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Report

Weekly continuous infusion of 5-fluorouracil with oral leucovorin in metastatic breast cancer patients with primary resistance to doxorubicin

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Summary

Doxorubicin-resistant metastatic breast cancer (MBC) is a very poor prognosis scenario, where only taxanes have shown activity, often at the expense of severe toxicity that compromises palliation. This study was undertaken to test the antitumor activity and tolerability of infusional 5-fluorouracil (5-FU) modulated with low-dose oral leucovorin (LV), in heavily pretreated patients with stringent criteria of primary resistance to doxorubicin, visceral involvement, and suboptimal performance status. Twenty-six patients with measurable MBC and primary resistance to anthracyclines received a weekly outpatient 48-hour infusion of high-dose 5-FU with low dose oral leucovorin. All patients were assessable for response and toxicity. Eight partial responses were seen (30% response rate) in soft tissue and visceral sites, with a median response duration of eight months (5 + to 12). 98% of the cycles were minimally toxic or non-toxic. Toxicities included mucositis, diarrhea, and plantar-palmar-syndrome. Our results suggest that this schedule of LV-modulated infusional 5-FU can produce a substantial number of long-lasting responses and meaningful palliation to this very poor prognosis population.

Introduction

5-fluorouracil (FU) is an active drug for metastatic breast cancer. Its mechanism of action is based on the inhibition of the thymidylate synthase (TS) enzyme in the presence of reduced folates. Calcium leucovorin (LV), a source of reduced folates, increases the stability of the ternary complex between FdUMP (an intracellular metabolite of FU), TS, and reduced folates. LV adds activity to bolus 5-FU in colorectal cancer [1]. In breast cancer patients FU plus LV can induce responses in patients previously exposed to bolus FU [2–5].

The rationale for the delivery of FU in continuous infusion (CI) is based on its short serum half-life, of about 11 minutes, which makes it only active against the small proportion of tumor cells in S-phase at any one time. Thus, when the drug is given over an extended period of time, a greater number of actively dividing cells will be exposed to it. CI of FU causes more mucositis and diarrhea and less myelosupression than the bolus administration.

The CI of FU has provided a significantly superior response rate to bolus injection in two randomized phase III trials in advanced colorectal cancer [6, 7]. While a more recent screening multiarm ran-

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domized phase II trial from SWOG did not show any differences between the two schedules, the nature of this study does not allow any significant statistical conclusion, and therefore, its results should not be overinterpreted [8]. In breast cancer patients a lack of cross-resistance between the two schedules has been shown, as a significant number of patients previously treated with bolus FU further respond to the protracted infusion of the drug [9, 10]. An infusional FU-based combination has shown to be highly active as neoadjuvant therapy for locally advanced breast tumors [11].

LV-modulation of the CI of FU may be a step forward. Preclinical data suggest that a greater benefit might be achieved by modulating protracted infusions, rather than the bolus administration of FU, contrary to common clinical practices. *In vitro* resistance to prolonged exposures of FU is related to a failure to retain folate cofactors (i.e. defective folylpolyglutamyl synthase), as opposed to the mechanisms of resistance to short exposures, that mainly depend on the defective activation of the drug [12]. *In vitro* addition of LV to extended exposures to FU markedly potentiates the cytotoxicity of the drug, whereas this enhancement with LV falls exponentially when exposure times are shorter [13]. Biochemical modulation of infusional FU requires lower doses of LV than bolus FU [13].

LV-modulated infusional FU has shown activity with low toxicity in advanced colorectal cancer [14], but has received very little attention in metastatic breast cancer. A regimen based on a weekly 48-hour infusion of high-dose 5-FU has shown remarkable activity and mild toxicity in metastatic colorectal cancer [15]. Likewise, heavily pretreated hormone- and doxorubicin-refractory metastatic breast cancer is a patient population prone to excessive toxicity from chemotherapy. We undertook this study to test the hypothesis that a high-dose infusional 5-FU regimen might be a 'friendly' and active treatment for these patients, similar to what it has proved in metastatic colon cancer. Low-dose leucovorin was added, based on the above mentioned *in vitro* data [13]. If this regimen shows significant antitumor effect and tolerability in these patients, it might merit inclusion in the oncologists' armamentarium as an effective palliative therapy for this common and very poor prognosis patient population.

Patients and methods

Eligibility criteria

Twenty-six consecutive patients with biopsy-proven, doxorubicin-refractory, measurable metastatic breast cancer, previously treated with bolus FU containing combinations, have been entered to date in this clinical study. Primary resistance to doxorubicin was defined as tumor progression during a doxorubicin-containing treatment for metastatic disease or a doxorubicin-based adjuvant therapy. Patients had to have an estimated life expectancy of at least four weeks. Hormone-receptor positive patients had to have failed at least one line of hormonal therapy to be considered eligible. Any prior radiotherapy must have been completed at least 4 weeks before study entry, with full resolution of toxicities. Prior hormonal therapy or chemotherapy had to be discontinued at least 4 weeks before protocol therapy. Patients without the criteria of doxorubicin-resistance defined above were excluded. A signed consent form was obtained from all patients before study entry.

Pretreatment evaluation and follow-up studies

Baseline studies included a complete history and physical examination with record of all measurable lesions, laboratory analysis that consisted of a blood cell count and a complete biochemical profile, a chest x-ray, and an ECG. Liver ultrasound or computed tomography were performed in the presence of liver enlargement or abnormal liver function tests.

Blood cell counts were repeated weekly, and serum electrolytes, blood urea nitrogen, serum creatinine, and liver function tests were performed monthly. Tumor measurements were required every three weeks, if they could be determined by physical examination or chest x-ray; otherwise, every eight weeks if abdominal CT or liver ultra-

sounds were used for the assessment of measurable disease.

A thorough symptomatic evaluation was made at baseline, and repeated on a weekly basis.

Treatment

Therapy consisted of a weekly 48-hour intravenous continuous infusion of 5-FU at 2 g/m^2, and oral calcium leucovorin (Lederle Laboratories, Pearl River, NY), 60 mg every 6 hours, during the infusion of 5-FU. This therapy started, in all cases, within one month after the documentation of primary resistance to doxorubicin. Patients had a single lumen central venous catheter with a subcutaneous port inserted before the onset of treatment. 5-FU was diluted with 5000 IU of heparin in 250 cc of 0.9% saline solution, and the whole solution was delivered with an infusion pump. No prophylactic antiemetics were given, unless grade 2 emesis was seen in prior cycles, in which case oral thiethylperazine (6.5 mg twice a day) was prescribed in subsequent courses. Toxicity was defined according to standard WHO criteria [16]. Treatment was delayed one week for any grade 2 toxicity still present at the time of treatment. For any WHO grade 3 toxicity treatment was discontinued for one week and restarted at a 25% dose reduction of 5-FU. The dose of leucovorin was constant in all patients regardless of toxicity.

Antidiarrheal agents were prescribed for grade 1 or 2 diarrhea. For grade 3 diarrhea, vigorous oral rehydration was performed. For grade 4 diarrhea, patients were admitted to the hospital for intravenous hydration. For mucositis, usual topical oral rinses were used.

Plantar-palmar syndrome is observed with infusional 5-FU. For mild to moderate plantar-palmar erythema (dryness and erythema with pain), patients continued chemotherapy and were prescribed pyridoxine (50 mg orally three times per day) until the syndrome was relieved. For the severe form of the syndrome (severe erythema with blistering and desquamation) pyridoxine was administered throughout treatment, treatment was postponed, and 5-FU dose was reduced as with any other grade 3–4 toxicity.

Response was strictly categorized according to standard WHO criteria [15]. 95% confidence intervals were calculated according to the exact two-sided confidence limits method. Remission duration and stable disease (SD) duration was measured since the first day of treatment until progression. Overall survival was calculated from study entry until death (Kaplan-Meier method). Patients received at least six courses of treatment before response was evaluated. Patients were continued on therapy unless they had a progressive disease.

Results

Twenty-six consecutive patients have been treated in this study. Patient characteristics are shown in Table 1. Most of them had visceral involvement, with multiple sites of disease (median number, three). Eleven patients (42%) had liver metastases, that was massive (> 50% liver involvement) in six of them.

Patients had received extensive prior chemotherapy, with a median of three regimens, along with radiotherapy and hormonal therapy. All patients had strict criteria of doxorubicin-resistance, either after FAC (22 patients), or FlexiFAC (4 patients). Both FAC and FlexiFAC combine doxorubicin, as a bolus IV infusion at 50 mg/m^2 Q3 weeks, and 20 mg/m^2/d ≥ 3 days Q3 weeks, respectively, with cyclophosphamide and bolus 5-fluorouracil. The mean dose-intensity of doxorubicin achieved with FlexiFAC is > 20 mg/m^2/week, 30% higher than the projected dose-intensity of standard FAC [17]. Seven patients had failed prior paclitaxel, at 175 mg/m^2 over 3 hours (seven patients), or 140 mg/m^2 in a 96-hour continuous infusion (two of those seven patients).

Antitumoral activity

All twenty-six patients were assessable for response. There were eight partial responses, for a 30.7% response rate (95% confidence interval 13%

to 47%). Median response duration was eight months (range, 5 + to 12 months). Responses were seen in liver (3 patients), lymph nodes (3 patients), skin and subcutaneous tissue (2 patients), pleura (1 patient), and lung nodules (1 patient). Pretreatment performance status was 50–60 in four responding patients, and > 60 in the other four. Objective tumor regression was seen in two of the seven patients with primary resistance to paclitaxel.

Nine patients had a stable disease (SD) of at least six months, with symptomatic relief. The median duration of SD was eight months (range, 6 to 15 + months). There were 6 SD among patients with visceral disease, and 3 SD among patients with soft tissue disease. Four patients remain free of tumor progression, at 6, and 12 months (visceral disease, one of them with prior massive liver involvement), 9 and 15 months (soft tissue disease). Of these, the first two were paclitaxel-resistant. Combining PR and SD, the overall tumor growth control rate was 65% (95% CI, 47 to 83%). Nine patients had progressive disease during treatment.

60% of the patients reported a significant relief of their tumor-related symptoms during treatment. Main symptoms improved were dyspnea (7/14 pts), bone pain (4/6 pts), asthenia and anorexia (13/21 pts), abdominal pain (4/6 pts), and soft tissue pain (8/13 pts).

Table 1. Patient characteristics (n = 26)

Total number of patients	26
Median age (years)	60 (29–69)
Median Karnofsky index (%)	55 (40–80)
N° of sites of disease	
1–3	14
> 3	12
Visceral disease	21
Soft tissue disease	5
Sites of disease	
Liver	11
Lung (nodular/lymphangitic)	17 (5/12)
Pleura	4
Pericardium	1
Bone marrow	2
Skin/soft tissue	11
Bone	9
Lymph nodes	13
Previous radiotherapy 15 (60%)	
Locoregional	11
Metastases	5
N° of prior chemotherapy lines for metastatic disease	
1	2
2	10
3	9
≥ 4	5
Primary resistance to paclitaxel	7

Table 2. Toxicities

Toxicity	Grade I [pts (%)/cycles (%)]	Grade 2	Grade 3
Mucositis	6 (24%)/37 (14%)	12 (48%)/23 (9%)	2 (8%)/3 (1%)
Diarrhea	4 (16%)/15 (6%)	5 (20%)/6 (2%)	1 (4%)/1 (0.4%)
PPS	3 (12%)/13 (5%)	3 (12%)/3 (1%)	1 (4%)/1 (0.4%)
Leukopenia	1 (4%)/6 (2%)	5 (20%)/8 (3%)	
Anemia	5 (20%)/12 (4%)	3 (12%)/3 (1%)	
Thrombocytopenia	2 (8%)/2 (0.8%)		
Emesis	6 (24%)/22 (8%)	5 (20%)/10 (4%)	
Other toxicities	Alopecia: 3 pts (12%) Conjunctivitis: 1 pt (4%)/3c (0.1%)		

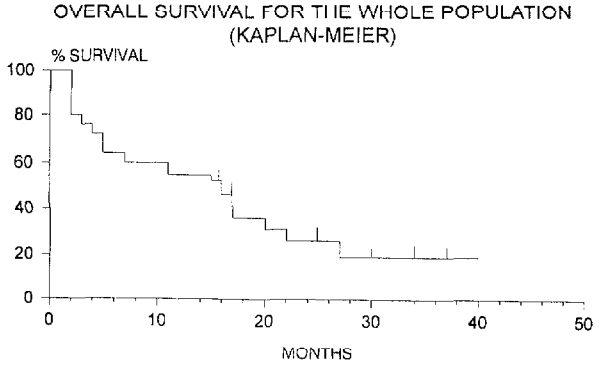

Figure 1.

Survival

Twenty patients have died to date. After a median follow-up of 31 months, the median overall survival is 16 months (range 2–37+) for all patients. The distribution of median survival time, according to response is 20 months (range 7–37+) for patients in PR, 18 months for patients with SD (range 11–34), and 3 months (range 2–8) for those with progressive disease. Figure 1 shows the Kaplan-Meier survival curve for the entire population.

The median progression-free survival for patients with PR + SD was 7 months (range, 4 to 33 + months).

Toxicities

A total of 262 cycles were delivered, median ten per patient (range, 5 to 17 cycles). 132 cycles were completely non-toxic (50%). 82 and 42 cycles had grade 1 and grade 2 toxicities, respectively. That makes for 98% of the cycles with mild to moderate toxicities at most. No grade 4 toxicities were seen. Just five cycles (2%) produced a grade 3 toxicity (three cases of mucositis, two of them in the same patient, despite the 25% dose reduction, one case of diarrhea, and one case of plantar-palmar syndrome, PPS). In all four cases, grade 3 toxicities reverted without any clinical consequences.

Mucositis was the most often encountered toxicity, in 80% of the patients and in 24% of the courses, followed by diarrhea, myelosupression, and PPS. It is noteworthy that less mucositis and diarrhea were seen in the present study than when this regimen was tested in colorectal cancer patients [14].

No CNS or cardiac toxicities were seen. There was one only case of a catheter-related thrombosis, which resolved favorably with heparin therapy and withdrawal of the catheter. The addition of heparin to the 5 FU solution may account for the low incidence of thrombotic events. The toxicities from the treatment are listed in Table 2.

Discussion

In the present study, a 30% response rate was seen with this regimen of weekly infusional 5-FU modulated with oral low-dose leucovorin. Patients had strictly defined doxorubicin-resistant disease and extensive prior therapy. Responses were seen in soft tissue and visceral sites, and in patients with one site or multisite involvement. The median overall survival for those patients who responded (20 months) and for the whole patient population (11 months) were unexpectedly high, considering their poor prognosis and the chemoresistance of their diseases. A possible bias, based on good pretreatment characteristics of subsequent responders, could theoretically account for their seemingly prolonged survival. However, this is not likely to be the case in the present study, since only patients with a very poor prognosis were included, and half of the responding patients had a marginal pretreatment performance status (50–60).

There are very few active drugs in this scenario, where the definition of anthracycline-resistance is a critical point. A recent large retrospective analysis showed that patients with progressive disease as best response to anthracycline therapy had significantly worse response to subsequent lines of chemotherapy than those who first responded to anthracyclines and later progressed, regardless of the time interval between completion of anthracycline therapy and disease progression [18]. Therefore, not only do the group of patients with progressive disease while on anthracyclines have the worst prognosis, but they should also be considered the truly anthracycline-resistant population. Our study

only included patients with progressive disease during anthracycline treatment. Other less stringent definitions, such as relapse or progression within 6, 12 or more months after completion of anthracycline-therapy, have been more commonly used in most published clinical trials.

A phase I/II trial of weekly 24-hour infusion 5-FU and high-dose leucovorin (500 mg/m2 in 2-hour IV infusion) included patients treated with a median number of two previous regimens. Among the subset of anthracycline-resistant patients (prior disease progression while on anthracyclines) there were 10/24 responses, for a 41% response rate [19].

Docetaxel is the drug with the highest reported activity in strictly anthracycline-refractory patients. Two phase II trials [20, 21] reported similar RR of 53–57%, although at the cost of substantial hematological (neutropenia) and non-hematological (fluid retention) toxicities. Paclitaxel has been tested at different schedules and doses requiring G-CSF support. Those studies that used non-strict definitions of resistance to anthracyclines reported significant RR between 30% and 48% [22–25]. Their results contrast sharply with the 6% RR seen in the only trial with paclitaxel limited to patients with primary anthracycline-refractoriness [26].

Vinorelbine is probably the most active vinca alkaloid used in front-line chemotherapy for metastatic breast cancer. Two large trials have tested it in patients with loose criteria of resistance to anthracyclines, with an objective response rate of about 15% in both of them [27, 28].

Table 3 shows the results of chemotherapeutic agents in this patient population. Of note, infusional 5-FU can produce the longest duration of response of all.

Several considerations must be made to assess the real value of the present schedule. First, besides the 30% response rate, there is a further 35% of patients who, while not achieving a measurable shrinkage of their lesions, do have their symptoms relieved and their disease stabilized for a substantial length of time (median, 7 months), beyond the duration of treatment. We are well aware of the fact that our assessment of improvement of tumor-related symptoms is not equal to a formal quality-of-life analysis, but it is nonetheless noteworthy that 65% of the patients with an overt symptomatic progres-

Table 3. Results of antitumoral agents in anthracycline-resistant MBC

Agent	# Pts	Median # of prior CT lines	RR (%)	Response duration (mo)	Main toxicity (% pts)	Definition of anthrac. resistance
Docetaxel/ 100 mg/m^2, 1 hr [20]	34	2	51	6	G-4 NP (88%) Febrile NP (51%)	PD during A.th.
Docetaxel/ Same regimen [21]	35	2	50	7	G-4 NP (95%) Febrile NP (33%)	PD during A.th.
3-h paclitaxel + G-CSF [26]	36	1	6	4	Neuropathy (83%) Arthromyalgia (83%)	PD during A.th.
24-h paclitaxel + G-CSF [23]	40	2	32	7	G-4 NP (47%) Febrile NP (21%)	R-12 m
96-h paclitaxel + G-CSF [22]	33	2	48	7	G-4 NP (44%)	Failure to achieve a CR during A.th.
Weekly vinorelbine [27]	115	2	15	4	G-4 NP (37%) Febrile NP (10%)	R-6 m
HD LV + weekly 24 h-FU [19]	24*	2	41	11	No major toxicities	PD during A.th.
Present study	26	3	30	8	No major toxicities	PD during A.th

CT: chemotherapy. NP: neutropenia. A.th.: anthracycline therapy. PD: progressive disease. R-6 m, R-12 m: relapse within x months of completion of treatment. CR: complete remission. HD LV: high-dose leucovorin. * Only anthracycline-resistant patients.

sive disease and previous failure to a median number of three regimens, reported a clear and clinically meaningful relief of their symptoms.

This regimen has a very low hematological and non-hematological toxicity. Most cycles were totally non-toxic. No severe (grade 4) toxic effects were seen. The excellent tolerance to this therapy should not be underrated. When considering an effective treatment for such an extremely poor-prognosis population, palliation, dependent on antitumoral activity at a low toxic cost, becomes the major aim.

The monthly cost of the regimen, including drug costs, lab tests, pump rental fees, and MD and clinic visits is around $1800, according to the cost analysis of infusional chemotherapy described elsewhere [29].

In conclusion, our results with this regimen of LV-modulated infusional 5-FU suggest that it is an active and good palliative treatment for this heavily pretreated, anthracycline-resistant MBC patient population with a poor overall prognosis. Based on its low toxicity profile, non-overlapping with that of paclitaxel or docetaxel, future research will test its combination with a taxane in anthracycline-refractory patients.

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