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Research paper

Phase II study with cisplatin and paclitaxel in combination with weekly high-dose 24 h infusional 5-fluorouracil/leucovorin for first-line treatment of metastatic breast cancer

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Results from our previous phase II study demonstrating high efficacy and low toxicity for a weekly schedule of 5-fluorouracil (5-FU)/leucovorin in intensively pretreated patients with metastatic breast cancer prompted addition of paclitaxel and cisplatin to this regimen for a phase II study of outpatient first-line treatment of metastatic breast cancer. (MBC). Twenty-eight patients with metastatic breast cancer have been evaluated. Pretreatment comprised adjuvant CTX in 24 out of 28 patients, but no prior CTX for MBC. Patients were treated with 5-FU 2 g/m^2 (24 h infusion) plus leucovorin 500 mg/m^2 (2 h infusion prior to 5-FU) weekly for 6 weeks (days 1, 8, 15, 22, 29 and 36); in addition, paclitaxel 175 mg/m^2 (3 h infusion) was administered on days 0 and 21, and cisplatin 50 mg/m^2 (1 h infusion) on days 1 and 22 prior to 5-FU/leucovorin, repeated every 50 days. All patients were treated as outpatients using Port-a-Cath systems and portable pumps. Aside from common total alopecia, neutropenia was common but only of short duration. No episodes of febrile neutropenia occured. Non-hematologic toxicities (NCI CTC grade, percent of patients) consisted of mild to moderate diarrhea (2+3, 47%), mucosits (2, 14%), and nausea and vomiting (2+3, 60%). Out of 28 patients with bidimensionally measurable disease 25% (seven out of 28) achieved a CR, 57% (16 out of 28) achieved a PR, 11% (three out of 28) had a SD and 7% (two out of 28) had a PD. Overall RR was 82% (95% confidence interval 66–100%). Median remission duration was 8 months, median time to progression 9 months and median survial time 28 months with a median follow-up of 21 months. We conclude that the combination of paclitaxel, cisplatin and 5-FU/leucovorin is an effective non-anthracycline-containing regimen for the first-line treatment of MBC. [© 1998 Rapid Science Ltd.]

Key words: 5-Fluorouracil, cisplatin, leucovorin, metastatic breast cancer, paclitaxel.

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Introduction

A phase I/II study of high-dose 5-fluorouracil (5-FU)/leucovorin at a dose of leucovorin 500 mg/m^2 2 h infusion and 5-FU 2000 mg/m^2 24 h infusion given weekly for 6 weeks demonstrated high efficacy with a response rate of 41% (13 out of 32 patients) and low toxicity in intensively pretreated patients with metastatic breast cancer (MBC).[1] Based on these results, we added paclitaxel to the 5-FU/leucovorin regimen in a second phase I/II study, also in pretreated patients with MBC.[2] The combination of paclitaxel with weekly high-dose infusional 5-FU/leucovorin was well tolerated and highly effective (response rate 59%; 32 out of 54 patients) in these patients, including those with anthracycline-resistant disease. The present study intended to estimate the efficacy and tolerance of adding cisplatin to weekly high-dose 5-FU/leucovorin and paclitaxel every 3 weeks as a non-anthracycline-containing regimen for the first-line treatment of MBC.

Patients and methods

Eligibility criteria

All patients had histologically proven breast cancer. Patients could have had previous chemotherapy in the adjuvant setting, but no chemotherapy for metastatic disease was allowed. Further requirements were: bidimensionally measureable disease with or without evaluable disease (i.e. bone metastases); and adequate hematologic, renal and hepatic functions and no

severe, uncontrolled co-morbidities. Adequate hematological, renal and hepatic functions were defined as absolute neutrophil count $\geq 2.0 \times 10^9$/l, platelets count $\geq 100 \times 10^9$/l, total bilirubin, AST (SGOT), ALT (SGPT) and serum creatinine $\leq 1.5 \times$ upper normal limit, respectively. Additional eligibility criteria include an Eastern Cooperative Oncology Group performance status of 0, 1 or 2, life expectancy of at least 3 months and age ≥ 18 years. Pregnancy was excluded prior to study entry. All patients gave informed consent before participating in this study protocol, which had been approved by the institutional ethical committee review board.

Study design

Patients were treated with 5-FU 2 g/m^2 (24 h infusion) plus leucovorin 500 mg/m^2 (2 h infusion prior to 5-FU) weekly for 6 weeks (days 1, 8, 15, 22, 29 and 36); in addition, paclitaxel 175 mg/m^2 (3 h infusion) was administered on days 0 and 21 after standard premedication with corticosteroids and H_1 and H_2 receptor antagonists and cisplatin 50 mg/m^2 (1 h infusion) was given on days 1 and 22 prior to HD-FU/leucovorin. Each cycle comprised of 6 weeks, followed by 2 weeks of rest, with a total of three cycles planned (Figure 1). Patients were treated as outpatients using Port-a-Cath systems and portable pumps.

Mode of administration/drug therapy

Leucovorin 500 mg/m^2 was dissolved in 500 ml of a 0.9% saline solution and given over 2 h as a continuous infusion prior to a 24 h continuous infusion of 5-FU (2 g/m^2), given by a portable pump. These applications were performed weekly for 6 weeks. Cisplatin 50 mg/m^2 was given on days 1 and 22, and paclitaxel at a dose of 175 mg/m^2 was given on days 0 and 21. We used standard premedication with corticosteroids and H_1 and H_2 receptor antagonists as well as polyvinyl chloride-free infusion material and filter systems for paclitaxel administration. Cisplatin and paclitaxel, dissolved in 1000 ml of 0.9% saline solution, were given prior to the 5-FU/leucovorin (Figure 1). 5-HT_3 antagonists were used as antiemetic therapy additionally on days 1 and 22, while only mild antiemetic therapy was given for weekly 5-FU/leucovorin: alizaprid 3×100 mg p.o./day. Three full cycles were planned for patients without tumor progression and without worsening of performance status or tumor-related symptoms during chemotherapy. Cytokines were not administered. Dose adjustments consisting of a reduction of the 5-FU dosage by 20% were to be performed in case of mucositis or stomatitis or diarrhea >2 CTC. If mucositis, stomatitis or diarrhea ≥ 1 CTC were present on the day of planned treatment, chemotherapy was delayed until full recovery from side effects and the dose of 5-FU was reduced by 20% for the remaining treatment period. Dose adjustments consisting of a reduction of the paclitaxel dosage to 135 mg/m^2 were to be performed if ANC $<0.5 \times 10^9$/l for more than 7 days, any episode of febrile neutropenia, absence of a recovery of granulocytes ($<1.5 \times 10^9$/l) and/or platelets ($<100 \times 10^9$/l) by day 50 and in case of non-hematological toxicities >2. The cisplatin was reduced by 20% in case of non-hematological toxicities >2 CTC, excluding alopecia, stomatitis and diarrhea.

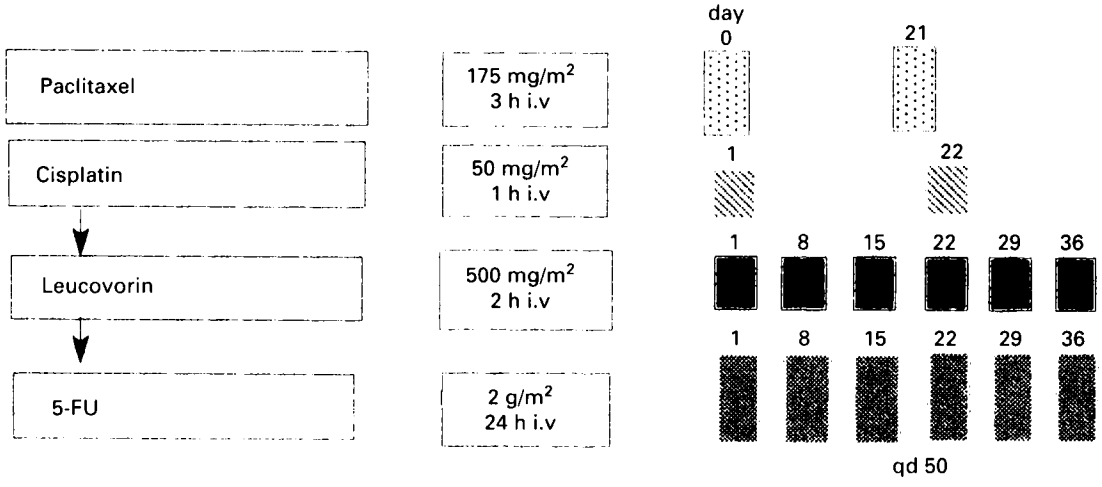

Figure 1. Study design.

Patient evaluation

Prior to treatment, all patients underwent physical examination, chest X-ray, abdominal ultrasound, ECG, echocardiogram, thoracic and/or abdominal CT scan, if indicated, bone scan, blood cell counts, routine biochemical tests and tumor marker screening. Tumor response was evaluated after each treatment cycle, using those techniques required to assess tumor locations present at study entry. Full restaging was done following the induction of an objective response or if progressive disease was suspected. Blood cell counts and assessment of toxiciites were done weekly during treatment, prior to each treatment period and after the last chemotherapy cycle. Biochemical parameters, tumor markers and ECG were measured after each treatment cycle. Toxicity was graded according to the NCI CTC scale.

Response criteria/statistical analysis

Response guidelines were performed according to standard WHO criteria: tumor response was documented in two evaluations performed at least 6 weeks apart. Complete remission (CR), partial remission (PR) and response duration were calculated from the date the response was first documented. The responses were confirmed by an independent institutional review. A CR was defined as the disappearance of all known metastatic sites and a PR was a greater than 50% decrease in the size of all measureable tumor areas. Patients achieving a CR of measureable extraosseous disease, but no complete resolution of bone lesions on X-ray were considered to have a PR. In lytic bone lesions a partial decrease in size was necessary to fullfil the criteria of a PR. Osteoblastic bone lesions as well as effusions did not qualify as measureable parameters, but as evaluable disease. Survival and time to progression were computed actuarially, using the Kaplan-Meier method, beginning with the date the patient was placed on study. The duration of response also was calculated according to Kaplan-Meier.[3]

Results

Patient characteristics

Twenty-eight patients entered this phase II study. Patients had progressive disease and/or tumor-related symptoms prior to study treatment. All patients had at least one bidimensionally measureable tumor site. The characteristics of the patients and their pretreatment are outlined in Table 1.

Table 1. Patient characteristics and pattern of pretreatment (n=28)

	n	(%)
Age (years; median)	45	(range 33–64)
Performance status		
0	15	(54)
1	12	(43)
2	1	(3)
Menopausal status		
pre	21	(75)
post	7	(25)
Hormone receptor		
postive	12	(43)
negative	16	(57)
Number of metastatic disease sites (median)	2	(range 1–4)
Distribution of metastatic disease		
lung	11	(39)
liver	9	(32)
lymph node	11	(39)
bone	13	(46)
skin	7	(25)
Radiotherapy (adjuvant)	26	(93)
Hormonal treatment (adjuvant)	7	(25)
Adjuvant CTX		
none	4	(14)
CMF or variants	18	(64)
anthracyclines	5	(18)
high dose	1	(4)

CMF: cyclophosphamide, methotrexate, 5-FU. CTX: chemotherapy.

Treatment and tolerance

All 28 enrolled patients were assessable for response, toxicity, and were included in the statistical analysis of time to progression and survival. There were no treatment-related deaths. The median number of cycles with weekly high-dose 5-FU/leucovorin in combination with paclitaxel and cisplatin was 2 (range 1–4). Eight patients received two cycles, 15 patients received three cycles, one patient four cycles and only two patients were removed after one cycle because of disease progression. Median treatment duration was 4 months. Eight patients received only two cycles because of early induction of remission of their disease and relief of disease-related symptoms. No dose reductions had to be performed with respect to the paclitaxel dose. During the first treatment cycle 3 patients had diarrhea CTC grade 3 and 10 patients CTC grade 2. According to guidelines, chemotherapy was delayed until full recovery from any side effect and the

dose of 5-FU was reduced by 20% for the remaining treatment period. Fifty-four of 67 treatment cycles were applied without the need for further 5-FU dose adjustments or treatment delays. The addition of cisplatin to the treatment regimen resulted in an increase of nausea, vomiting, fatigue and, as a cumulative toxicity, in an increase of moderate neurotoxicity. However, the cisplatin dose did not have to be reduced in any patient.

Toxicity

A total of 67 treatment cycles in 28 patients were analyzed for toxicity. No serious acute hypersensitivity reactions were attributed to paclitaxel. Neutropenia was common but moderate in most patients [CTC grade 3 out of 4 in 36% of patients (10 out of 28)] (Table 2). No hospitalizations due to febrile neutropenia were necessary. The duration of grade 3 or 4 neutropenia was generally brief with a range of 3–5 days. No cytokines were used. Neutropenia had no consequences with respect to treatment delay since weekly 24 h infusional 5-FU/leucovorin as well as cisplatin has negligible hematotoxicity and could be administered safely despite short neutropenia. Toxicity to platelets and erythrocytes was mild. No patient required platelet transfusions. Only one out of 28 patients required a single red blood cell transfusion during the treatment period. Aside from common total alopecia, non-hematologic toxicities consisted mainly of gastrointestinal toxicity (percent of patients): diarrhea (54% CTC grade 1+2, 11% CTC grade 3), mucosits (39% CTC grade 1+2), and nausea and vomiting (89% CTC grade 1+2, 7% CTC grade 3). Peripheral neuropathy was cumulative and occured most frequently during the third treatment cycle (35% CTC grade 1+2). No acute or chronic cardiotoxicity was observed. Fatigue syndrome was cumulative and significantly higher than described in the former studies[1,2] due to the addition of cisplatin. Twelve out of 28 patients (43%) suffered from this side effect after the first treatment cycle (CTC grade 1+2) (Table 2).

Table 2. Toxicity

	NCI CTC grade [% of patients (*n*=28)]				
	0	1	2	3	4
Neutropenia	–	11	54	29	7
Anemia	46	54	–	–	–
Thrombocytopenia	82	18	–	–	–
Myalgia	75	11	4	–	–
Hand/foot syndrome	71	11	18	–	–
Mucositis	61	25	14	–	–
Diarrhea	35	18	36	11	–
Nausea/vomiting	4	36	53	7	–
Neuropathy	68	21	11	–	–
Cardiac	100	–	–	–	–
Fatigue	57	25	18	–	–
Alopecia	–	–	–	100	–

Table 3. Response to chemotherapy (*n*=28)

	CR	PR	SD	PD	RR
All patients (*n*=28)	7 (25%)	16 (57%)	3 (11%)	2 (7%)	22 (82%)
	95% confidence interval (66–100%)				
Response duration	median 8 months (range 5–24)				
Time to progression	median 9 months (range 6–25)				
Survival	median 28 months (range 2–32)				
Follow-up	median 21 months				

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RR, response rate.

Response to therapy

Twenty-three out of 28 assessable patients (82%) had an objective response to therapy [CR 25% (seven out of 28) of patients and PR 57% (16 out of 28) of patients]. All patients with CR did not have additional bone metastases. Three patients (11%) had a stable disease and only two out of 28 patients (7%) had disease progression. Overall response rate was 82% (95% confidence interval 66–100%) (Table 3). Median remission duration was 8 months with a range of 5–24 months. Time to progression was 9 months at median, with a range of 6–25 months. Ten out of 28 patients died, all due to tumor progression. The median survival time for the entire group of patients was 28 months (range 2–32 months). The median follow-up was 21 months.

Discussion

During this decade, one in nine women in the US and Europe will be diagnosed with breast cancer. Recent changes in the primary therapy of operable breast cancer have not altered overall patient prognosis. Adjuvant chemotherapy delays systemic recurrence and improves survival only for a selected fraction of patients. Therapy for MBC has not improved significantly in recent years. While combination chemotherapy may prolong survival for

selected patients, few, if any, are cured. The standard chemotherapy regimens used to treat MBC, e.g. CMF (cyclophosphamide/methotrexate/5-FU), FAC (5-FU/doxorubicin/cyclophosphamide) and FEC (5-FU/epirubicin/cyclophosphamide), were developed over a decade ago. Current efforts to improve therapeutic efficacy have concentrated on decreasing drug toxicity and increasing drug doses (e.g. high-dose chemotherapy with peripheral stem cell support). Another possible alternative to increase therapeutic is altering the administration schedules of well-known chemotherapeutic agents and introducing active new cytotoxic agents. Cisplatin has a significant activity as a single agent for first-line treatment of MBC.[4] Additionally, preclinical data suggest a synergistic interaction for combining cisplatin with either paclitaxel or 5-FU.[5] Clinical phase II studies using the combination of paclitaxel and cisplatin as first-line treatment of MBC have reported response rates from 49 to 85%.[6,7] Furthermore, our recent phase II study of the combination of paclitaxel plus high-dose 5-FU/leucovorin showed moderate toxicity and allows the addition of a third combination partner in a less heavily pretreated patient population.[2] This addition of cisplatin to paclitaxel in combination with weekly 5-FU/leucovorin resulted in an increase of mainly gastrointestinal toxicity. However high activity with a response rate of 82% (95% confidence interval 66–100%) was achieved. In particular, the high rate of complete responses (25%) is encouraging, though we have to consider that all patients who achieved CR with cisplatin, paclitaxel and weekly 5-FU/leucovorin have had either pulmonary (five out of seven patients) or lymph node (two out of seven patients) metastases as site of manifestation of their disease and none of the patients had additional bone or hepatic involvement. Clearly these promising early results have to be confirmed in a larger number of patients looking also at certain biologic characteristics which might help to identify subsets of patients who will significantly profit from such an intensive first-line regimen.

Conclusions

The final results of this phase II study demonstrated that weekly high-dose 24 h infusional 5-FU/leucovorin with paclitaxel and cisplatin constitutes an active outpatient regimen for the first-line treatment of women with MBC without the use of anthracyclines. This active combination could have an impact on the management of MBC, because of the frequent use of anthracycline-containing combinations in the adjuvant setting. With the introduction of new chemotherapeutic agents into the treatment of breast cancer, effective non-cross-resistant regimens to anthracyclines could be used as salvage protocols in MBC patients who have had anthracyclines as prior treatment either in adjuvant treatment or for metastatic disease.

References

1. Wilke H, Klaassen U, Achterrath W, *et al.* Phase I/II study with a weekly 24 hour infusion of 5-fluorouracil plus high dose folinic acid (HD-FU/FA) in intensively pretreated patients with metastatic breast cancer. *Ann Oncol* 1996; **7:** 55–8.
2. Klaassen U, Wilke H, Phillippou Pari C, *et al.* Phase I/II study with paclitaxel in combination with weekly high dose 5-fluorouracil/folinic acid (HD-FU/FA) in the treatment of metastatic breast cancer. *Semin Oncol* 1995; **22**(suppl 14): 7–11.
3. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53:** 457–81.
4. Sledge J, Loehrer PJ, Roth BJ, Einhorn LH. Cisplatin as first-line therapy for metastatic breast cancer. *J Clin Oncol* 1988; **6:** 1811–4.
5. Vanhoefer U, Harstrick A, Wilke H, *et al.* Schedule dependent antagonism of paclitaxel and cisplatin in human gastric and ovarian carcinoma cell lines *in vitro*. *Eur J Cancer* 1995; **31A:** 92–7.
6. Wasserheit C, Frazein, A, Oratz R, *et al.* Phase II trial of paclitaxel and cisplatin in women with advanced breast cancer: an active regimen with limiting neurotoxicity. *J Clin Oncol* 1996; **14:** 1993–9.
7. Gelmon K, O'Reilly SE, Tolcher AW, *et al.* Phase I/II trial of biweekly paclitaxel and cisplatin in the treatment of metastatic breast cancer. *J Clin Oncol* 1996; **14:** 1185–91.

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