1 had unacceptable CNS toxicity related to treatment, and 1 was lost to follow-up after the first course of treatment.

Table 1 shows some of the characteristics of the 19 patients. PR was induced in 6 patients (40%). The sites of metastasis in these patients were pleura; soft tissue and pleura; lung; local, nodes and pleura; local and soft tissue; and local, pleura, and lung. On assessment, 6 patients (40%) were considered to have NC and 3 patients (20%) were unresponsive (PD) (Table 2). All patients responding to IFO/MTZ had previously responded to anthracyclines (2CR, 2PR), except for 1 patient whose disease had progressed during previous chemotherapy.

The median duration of response was 6+ months (range 3–12 months) for objective responders. In nonresponders the median time to progression was 4 (range 3–8) months. Median survival was 10 months for all patients, 12 months for responders, 9 months for those with NC, and 7 months for nonresponders. Main sites of response were soft tissue, pleura and lung.

Toxicity was tolerable, with only one case of grade 4 toxicity (myelotoxicity). Alopecia grade 2 (ECOG) was documented in 75% of patients. Myelotoxicity grades 3–4 was observed in 3 of 57 cycles. One patient had grade 3 neurological toxicity. No hemorrhagic cystitis was seen. All patients had previously had a left ventricular ejection fraction (LVEF) greater than 45%. The LVEF after three cycles was checked in responders; no decrease greater than 5% was seen. In non-responding patients no signs of clinical cardiac toxicity or ECG changes were observed, except in one patient who had cardiac failure grade I secondary to a fluid overload. The grading and frequency of concomitant toxicities are shown in Table 3. No treatment-related deaths occurred. Of 6 patients with PR, 3 refused to continue treatment due to poor acceptance of therapy.

Discussion

Because little progress has been made in recent years in the cytotoxic treatment of advanced breast cancer with new combinations or by dose modifications of conventional drugs, efforts should be made to improve response by evaluating new drugs with a high therapeutic index.

IFO is an oxazaphosphorine analogue with different pharmacological and toxicological properties from cyclophosphamide (CYC). Few studies have evaluated the effectiveness of IFO together with the concomitant use of mesna as a uroprotective agent in advanced breast cancer. Data obtained from experimental tumor systems, including that of the C3H mammary tumor, have shown an effectiveness of IFO that is even superior to that of CYC [10]. In several trials of single-agent therapy IFO has been shown to be active in the treatment of advanced breast cancer, with an overall response rate somewhat superior to 35% [1, 6].

IFO has been demonstrated to be less leukotoxic than CYC, which suggests that it might advantageously be used in combination chemotherapy [5]. Experience with IFO-containing regimens in the treatment of refractory breast cancer is still sparse. IFO has been substituted for CYC in the CMF regimen by some authors [2, 9], with objective response rates between 15% and 25%. In combination with other chemotherapeutic agents, such as VP16, as a second-line regimen it has yielded response rates of 33% [13].

MZT is a bis-substituted anthraquinone with a mechanism of action similar to that of ADR. A cumulative response rate of 33% (30–37%) has been obtained with MZT as a single agent in patients with advanced metastatic breast cancer not previously treated with chemotherapy. The median duration of response was 10 months [7, 17].

In previously treated patients, the overall response rate with MZT as a single agent is approximately 12% (6–25%) [12, 27]. In second-line therapy, MZT has been used in combination with drugs such as MMC and vindesine giving response rates comparable to the best obtained with other second-line combination therapies [3]. Combinations with drugs such as prednimustine have achieved response rates of 16–23% [15, 24].

There are some theoretical advantages that justify the use of IFO and MZT in combination therapy as a second-line treatment in advanced breast cancer previously treated with anthracyclines.

A review of the data obtained from several experimental tumor systems has revealed a synergistic action of MZT with alkylating agents such as CYC in P388 leukemia [8].

IFO has proven to be experimentally active in tumoral cell lines resistant to anthracyclines and to the combination ADR/CDDP, as well as in tumor cells primarily resistant to CYC [4].

The response rate to MZT in patients failing to respond to ADR has been reported to be 21%, which suggests a lack of absolute cross-resistance between these two agents [22]. Although not completely devoid of cardiac toxicity, MZT has been significantly less cardiotoxic than doxorubicin in experimental and clinical studies [25].

Treatment with MZT after prior doxorubicin therapy could then be justified, provided adequate monitoring of the left ventricular ejection fraction (LVEF).

In the present study, we evaluated the IFO-MZT combination in a group of patients previously treated with and resistant to ADR. We observed a 40% response rate, which is within the best range of results reported for second-line therapy [20, 23]. The best response was achieved in patients with single metastatic lesions predominantly in the soft tissues, pleura and lung. Most patients responding to IFO-MZT had previously responded to ADR.

We have not observed life-threatening secondary effects with the administration of our regimen, and monitoring of the LVEF has not revealed any cardiotoxic events. Since, after a median of four cycles, 3 of 6 patients in stabilized PR refused to continue chemotherapy because of global intolerance, a careful evaluation of the quality of life must be seriously considered in this group of patients with refractory disease.

The search for therapies that combine effectiveness with acceptable toxicity and easy application (ambulatory treatments, oral formulations, etc.), which would improve patient acceptance of the treatment, is clearly necessary.

The results obtained show that the IFO-MZT combination is an effective second-line regimen in advanced breast carcinoma previously treated with anthracyclines and that the initial response rate observed justifies future testing with this combination.

References

1. Ahman DL, Bisel HF, Hahn RG (1974) Phase II clinical trial of isophosphamide (NSC-109724) in patients with advanced breast cancer. Cancer Chemother Rep 58: 861
2. Becher R, Höfeler H, Kloke O, Kurschel E, Schilcher RB, Weinhardt O, Schmidt CG (1989) Ifosfamide, methotrexate, and 5-fluorouracil in advanced pretreated breast cancer. Semin Oncol 16: 59
3. Belpomme D, Gisselbrecht C, Marty M, Cour V, Hertier F, Le Rol A, Mignot L, Maral J (1987) Long duration of response induced by vindesine, mitoxantrone and mitomycin C in metastatic breast carcinoma. Proc ASCO 23: 224
4. Brade WP, Seeber S, Herdrich K (1985) Experimental and clinical comparative activity of ifosfamide and cyclophosphamide. In: Recent experience with ifosfamide/mesna in solid tumors. Proc ECCO 3: 5
5. Bramwell VH, Mouridsen HT, Santoro A, Blackledge G, Somers R, Verwey J, Dombernowsky P, Onsrud M, Thomas D, Sylvester R, Van Oosterom A (1987) Cyclophosphamide versus ifosfamide: final report of a randomized phase II trial in adult soft tissue sarcomas. Eur J Cancer Clin Oncol 23: 311
6. Brema F, Porcile GF, Parodi GC (1977) Clinical evaluation of isophosphamide in solid epithelial advanced tumors. Clin Pharmacol Ther 5: 122
7. Carmo-Pereira J, Costa FO, Henriques E, Carvalho V, Catineho-Lopes MG, Grodinho F, Sales-Luis A (1987) First-line chemotherapy with mitoxantrone and prednisone in advanced breast carcinoma. A phase II study. Proc ASCO 23: 209
8. Durr FE (1984) Biological and biochemical effects of mitoxantrone. Semin Oncol 11: 3
9. Gad-el-Mawla N, Hamza MR, El-Serafi M (1984) Ifosfamide, methotrexate, and fluorouracil effective combination in refractory breast cancer. J Egypt Natl Cancer Inst 1: 81
10. Goldin A (1982) Ifosfamide in experimental tumor system. Semin Oncol 4: 14

11. Hartlapp JH, Wolter H, Musch E, Illiger HJ (1986) Third line chemotherapy in metastasized breast cancer. Proceedings of the 14th International Cancer Congress, Budapest 51: 735
12. Henderson IC (1983) Chemotherapy of breast cancer. A general overview. Cancer 51: 2553
13. Hoffman G, Worst P, Heim ME (1986) Ifosfamide and etoposide as second line therapy in advanced breast cancer. Proceedings of the 12th Annual Meeting of ESMO 20: 67
14. Howell A, Morrison JM, Bramwell VH (1984) Dibromodulcitol, mitomycin C and vinblastine (DMV) chemotherapy in advanced breast cancer. Eur J Cancer Clin Oncol 20: 873
15. Kaufmann M, Manegold C, Schmid H, Kubli F (1987) Phase II study of mitoxantrone and prednimustine in advanced breast cancer. In: Bonadonna G (ed) Clinical progress with mitoxantrone. Royal Society of Medicine Services, London, p 17
16. Konits PH, Aisner J, Van Echo DA, Lichtenfeld K, Wiernik PH (1981) Mitomycin C and vinblastine chemotherapy for advanced breast cancer. Cancer 48: 1295
17. Landys K, Borgstrom S, Andersson T, Noppa H (1985) Mitoxantrone as a first line treatment of advanced breast cancer. Invest New Drugs 3: 133
18. Legha SS, Blumenschein GR (1982) Systemic therapy of metastatic breast cancer: A review of the current trends. Oncology 39: 140
19. Lenaz L (1985) Mitomycin C in advanced breast cancer. Cancer Treat Rev 12: 235
20. Luikart SD, Witman GB, Portlock CS (1984) Adriamycin (doxorubicin), vinblastine, and mitomycin-C combination chemotherapy in refractory breast carcinoma. Cancer 54: 1252
21. Navarro M, Bellmunt J, Balaño C, Colomer R, Jolis L, Del Campo JM (1989) Mitomycin-C,s vinblastine in advanced breast cancer. Oncology 46: 137
22. Neidhart JA, Gochnour D, Roach R, Hoth D, Young D (1986) A comparison of mitoxantrone and doxorubicin in breast cancer. J Clin Oncol 4: 672
23. Petru E, Schmäl D (1986) On the relevance of "second line" cytotoxic chemotherapy in patients with metastatic breast cancer resistant to standard combinations. Wien Klin Wochenschrift 98: 790
24. Preiss J, Hilfrich J, Corterier H, Rauschecker H, Hohlweg-Majert P, Bodenstein H (1987) Novantrone and Sterecyt in metastatic breast cancer: a multicenter study with first and second line therapy. ECCO [4] 497: 130
25. Vorobiof DA, Iturralde M, Falkson G (1985) Assessment of ventricular function by radionuclide angiography in patients receiving 4'-epidoxorubicin and mitoxantrone. Cancer Chemother Pharmacol 15: 253
26. Yap Hy, Blumenschein GR, Schell FC, Buzdar AV, Valdivieso M, Bodey GP (1981) Dihydroxyanthracenedione: a promising new drug in the treatment of metastatic breast cancer. Ann Intern Med 95: 694
27. Yap HY, Blumenschein GR, Hortobagyi GN, Buzdar AU, Schell FC, Bodey GP (1982) Combination chemotherapy with continuous infusion vinblastine and peptichemio for patients with advanced metastatic breast cancer. Am J Clin Oncol 5: 511