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Phase I studies of fluorouracil, doxorubicin and vinorelbine without (FAN) and with (SUPERFAN) folinic acid in patients with advanced breast cancer

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Abstract *Purpose*: The Breast Cancer Site Group of the National Cancer Institute of Canada – Clinical Trials Group (NCIC-CTG) undertook two parallel phase I studies to determine the maximum tolerated dose (MTD) and recommended phase II dose of vinorelbine in combination with doxorubicin and fluorouracil (with or without folinic acid) in metastatic breast cancer. *Methods*: Cohorts of five patients were to receive: (a) fluorouracil 500 mg/m^2 and doxorubicin 50 mg/m^2 on day 1 only and escalating doses of vinorelbine (15, 20, 25, 30 mg/m^2) on days 1, 8 and 15 every 3 weeks (FAN regimen), or (b) fluorouracil 340 mg/m^2 and folinic acid 200 mg/m^2 on days 1, 2, 3, 4 and 5, doxorubicin 40 mg/m^2 on day 1 only and escalating doses of vinorelbine (15, 20, 25, 30 mg/m^2) on day 1 and again on day 5 every 4 weeks (SUPERFAN regimen). Eligibility included measurable or evaluable metastatic breast cancer and having received neither previous chemotherapy for metastatic disease nor anthracycline-containing adjuvant therapy. *Results*: Of 26 and 12 patients enrolled in the FAN and SUPERFAN regimens, 26 and 12 were evaluable for toxicity and 21 and 9 for response, respectively. Median ages were 60.3 years (41–71 years) and 64.2 years (51–73 years). Both regimens required amendment after the first cohort with an original day-15 vinorelbine dose omitted from the FAN regimen and more prolonged nadir granulocyte counts allowed. Myelosuppression was dose limiting. MTDs in the FAN and SUPERFAN regimens were vinorelbine 25 mg/m^2 and 20 mg/m^2. Other toxicities included mucositis, septicemia and febrile neutropenia. Peripheral neuropathy and constipation were mild. Of the 21 FAN patients evaluable for response, 3 (14%) had complete responses and 7 (33%) had partial responses, for an overall response rate of 48%; 9 (43%) had stable disease and 2 (9%) had progressive disease as their best response. Of the nine SUPERFAN patients evaluable for response, none had a complete response. There were two (22%) with partial responses, and six (67%) had stable disease and one (11%) had progressive disease as their best response. *Conclusions*: The SUPERFAN regimen was too toxic to pursue even at the lowest dose. The recommended phase II starting dose for the FAN regimen was vinorelbine 20 mg/m^2. Although these were phase I studies response rates in evaluable patients were less than expected and toxicity did not allow the use of as much vinorelbine in the combinations as had been anticipated. The limited response data from our study would imply that combining vinorelbine with more toxic agents may not enhance response rates and may defeat the advantage of tolerability, especially in elderly patients.

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Introduction

Combination chemotherapy is usually used as initial therapy for patients with oestrogen receptor-negative metastatic breast cancer, for those with rapidly progressing disease and in patients with oestrogen receptor-positive disease refractory to hormonal therapy. Among the combinations most frequently used are cyclophosphamide and fluorouracil with methotrexate or doxorubicin (CMF or FAC, respectively), and doxorubicin plus vincristine (AV). Of patients with metastatic breast cancer, 45–85% achieve objective responses with these regimens, but only 4–27% have complete remissions of their disease [18]. The median duration of responses are 10 to 18 months and median survival rarely exceeds 2 years [25]. The traditional third-line regimen of vinblastine and mitomycin C has produced response rates of up to 40%, but with a median duration of response of only 4 months [19, 22].

The two traditional vinca alkaloids, vincristine and vinblastine, both have demonstrable single-agent activity against advanced breast cancer. Vinorelbine or 5′-noranhydrovinblastine (Navelbine) is a recently developed semisynthetic vinca alkaloid. It is the only vinca modified in the catharanthine ring rather than the vindoline ring of the molecule. Vinorelbine has shown encouraging single-agent activity in both untreated and previously treated patients with metastatic breast cancer. Myelosuppression, the dose-limiting toxicity (DLT), is mild to moderate in previously untreated patients. Neurotoxicity is less than with the other vinca alkaloids. In particular, peripheral neuropathy is uncommon and paralytic ileus has been infrequent in studies reported to date.

Several phase II studies of vinorelbine as a single agent have been conducted in women with advanced breast cancer. In patients variably treated with prior chemotherapy including anthracyclines in the adjuvant or metastatic setting, overall response rates of 16–51% have been reported [5, 6, 9, 14–16, 21, 23, 28, 33, 34, 36]. In all studies alopecia, nausea and vomiting were mild to moderate and neutropenia was dose limiting. Infrequently, peripheral vein toxicity prompted prophylactic insertion of a central venous catheter.

Several phase I and II studies of vinorelbine in combination with other agents have also been conducted in patients with metastatic disease. In combination with doxorubicin as first-line treatment, response rates of 54–76% have been noted in five studies [3, 8, 20, 30, 31]. Dieras et al. treated patients with infusional fluorouracil and vinorelbine and achieved a response in 67% of patients [10]. In six studies of two or three drug regimens containing mitoxantrone or epirubicin, responses of 36–78% were noted [4, 7, 13, 24, 32, 35]. Finally, in three studies of vinorelbine in combination with mitomycin C, response rates of 35, 40 and 48% were observed [2, 29]. In all cases combination regimens produced more profound myelosuppression than single-agent vinorelbine.

In view of the apparent improved therapeutic index of vinorelbine over other vinca alkaloids used in the treatment of breast cancer, we conducted phase I studies of two vinorelbine-containing regimens. Our long-term goal was to develop a novel chemotherapy combination which would yield improved response rates, duration of responses and quality of life in patients receiving first-line chemotherapy for metastatic breast cancer. Escalating doses of vinorelbine were studied in conjunction with fluorouracil and doxorubicin (FAN) and with fluorouracil, folinic acid and doxorubicin (SUPERFAN). The latter regimen was selected because of the theoretically enhanced efficacy of fluorouracil when combined with folinic acid. This has been borne out in particular in colon cancer where in a randomized trial, the combination of fluorouracil and folinic acid was shown to be superior to fluorouracil alone [12].

Materials and methods

Patients

Inclusion criteria for both the FAN and SUPERFAN regimens were: histological or cytological proof of measurable or evaluable anthracycline-naive metastatic breast cancer; prior hormone therapy allowable; previous irradiation allowable to $< 40\%$ of red bone marrow; life expectancy ≥ 12weeks; Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2; age ≥ 18 years; absolute granulocyte count of $\geq 2.5 \times 10^9$/l, a platelet count of $\geq 100 \times 10^9$/l and a hemoglobin of ≥ 100 g/l; normal bilirubin AST (SGOT) not more than three times normal; serum creatinine not more than 1.3 times normal; pretreatment resting MUGA LVEF $\geq 50\%$ (normal). Exclusion criteria were: prior anthracycline-containing adjuvant chemotherapy and prior chemotherapy for metastatic disease; uncontrolled systolic BP > 180 and/or a diastolic BP of > 100 mmHg; myocardial infarction within 12 months; congestive heart failure; unstable angina; cardiomyopathy; atrial or ventricular arrhythmias (even if controlled medically); active infection; previous cancer except in situ cervix cancer or curatively treated nonmelanomatous skin cancer, or carcinomas of the colon, cervix or uterus treated (and the patient disease free) more than 5 years prior to the diagnosis of breast cancer; unstable hypercalcemia; severe psychiatric or mental disability; significant neuropathy or brain metastases. These studies were approved by the ethics committees of all participating hospitals and all patients gave written informed consent.

Study design

Cohorts of five patients were to receive: (a) fluorouracil 500 mg/m^2 and doxorubicin 50 mg/m^2 on day 1 only and escalating doses of vinorelbine (15, 20, 25, 30 mg/m^2) on days 1, 8 and 15 every 3 weeks (FAN regimen); or (b) fluorouracil 340 mg/m^2 and folinic acid 200 mg/m^2 on days 1, 2, 3, 4 and 5, doxorubicin 40 mg/m^2 on day 1 only and escalating doses of vinorelbine (15, 20, 25, 30 mg/m^2) on day 1 and again on day 5 every 4 weeks (SUPERFAN regimen). Vinorelbine was given in a 1:4 dilution by slow intravenous push over 5–10 min and the vein flushed to prevent injection site reactions. Patients were treated at each dose level of the FAN or SUPERFAN regimens until the maximum tolerated dose

(MTD) and the recommended phase II starting dose levels were established. Intrapatient dose escalation was not allowed. Each cohort was evaluated on day 1 of cycle 2 for toxicity. Dose escalation occurred if two or fewer patients in a cohort had experienced DLT.

In both the FAN and SUPERFAN regimens, patients were treated to a cumulative dose of 400 mg/m^2 of doxorubicin. Thereafter, both regimens could be continued indefinitely, only omitting the doxorubicin, for as long as the physician felt the patient was benefiting. In both regimens an electrocardiogram and a MUGA scan to evaluate the resting LVEF were performed at a cumulative doxorubicin dose of 300 mg/m^2.

Doses were modified for hematologic and other toxicities according to the organ system showing the greatest degree of toxicity and doses were reduced to the next lower dose level.

Study endpoints

Toxicity

All patients were evaluable for toxicity. MTD was defined as that dose which produced DLT in at least three of five patients at that level. DLT was defined as one or more of the following hematologic or nonhematologic criteria: hematologic – nadir granulocytes $\leq 0.5 \times 10^9$/l, nadir platelet count $\leq 25 \times 10^9$/l persisting for at least 5 days or the development of septicemia or febrile neutropenia during that cycle; nonhematologic – stomatitis grade 3 or more and/or diarrhea grade 3 or more; neuromotor grade 2 or more and/or neurosensory grade 3 or more. The recommended starting dose for considering phase II evaluation for the combination was the MTD less one level. Five additional patients were enrolled at the recommended dose level to ensure safety. Toxicities were graded using the NCIC-CTG Expanded Common Toxicity Criteria.

Response criteria

Response was not an endpoint in this study before a protocol amendment introducing a duration criterion for granulocytopenia was made. However, all patients had evaluable and/or measurable disease and if they received one cycle of chemotherapy were considered evaluable for response. All bidimensionally measurable lesions were recorded sequentially. The minimum sizes of measurable lesions were: on chest X-ray $>1 \times 1$ cm, skin/nodes $>1 \times 1$ cm, CT scan $>2 \times 2$ cm, ultrasound $>2 \times 2$ cm, liver metastases $>2 \times 2$ cm.

Standard WHO criteria were used to determine response [17]. Response duration was measured from the time response criteria were first met until disease progression was objectively documented.

Criteria for removing a patient from study

The development of severe toxicity not manageable by dose reduction or other means; a rise in serum bilirubin to >50 μmol/l; a fall in LVEF by $>20\%$ from baseline or to an absolute value of $\leq 45\%$; persistence of grade 2 or more neurotoxicity for more than 4 weeks; patient request for removal from the study; doxorubicin cumulative dose of 400 mg/m^2.

Statistical methods

The MTD was defined as that dose level at which three or more patients of a cohort of five attained the defined MTD criteria. There is a probability of 0.84 of finding that three or more patients in a sample of five meet the criteria if the true incidence of such criteria in the MTD population were 70%, or a probability of 0.95 of finding this if the true incidence in the MTD population were 80%.

Table 1 Accrual numbers

	FAN regimen	SUPERFAN regimen
Number of patients entered on study	26	12
Number with measurable disease	21	11
Number with evaluable disease only	5	1
Evaluable for toxicity	26	12
Evaluable for DLT	22	12
Evaluable for response	21	9
Died of disease	6	7

Results

Patient characteristics and evaluation

Enrolment on study was temporarily halted when each of the dose levels had been filled until all patients in that cohort had been evaluated for toxicity. In the absence of DLT, enrolment to the next cohort then ensued. Significant toxicity experienced by the first cohort led to revision of the treatment schedule and starting dose level for both the FAN and SUPERFAN regimens. The starting dose of vinorelbine was reduced to 15 mg/m^2 and treatment on day 15 was removed. Nadir neutropenia criteria were extended from 1 to at least 5 days to be considered dose limiting, and febrile neutropenia and sepsis were added as DLTs.

All patients enrolled on the studies were eligible and all were evaluable for toxicity. More complete information is contained in Table 1. The clinical

Table 2 Pretreatment patient characteristics

Age (years)		
Median	60.3	64.2
Range	41–71	51–73
Performance status (ECOG)		
0	5	5
1	11	4
2	10	3
Prior therapy		
Chemotherapy	5	4
Hormonal	23	10
Radiotherapy	17	6
Sites of disease		
Abdomen		1
Ascites		1
Bone	15	4
Breast	5	2
Pleural effusion	6	
Liver	11	7
Lung	8	2
Pelvis	2	1
Skin	1	2
Soft tissue	11	4
Number of sites		
1	5	5
2	13	4
3	4	1
4 or more	4	2

Table 3 FAN cohorts (the dose was escalated if two or fewer patients in a five-member cohort experienced a DLT)

Cohort number	Vinorelbine dose	Number of patients entered	DLT
1	15 mg/m^2 days 1, 8 and 15[a]	5	4
2	15 mg/m^2 days 1 and 8	4[b]	1
3	20 mg/m^2 days 1 and 8	5	2
4	25 mg/m^2 days 1 and 8	7[c]	5[d]
5	20 mg/m^2 days 1 and 8	5	0

[a]The day-15 dose was then omitted and a granulocytopenia duration criterion introduced for a DLT
[b]The fifth patient was not entered since the nonescalation criterion could never be met
[c]Two extra patients were allowed in this cohort because they had been offered the trial by their physicians before the cohort was closed
[d]In four patients the day-8 dose could not be given because of granulocytopenia

Table 4 SUPERFAN cohorts

Cohort number	Vinorelbine dose	Number of patients entered	DLT
1	15 mg/m^2 days 1 and 5[a]	5	4
2	15 mg/m^2 days 1 and 5	5	2
3	20 mg/m^2 days 1 and 5	2[b]	2

[a]A granulocytopenia duration criterion was introduced for a DLT. The cohort was repeated because, since intermediate counts had not been performed, it was not known how many DLTs by the earlier definition met the new criterion
[b]The toxicities experienced by these patients were so severe as to lead the investigators to agree that no future patients should be treated at this dose level

characteristics of the patients at study entry are displayed in Table 2.

FAN regimen

A total of 26 patients in five cohorts were entered on study. Four patients in the highest dose cohort were unable to receive the day-8 vinorelbine dose owing to myelosuppression and were thus considered as if they had had DLT. Another patient in this cohort could not receive the day-8 dose but also experienced a protocol-defined DLT. Five patients had disease that was inevaluable for response. The median number of cycles of FAN administered to patients was five. Of the 26 patients, 5 (19%) received eight or more cycles (3 receiving eight cycles and 2 as many as 24 cycles). In the two latter cases, responses had been observed and the planned doxorubicin dose given, and vinorelbine and fluorouracil (day 1 only) were continued on a three-weekly cycle. To date, six of the FAN patients have died, all from cancer and more than 30 days after the end of protocol therapy. A summary of the FAN patient cohorts, vinorelbine doses and DLTs is shown in Table 3.

SUPERFAN regimen

A total of 12 patients were enrolled in three cohorts. Three patients had inevaluable disease. Only two of the nine patients evaluable for response had a partial response of their metastatic disease. The SUPERFAN regimen was stopped before the last cohort was filled because of severe toxicity in the final cohort. Results of the SUPERFAN regimen are thus shown for comparison with the FAN regimen. The median number of cycles delivered was between five and six and only 1 of 12 patients (8%) received eight or more cycles. There were seven deaths on study, all of them a consequence of malignant disease and all but one more than 30 days after the end of protocol therapy. A summary of the SUPERFAN patient cohorts, vinorelbine doses and DLTs is shown in Table 4.

Toxicity

FAN regimen

The MTD of vinorelbine in the FAN regimen as defined by the study was 25 mg/m^2. Neutropenia was dose limiting. Grade III and IV hematologic toxicities at this dose level are summarized in Table 5. Other grade I/II hematologic toxicities observed included anemia, thrombocytopenia and leukopenia. Alopecia, gastrointestinal toxicity and local pain at the injection site were the commonest nonhematologic side effects of treatment as outlined in Table 5. Constipation secondary to neurologic toxicity occurred in three patients. Unexpected severe bilateral cataracts thought to be treatment-related occurred in one of the patients who received 24 cycles.

Serious toxicities were otherwise uncommon. These included, hypotension (one patient), infection (one patient), vomiting (two patients) and shortness of breath (one patient).

Table 5 Toxicity at MTD. Values are number of patients (%)

Adverse events	FAN regimen		SUPERFAN regimen	
	Serious	Life-threatening	Serious	Life-threatening
Allergy	1 (4)	0	0	0
Cardiovascular				
Hypotension	1 (4)	1 (4)	0	0
DVT	0	0	0	1 (8)
Flu-like symptoms	2 (8)	0	1 (8)	0
Gastrointestinal				
Anorexia	2 (8)	0	1 (8)	0
Diarrhea	1 (4)	0	0	2 (17)
Dysphagia	1 (4)	0	0	0
Dry mouth	1 (4)	0	0	0
Heartburn	1 (4)	0	0	0
Nausea	6 (23)	0	1 (8)	0
Stomatitis	4 (15)	0	4 (33)	1 (8)
Vomiting	1 (4)	2 (8)	0	0
Hematologic				
WBC	4 (15)	2 (8)	0	1 (8)
Granulocytes	0	7 (27)	0	1 (8)
Platelets	0	0	0	1 (8)
Infection				
Infection	0	1 (4)	0	0
Febrile neutropenia	2 (8)	0	2 (17)	0
Neurologic				
Constipation	3 (12)	0	1 (8)	0
Cortical	1 (8)	0	1 (8)	0
Other	2 (8)	0	0	0
Ocular	1 (4)	0	0	0
Pulmonary				
Shortness of breath	0	1 (4)	0	1 (8)
Pneumonitis	0	0	0	1 (8)
Skin				
Alopecia	9 (35)	0	0	0
Local toxicity	3 (12)	0	0	0
Metabolic				
Hyperglycemia	0	0	0	1 (8)

SUPERFAN regimen

The MTD of vinorelbine in the SUPERFAN regimen was 20 mg/m^2 as shown in Table 5. Both hematologic and nonhematologic toxicities were dose limiting. After the initial amendment to the protocol as outlined above, the dose of vinorelbine was escalated from 15 to 20 mg/m^2. At 20 mg/m^2 only two patients were treated and both experienced severe toxicity. One patient had constipation leading to an ileus stomatitis and the other febrile neutropenia, stomatitis and diarrhea. For this reason no further patients were enrolled to that cohort nor were the additional five patients added to the previous cohort as originally planned. Grade IV granulocytopenia and thrombocytopenia occurred, and hyperglycemia, diarrhea, nausea, stomatitis, shortness of breath with pneumonitis, and an episode of deep vein thrombosis were among the nonhematologic side effects recorded as shown in Table 5.

Response to treatment

FAN regimen

Five patients were not evaluable for response. Of 21 evaluable patients, 10 (48%) on study responded to treatment. The details pertaining to disease response are outlined in Table 6.

Table 6 Responses to treatment

	FAN regimen		SUPERFAN regimen	
Complete response	3	(12%)	0	(0%)
Duration in days (range)	91	(77–281)	–	
Partial response	7	(33%)	2	(22%)
Duration in days (range)	147	(65–372)	312.5	(120–499)
Stable disease	9	(43%)	6	(67%)
Progressive disease	2	(9%)	1	(11%)
Overall response rate	10/21	(48%)	2/9	(22%)
Inevaluable for response	5		3	

SUPERFAN regimen

Two of the nine patients evaluable for response had partial response of their metastatic disease. Details are given in Table 6.

Discussion

Vinorelbine is an active new drug for the treatment of breast cancer. These two phase I studies were performed in order to determine the maximum amount of vinorelbine that could be combined with doxorubicin and fluorouracil in doses conventionally used in the CAF breast cancer regimen or with doxorubicin and fluorouracil with folinic acid as in the SUPERCAF regimen, as folinic acid theoretically enhances the efficacy of fluorouracil considerably. Our long-term objective was to develop a regimen which would show better responses than these conventional regimens with equivalent or better toxicity profiles.

Since this trial was initiated, taxanes (paclitaxel, docetaxel) have become more widely used for the treatment of metastatic breast cancer. These agents have significant single-agent activity and their DLTs relate to myelosuppression. Combination studies with taxanes are under evaluation. To date there are no data on a head-to-head comparison of vinorelbine or the taxanes; however, preclinical data have shown this combination to be synergistic when given simultaneously [1]. Neutropenia will be the DLT of such a combination, and another concern is the potential for significant additive neuropathy. Cumulative neurotoxicity has been reported in patients with a history of paclitaxel treatment who were subsequently treated with vinorelbine [11] .

In both the FAN and the SUPERFAN regimens the starting dose exceeded the MTD defined by the original study criteria. This reflected greater myelosuppression than anticipated. It was decided that our original toxicity criteria were too stringent. These were therefore relaxed and the number of doses of vinorelbine per cycle in the FAN regimen was reduced from three to two. Thus in the SUPERFAN regimen, after five patients were treated with the initial 15 mg/m^2 dose, a further five were enrolled at the same level. However, when a subsequent escalation to 20 mg/m^2 was made, only two patients were treated before the SUPERFAN regimen was terminated owing to unacceptable myelosuppression and nonhematologic toxicity. The study parameters in terms of patient selection and treatment protocol were very similar for the two phase I protocols and the differences in toxicity seen can only be attributable to the use of higher dose of fluorouracil together with folinic acid in the SUPERFAN regimen.

The FAN regimen was better tolerated than the SUPERFAN regimen, and it was possible to determine a recommended starting dose for further phase II testing. Neutropenia was the predominant toxicity of the FAN regimen and other toxicities were in general mild. The one patient who developed bilateral cataracts was aged 53 years and had received prolonged chemotherapy before developing rapidly progressive cataracts. She also received a total dose of 230 mg (10 mg with each chemotherapy treatment) of dexamethasone as part of her antiemesis treatment and this may have contributed to the cataract formation. Nevertheless, this unexpected and serious potential side effect should be noted and looked for in elderly patients receiving long-term vinorelbine. This is particularly important in elderly patients in whom this drug might be particularly useful, as they are more vulnerable to cataract formation.

The gastrointestinal side effects (apart from constipation) of the FAN regimen are attributable to doxorubicin. Of particular note was the excellent hematological tolerability of the ''maintenance'' part of the treatment, suggesting that the earlier toxicity seen on the study was again predominantly a consequence of the addition of doxorubicin.

Differences in response rates between phase II studies can be attributed as much to patient selection and response assessment as to biologic efficacy [27]. Nevertheless, the overall disease response rate with the FAN regimen (48%) appeared low and not different from those reported with single-agent vinorelbine (16–51%) [6–10, 13–18] or doxorubicin [18]. In particular the FAN regimen did not yield response rates comparable to the 74% reported for a similar patient population by Spielmann et al. [31]. A median duration of response of 136.5 days (65–372 days) in all responding FAN-treated patients was also no different from the 150 days (98–270 days) reported in the single-agent vinorelbine studies. Furthermore, in a preliminary study by Blajman et al. of vinorelbine plus doxorubicin versus FAC, no difference in overall response rates or duration of responses was found [3].

These factors, together with the enhanced toxicity seen from the combination, prompted us not to proceed to the intended phase II component of these studies. Furthermore, the NCIC-CTG has recently completed a randomized study of doxorubicin versus doxorubicin/vinorelbine in metastatic breast cancer and the preliminary results do not show an advantage of the combination over single-agent doxorubicin [26].

Vinorelbine as monotherapy has been shown to have significant activity against breast cancer and an excellent toxicity profile. The limited response data from our study would imply that combining vinorelbine with more toxic agents may not enhance response rates, defeating the advantage of tolerability, especially in elderly patients. Thus, unless and until novel scheduling or combinations with vinorelbine show otherwise, use should probably be restricted to single-agent therapy. Vinorelbine's good tolerability profile merits further investigation of its applicability in the adjuvant setting, particularly in postmenopausal and elderly patients.

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