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Clinical trial report

Weekly 5-fluorouracil and high-dose folinic acid in combination with epidoxorubicin as first-line therapy in advanced breast cancer: a phase II study

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Abstract. A total of 25 patients with advanced breast cancer were treated weekly with i.v. 5-fluorouracil at 350 mg/m^2, folinic acid at 500 mg/m^2, and epidoxorubicin at 35 mg/m^2 as first-line chemotherapy for a maximum of 18 cycles. In all, 24 patients were evaluable for response. Overall, 1 patient achieved a complete response and 11 patients showed a partial response, for an objective response rate of 50%; the median duration of response was 18.3+ months and median survival amounted to 18.8+ months. Side effects were generally mild, with grade II leukopenia occurring in 10 patients and grade III leukopenia, in 1 patient. Other toxicity included nausea and vomiting (82%), diarrhea (48%), stomatitis (48%), and alopecia (92%), all of which were mainly restricted to WHO grades I and II. Our results suggest that leucovorin modulation of 5-fluorouracil can safely be incorporated into combination chemotherapy with epidoxorubicin on the investigated schedule. The observed response rate appears comparable with that obtained with other first-line regimens.

Introduction

Depending on patient selection, reported response rates to first-line combination chemotherapy in metastatic breast cancer vary from 40% to 80% [9, 19, 21]. The median duration of response is usually <1 year, and the reported median survival of patients with metastatic disease ranges from 18 to 24 months. Clinical research has concentrated its efforts on improving treatment efficacy by manipulations of doses, schedules, and combinations as well as by modulation of known cytotoxic drugs.

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Since its introduction into clinical therapeutics, 5-fluorouracil (FU) has proved to be one of the most important agents for the treatment of advanced breast cancer, remaining a standard part of combination programs applied to the therapy of this disease [8, 10]. One potential method of enhancing the efficacy of FU is biochemical modulation with leucovorin (LV). Biochemical modulation of FU with LV has been studied, with encouraging results being obtained in patients with colorectal carcinoma [5, 6, 14, 16]. The combination of FU and LV has also shown activity in heavily pretreated breast cancer patients, suggesting that the efficacy of the fluoropyrimidines may be significantly enhanced by manipulation of the folate status of this tumor [1, 2, 18]. Since the side effects of this combination were mainly represented by oral mucositis, diarrhea, and conjunctivitis, whereas hematological toxicity was reportedly very mild, it appeared to be useful to combine this regimen with drugs characterized by a different pattern of toxicity, e.g., 4-epidoxorubicin (EPI).

EPI is a doxorubicin analog that exhibits a pattern of activity and toxicity similar to that of the parent compound but probably has a better therapeutic index due to its minor toxicity, in particular cardiotoxicity [4, 11, 12]. In a further attempt to reduce toxicity, EPI has more recently been given on a weekly schedule [3, 13, 17].

This current phase II study was designed to evaluate the antitumor activity and toxicity of FU plus high-dose folinic acid (HDFA) given in combination with EPI on a weekly schedule in advanced breast cancer patients who had not been pretreated with chemotherapy in a palliative setting in the search for an active but less toxic treatment modality.

Patients and methods

From May 1989 to February 1991, a total of 25 consecutive patients with histologically proven advanced breast cancer were entered in this study. The characteristics of the patients are shown in Table 1. Previous chemotherapy for metastatic disease excluded patients from entering the study, whereas adjuvant cytotoxic therapy did not, provided that the therapy had been stopped for a minimum of 12 months before entry

Table 1. Patients' characteristics[a]

Entered	25
Evaluable	24
Median age (years)	52 (40–79)
Median performance status (% Karnovsky)	90 (60–100)
Menopausal status:	
Premenopausal	9
Postmenopausal	16
Relapse-free interval:	
>2 years	7
<2 years	18
Estrogen receptor status:	
Positive	11
Negative	10
Unknown	4
Prior systemic therapy:	
adjuvant chemotherapy	3
palliative hormonal therapy	4
Dominant site of disease:	
Viscera	11
Bone	3
Soft tissue	8
Advanced primary lesion	3
Number of organ systems involved:	
1	11
2	12
3	2

[a] Unless otherwise specified, values represent numbers of patients (ranges are given in parentheses)

and did not contain anthracyclines. Eligibility requirements included the presence of progressive measurable and/or evaluable disease, an age of <80 years, a Karnovsky performance status of >30%, a white blood cell count (WBC) of ≥4,000/mm^3, a platelet count of ≥100,000/mm^3, serum creatinine and serum bilirubin of ≤2 mg/dl, and levels of serum transaminases ≤4 the normal value. Patients with brain metastases or other serious medical problems were excluded from the trial. A normal left ventricular ejection fraction (LVEF), as measured by radionuclide cardiography or echocardiography, was required. The study was conducted according to the ethical standards described in the Helsinki declaration. Informed consent was required before entry into the study. Leukocyte and platelet counts, hemoglobin values, and biochemical profiles were obtained prior to each treatment cycle; follow-up LVEF measurements were obtained prior to every ninth course of therapy of whenever indicated by individual clinical situations.

The regimen consisted of 1- day courses followed by a drug-free interval of 6 days. HDFA was given at a dose of 500 mg/m^2 by i.v. infusion over 2 h, and FU at 350 mg/m^2 was given by i.v. bolus injection 1 h after the start of the HDFA infusion. EPI was given i.v. immediately after HDFA at a dose of 35 mg/m^2 over 15 min. Treatment courses were repeated every 8 days. At the start of subsequent courses of therapy, dose modifications were made on the basis of the toxicity encountered during the preceding course; doses of EPI, HDFA, and FU were reduced by 25% when the WBC count was <3,500/mm^3 but ≥3,000/mm^3 and/or when the platelet count was <100,000/mm^3 but ≥75,000/mm^3 as well as in any case of grade III or IV toxicity except for alopecia. For a WBC count of <3,000/mm^3 and/or a platelet count of <75,000/mm^3, courses were postponed for 8 days. All cycles were given on an outpatient basis.

In the absence of progressive disease (PD), a total of 18 courses was scheduled to be delivered to each patient; then, patients were planned to be followed without any form of maintainance therapy until PD occurred. Treatment was also planned to be discontinued in cases of severe toxicity or patients' refusal of further therapy. The first evaluation of response took place after six cycles of therapy, and WHO criteria were used for the evaluation of response and toxicity [20].

Results

Response data

Of the 25 patients entered in this study, 24 were evaluable for response; in 1 case, treatment was disrupted after 3 courses due to a pathological bone fracture, which caused postponement of the therapy for >3 weeks, and the patient was therefore considered as lost for treatment. The response according to the metastatic site and the number of organ systems involved is shown in Table 2.

In all, 1 (4%) patient obtained a complete remission (CR) and 11 (46%) reached a partial remission (PR), for an overall response rate of 12/24 (50%) with a 95% confidence interval of between 25% and 72%; 10 (42%) patients achieved stabilization of their disease (NC), and 2 (8%) patients progressed under treatment.

Of the 12 patients responding to the regimen with primary advanced lesions, 3 underwent surgery and were therefore considered not to be evaluable for duration of response. The median duration of response was 18.3+ months (range, 5.3–28+ months), and the median time to disease progression in patients achieving disease stabilization (NC) amounted to 8.5 months (range, 3.1–17 months). The median survival was 18.8+ months (range, 2.8–38+ months) for all patients entered and 28+ months (range, 22–38+ months) for responders.

Table 2. Response according to the dominant site of disease and the number of organ systems involved

Response	DMS			PAL	Number of OSI		
	V	O	ST		1	2	3
CR	–	–	1/8	–	1/11	–	–
PR	5/10	1/3	2/8	3/3	4/11	7/11	–
NC	4/10	2/3	4/8	–	6/11	2/11	2/2
PD	1/10	–	1/8	–	0/11	2/11	–
*R*R (%)	50	33	38	100	36	63	0

Values represent the number of patients/patients per collective. DMS, Dominant metastatic site; V, visceral; O, osseous; ST, soft tissue; PAL, primary advanced lesion; OSI, organ system involved; RR, response rate

Table 3. Maximal level of toxicity over all courses of therapy[a]

Toxicity	WHO grade				
	0	I	II	III	IV
Anemia	12 (48)	11 (44)	2 (8)	–	–
Leukopenia	9 (36)	5 (20)	10 (40)	1 (4)	–
Thrombocytopenia	24 (96)	1 (4)	–	–	–
Oral mucositis	13 (52)	7 (28)	5 (20)	–	–
Diarrhea	13 (52)	8 (32)	3 (12)	1 (4)	–
Alopecia	2 (8)	2 (8)	21 (84)	–	–
Nausea/vomiting	4 (16)	5 (20)	13 (52)	3 (12)	–

[a] Values represent number of patients; the corresponding percentages are given in parentheses

Toxicity

All 25 patients entered were evaluable for toxicity. A total of 312 cycles were given, with the median being 12 (range, 3–18) for each patient. The degrees of toxicity encountered are outlined in Table 3. Grade III leukopenia was encontered in 1 (4%) patient, 15 (60%) patients presented with leukopenia of grade I–II, and 13 (52%) patients developed grade I–II anemia. Persistent leukopenia or thrombocytopenia was not documented in any case. In all, 18 (72%) patients experienced grade I–II episodes of nausea and vomiting and 3 (12%) patients reported grade III episodes. Oral mucositis of grade I–II developed in 12 (48%) patients, and 11 (44%) patients suffered from grade I–II diarrhea. In addition, 2 (8%) patients experienced grade I alopecia and 21 (84%) developed grade II hair loss.

Local thrombophlebitis at the site of administration and/or hyperpigmentation of the skin along the draining veins appeared in 5 (20%) patients without any accidental extravasation, whereas 1 (4%) patient had more or less refractory conjunctivitis. In 1 (4%) patient a dry skin rash developed and 2 (8%) patients had some degree of transient disorder of smell and hypogeusia, respectively. Neither drug-related death nor any form of cardiac toxicity was observed. A number of patients found weekly attendances inconvenient and others found weekly cannulation an ordeal. In all, 6 (24%) patients refused to continue the treatment after courses 9, 9, 11, 11, 12, and 12, respectively. Therapy was discontinued in 1 (4%) patient because of lack of compliance and in 1 (4%) individual because of geographical factors connected with weekly appearance after 7 and 12 cycles, respectively.

Discussion

The combination of HDFA and FU remains under active investigation in an increasingly broader spectrum of solid tumors [7, 15]. We combined this regimen with EPI, as we were encouraged by the different pattern of toxicity of this drug (mainly hematological) as compared with HDFA and FU (mainly mucositis and diarrhea). In the search for treatments that produce minimal disturbance of a normal life style, a low degree of toxicity is important, particularly since the present therapeutic aim of treatment of advanced breast cancer remains optimal palliation. Weekly treatment courses were chosen to diminish the dose per course in an attempt to reduce the absolute degree of acute toxicity while maintaining the dose intensity.

Chemotherapy in advanced breast cancer produces relatively high response rates of around 40%–55% in previously untreated patients, which increase to 70%–80% with the use of more intensive regimens [9, 21]. However, toxicity is considerable, responses are often short-lived, and second-line treatment is less successful, with the therapeutic benefit of cytotoxic chemotherapy being questionable in many cases.

The response rate of 50% obtained in the present study confirms the effectiveness of the HDFA-FU/EPI regimen against breast cancer. A response was achieved at all sites of disease, with the best results occurring in visceral and soft-tissue metastases, respectively. The median duration of response of 18.3+ months appears to be of interest, especially considering the median treatment period of 4.8 months (range, 2.3–6.4 months). However, it should be borne in mind that the population of patients evaluated was rather small. That 42% of the patients achieved stabilization of their disease for a median duration of 8.5 months represents another indication of the antitumor activity of this schedule.

As expected, the toxicity observed was in general mild to moderate, mainly being restricted to WHO grades I–II with no life-threatening secondary effects, and monitoring of the LVEF did not reveal any cardiotoxic event. Another important observation during this study was the lack of the severe (grade III or IV) diarrhea and stomatitis generally experienced with "conventional" 4-weekly (days 1–5) HDFA-FU regimens [1, 18], which was probably related to the lower and shorter plasmatic peak drug exposure due to weekly administration.

After a median of 11 cycles, 6 patients – 4 of them responding to therapy and 2 presenting with stable disease – refused to continue chemotherapy because of global intolerance, despite the generally low incidence of acute side effects associated with the use of this regimen. This intolerance may have been due to the inadequate time allowed for these patients to recover from toxicity caused by weekly courses of treatment. Steady, low levels of toxicity seem to be less well tolerated in this subset of patients. Another explanation could be the potential problem of inconvenience to patients caused by weekly attendance. On the other hand, from a psychological point of view, the relatively low incidence of hair loss was relevant in patients treated on the weekly schedule. Hence, a careful evaluation of the quality of life must seriously be considered in this group of patients.

Nevertheless, the HDFA-FU/EPI regimen seems to represent a possible alternative in the search for therapies that combine effectiveness with acceptable toxicity and easy application, which would improve patient acceptance. LV modulation of FU can safely be incorporated into combination chemotherapy with EPI on the investigated schedule to provide an active regimen for the treatment of advanced breast cancer.

References

1. Allegra JC, Sholar PW, Drake JC, Bagley C, Lippman ME, Chabner BA (1986) A phase II trial for the treatment of metastatic breast cancer with 5-fluorouracil (5-FU) and leucovorin. Proceedings, Symposium on the Development of Folates and Folic Acid Antagonists in Cancer Chemotherapy, Innisbrook Tarpon Springs, January 23–26, 1986, p 5
2. Allegra CJ, Egan GF, Drake JC, et al (1988) The treatment of metastatic breast cancer with 5-fluorouracil and leucovorin. In: Rustum Y, McGuire J (eds) The expanding role of folates and fluoropyrimidines in cancer chemotherapy. Plenum, New York, pp 107–110
3. Beretta G, Locatelli C, Tabiadon D, et al (1987) Epirubicin treatment of advanced breast carcinoma with the weekly low-dose regimen. Oncology 44: 6–12
4. Brambilla C, Rossi A, Bonfante V, et al (1986) Phase II study of doxorubicin versus epirubicin in advanced breast cancer. Cancer Treat Rep 70: 261–266
5. Doroshow TH, Bertrand M, Multhauf P, et al (1987) Prospective randomized trial comparing 5-FU versus 5-FU and high dose folinic acid (HDFA for treatment of advanced colorectal cancer (abstract). Proc Am Soc Clin Oncol 6: 96
6. Erlichman C, Fine S, Wong A, et al (1986) A comparison of 5-fluorouracil (5-FU) and folinic acid (FA) versus 5-FU in metastatic colorectal cancer (MCC) (abstract). Proc Soc Clin Oncol 5: 82
7. Grem JL, Hoth DF, Hamilton JM, King SA, Leyland-Jones B (1987) Overview of current status and future direction of clinical trials with 5-fluorouracil in combination with folinic acid. Cancer Treat Rep 71: 1249–1264
8. Hellman S, Harris J, Canellos GP, et al (1982) Cancer of the breast. In: De Vita V, Hellman S, Rosenberg S (eds) Cancer, principles and practice of oncology. J. B. Lippincott, Philadelphia, pp 914–970
9. Henderson IC, Cancellos GP (1980) Cancer of the breast – the past decade. N Engl J Med 302: 17–30, 78–90
10. Henderson IC, Hayes DF, Come S, et al (1987) New agents and new medical treatments for advanced breast cancer. Semin Oncol 14: 34–64
11. Hoogstraten B, Fabian C (1979) A reappraisal of single drugs in advanced breast cancer. Cancer Clin Trials 2: 101–109
12. Italian Multicenter Breast Study with Epirubicin (1988) Phase III randomized study of fluorouracil, epirubicin and cyclophosphamide in advanced breast cancer: an Italian multicenter trial. J Clin Oncol 6: 976–982
13. Jones WS, Mattson W (1984) Phase-II study of weekly-low doses of 4-epi-doxorubicin in advanced postmenopausal breast cancer. Cancer Treat Rep 68: 675–677
14. Machover D, Goldschmidt E, Chollet P, et al (1986) Treatment of advanced colorectal and gastric adenocarcinomas with 5-fluorouracil and high dose folinic acid. J Clin Oncol 4: 685–696
15. Marini G, Zaniboni A, Gorni F, Marpicati P, Montini E, Simoncini E (1987) Clinical experience with 5-fluorouracil (5-FU) and high-dose folinic acid in solid tumors. Drugs Exp Clin Res 13: 373–376
16. Petrelli N, Herrera L, Rustum YM, et al (1987) A prospective randomized trial of 5-fluorouracil versus 5-fluorouracil and high-dose leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. J Clin Oncol 5: 1559–1565
17. Scheulen ME, Niederle N, Schmidt CG (1987) Weekly low-dose epirubicin treatment of metastatic breast cancer (abstract). Proc Am Assoc Cancer Res 28: 197
18. Swain SM, Lippman ME, Eagan EF, et al (1989) Fluorouracil and high-dose leucovorin in previously treated patients with metastatic breast cancer. J Clin Oncol 7: 890–899
19. Tormey DC, Gelman R, Band PR, Sears M, Rosenthal SN, Dewys W, Perlia C, Rice MA (1982) Comparison of induction chemotherapies for metastatic breast cancer. Cancer 50: 1235–1244
20. WHO (1979) Handbook for reporting results of cancer treatment. Offset publication 48. WHO, Geneva
21. Zaniboni A, Simoncini E, Marpicati P, Montini E, Ferrari V, Ferragni A, Boari L, Marini G (1989) Cyclophosphamide, epirubicin, high-dose folinic acid and 5-fluorouracil (super-FEC) as first-line chemotherapy for advanced breast cancer: preliminary results. Eur J Clin Oncol 25: 1151–1155