Cancer Chemother Pharmacol (1999) 43: 497–502 © Springer-Verlag 1999

ORIGINAL ARTICLE

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A phase I/II study of vinorelbine, doxorubicin, and methotrexate with leucovorin rescue as first-line treatment for metastatic breast cancer

Received: 27 April 1998 / Accepted: 17 September 1998

Abstract *Purpose*: This study was performed to determine the maximum tolerated dose (MTD) and toxicity of vinorelbine when used in combination with doxorubicin and methotrexate with leucovorin rescue in women with metastatic breast cancer. *Methods*: Enrolled in the study were 23 women with metastatic breast cancer who had not received prior chemotherapy for metastatic disease. Patients treated at the first dose level received vinorelbine 20 mg/m^2 on day 1, doxorubicin 40 mg/m^2 on day 1, methotrexate 100 mg/m^2 on day 1 and leucovorin 20 mg orally every 6 h for six doses beginning on day 2. Treatment was repeated every 21 days. The vinorelbine dose was escalated by 5 mg/m^2 for patients treated at subsequent dose levels. The MTD was defined as the dose level at which fewer than one-third of patients enrolled experienced dose-limiting toxicity (DLT). When the MTD of vinorelbine had been determined, the doxorubicin dose was then escalated by 10 mg/m^2 with the vinorelbine dose held at its MTD. Results: total of 98 courses of treatment (median of 4 per patient, range 2–8) were administered. The MTD of this regimen was found to be vinorelbine 25 mg/m^2, doxorubicin 40 mg/m^2, and methotrexate 100 mg/m^2 with leucovorin rescue. At higher doses of vinorelbine, neutropenia, fatigue, arm pain, malaise, nausea and vomiting were dose-limiting. Higher doses of doxorubicin resulted in universal dose limiting neutropenia, and frequent nonhematologic DLT consisting of arm pain, malaise, stomatitis, nausea and vomiting. Amongst the 20 patients with measurable disease, there were 3 complete responses (15%, 95% confidence interval 3%–38%), 5 partial responses (25%, 95% confidence interval 9%–49%) and an overall response rate of 40% (95% confidence interval 19%–64%). The median survival was estimated to be 25 months from the start of chemotherapy. *Conclusions*: Vinorelbine at 25 mg/m^2 can be safely administered with doxorubicin at 40 mg/m^2 and methotrexate at 100 mg/m^2 with leucovorin rescue. Response rates observed with this regimen suggest that this combination of chemotherapeutic agents may not be more effective than the combination of vinorelbine and doxorubicin.

Key words Chemotherapy · Doxorubicin · Metastatic breast cancer · Methotrexate · Vinorelbine

Supported by Glaxo Wellcome.

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Introduction

Vinorelbine (Navelbine; Glaxo Wellcome Co., Research Triangle Park, N.C.) is a semisynthetic vinca alkaloid which has been found to have significant single-agent activity in the treatment of metastatic breast cancer. Several phase I and phase II studies have demonstrated overall response (OR) rates ranging from 41% to 50% for vinorelbine as first-line therapy for patients with metastatic breast cancer [6, 8, 15, 17, 18]. Vinorelbine has been found to be efficacious in women previously treated for metastatic breast cancer with single-agent major objective response rates of 36% (95% CI, 24% to 47%) and 32% (95% CI, 20% to 47%) in two studies [10, 19]. In women with anthracycline-resistant advanced breast cancer treated with weekly vinorelbine at 30 mg/m^2, the objective response rate has been found to be 15% [12].

The main toxicity encountered with vinorelbine is dose-limiting neutropenia, generally lasting less than 7 days. Despite this, the incidence of febrile neutropenia is modest, perhaps related to the low incidence of stomatitis with vinorelbine use. Unlike the related drugs vincristine, vinblastine, and vindesine, vinorelbine has a

modification of the catharanthine moiety, resulting in a much higher affinity for microtubular tubulin than axonal tubulin. This is thought to account for vinorelbine's relative lack of neurotoxicity compared to other vinca alkaloids. Vinorelbine-induced peripheral neuropathy is generally mild, but autonomic neuropathy may result in grade 3 or 4 constipation and even paralytic ileus. Pain and/or phlebitis at the injection site is another commonly encountered toxicity of vinorelbine. Given its significant single-agent activity and relatively mild toxicity profile, vinorelbine is an ideal drug to study in combination with other chemotherapeutic agents. In combination with doxorubicin, it has been found to produce OR rates of 57% to 74% [7, 11, 16].

In this study, vinorelbine was combined with doxorubicin and methotrexate as first-line treatment for women with metastatic breast cancer. Previously at our institution, a 16-week dose-intense regimen of cyclophosphamide, doxorubicin, methotrexate with leucovorin rescue, 5-fluorouracil, and vincristine has been evaluated for the treatment of breast cancer in the high-risk adjuvant and metastatic settings [1, 2]. A response rate of 85% was observed in patients with metastatic disease. In an initial pilot study, vinorelbine was then substituted for vincristine, but mucositis proved to be dose limiting at low doses of vinorelbine. In the current study, we omitted cyclophosphamide and 5-fluorouracil in an attempt to further escalate the dose of vinorelbine and doxorubicin and administer therapy on a three-weekly schedule. The goals of this study were to determine the maximum tolerated dose (MTD) of vinorelbine when used in combination with doxorubicin and methotrexate, and to determine the toxicity of this combination regimen in women with advanced breast cancer.

Patients and methods

Patient selection

Eligible patients had histologically documented breast cancer which was metastatic and included at least one measurable or evaluable lesion. Patients had not received prior chemotherapy for metastatic disease, but adjuvant chemotherapy or hormonal therapy was permitted. Eligible patients had either estrogen receptor-negative tumors or estrogen receptor-positive tumors which had relapsed or progressed through at least one endocrine therapy. Other inclusion criteria were as follows: less than 250 mg/m^2 lifetime doxorubicin treatment, prior radiation therapy to no more than 25% of the marrow-containing bones, age over 18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, white blood cell count (WBC) >3500/mm^3, platelet count >125 000/mm^3, creatinine <1.5 mg%, bilirubin <1.5 mg% and aspartate aminotransferase (AST) <60 iu/ml, unless the abnormalities were due to metastatic involvement. Patients were also required to have adequate cardiac function, as demonstrated by a left ventricular ejection fraction ≥45% by gated blood pool imaging. Adequate pulmonary function with diffusing capacity for carbon monoxide (DLCO), forced expiratory volume in one second (FEV1), and forced vital capacity (FVC) at least 60% of predicted values was required due to one incidence of allergic pneumonitis in the pilot study. Exclusion criteria were active cardiac illnesses such as congestive heart failure, angina pectoris, arrhythmia, or myocardial infarction within the preceding 12 months; other major medical illnesses such as uncontrolled diabetes mellitus; and pregnancy. All patients provided written, informed consent prior to enrollment into the study.

Study design

Patients meeting the above criteria were sequentially enrolled and stratified into treatment groups based on drug dosages. Chemotherapy at dose level 1 consisted of vinorelbine 20 mg/m^2 intravenously (IV) on day 1, doxorubicin 40 mg/m^2 IV on day 1 methotrexate 100 mg/m^2 IV on day 1 (V20/D40/M100), and leucovorin 10 mg/m^2 orally (p.o.) every 6 h for six doses beginning on day 2. Therapy was repeated every 21 days. The dose of vinorelbine was increased by 5 mg/m^2 for the subsequent dose level if no dose-limiting toxicities (DLT) occurred in course one for the patients at the current dose level. A minimum of four patients were enrolled at each level as significant toxicity was anticipated due to the high starting doses. At least three patients at a given dose level completed the 21-day course before subsequent patients were entered into the next higher dose level. When the MTD of vinorelbine was determined, the doxorubicin dose was then escalated. (Table 1)

Dose escalation of chemotherapy agents was not performed in individual patients. Dose reduction was permitted by one or two levels in patients who had experienced a DLT but appeared to be responding to the regimen. The treatment protocol was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions.

Study endpoints

Toxicity

Toxicity was graded according to the National Cancer Institute's (NCI) Common Toxicity Criteria. Nonhematologic toxicity of grade 3 or 4 was considered a DLT. Hematologic toxicities were considered dose limiting if either an absolute neutrophil count (ANC) <500/μl occurred for more than 5 days, platelet count <25 000/μl occurred for more than 5 days, or subsequent chemotherapy was delayed for more than 7 days due to unresolved toxicities. If one instance of DLT was observed among the initial four patients at a given dose level, then two more patients were to be enrolled at that dose level. If no further instances of DLT were observed, dose escalation continued for the next four patients. The MTD was defined as the maximum dose level at which fewer than one-third of the patients experienced DLT, i.e. one out of four or fewer than two out of six patients.

Response

Patients were followed weekly while participating in the study. At every course a history and physical examination was performed

Table 1 Dose levels

Dose level	Vinorelbine/doxorubicin/methotrexate dose (mg/m^2)	Number of patients entered New/Total	Number of courses
1	20/40/100	5/5	19
2	25/40/100	4/5[a]	14
3	30/40/100	6/6	30
4	25/50/100	4/6[a]	22
5	25/60/100	4/4	9

[a] One patient initially treated at dose level 5 required a reduction of dose and was subsequently treated at dose level 4 and then dose level 2. Another patient initially treated at dose level 5 required a reduction of dose after one course of chemotherapy and was thereafter treated at dose level 4

which included clinical tumor assessment and performance status assessment. Electrolytes, chemistries, prothrombin time and urinalysis were checked every 21 days. Hematology profiles were to be obtained on days 3, 6, 8, and 10 and three times per week thereafter. Radiographic tumor measurement was performed at every second course or sooner if clinically indicated.

The ECOG criteria for tumor response in measurable disease were employed [14]. Patients were removed from study at the observation of progressive disease, at their own request, or at the discretion of the study chairman because of unacceptable toxicity or to proceed to high-dose consolidation therapy.

Statistical analysis

Stata statistical software (Stata Corporation, College Station, Texas) was used to calculate exact binomial 95% confidence limits for response rates. Median survival in months from the start of chemotherapy was estimated using the Kaplan-Meier method [13] with Stata as well.

Results

Patient characteristics

A total of 23 patients were enrolled into the study from 13 October 1993 through 31 July 1996. All patients were evaluable for toxicity. Response could be assessed in all but one patient. This patient entered the study with a chest wall nodule that was proven on biopsy to represent recurrent disease. A second nodule persisted on clinical examination through four courses of chemotherapy and was found to be benign upon excision at the end of treatment. It remains unknown whether this patient entered the study with measurable disease (stage IV) that responded to chemotherapy or whether the mass was simply residual fibrotic tissue (no evidence of disease). Of the 23 patients, 20 had measurable disease. Table 2 displays patient characteristics at the time of enrollment into the study.

One patient was enrolled into the study with a large breast mass and a lung nodule, which was proven with fine needle aspiration to be an adenocarcinoma with an appearance similar to the primary breast tumor. This patient had no response at either site to chemotherapy or subsequent tamoxifen. She underwent a modified radical mastectomy 18 months after treatment on the present study. One year later her lung nodule remained stable and was resected as part of a right upper lobectomy. The pathologic diagnosis of this 2.3-cm lung nodule was bronchioalveolar carcinoma. Thus, in retrospect, this patient had stage II breast cancer with a separate primary lung cancer. She was included in the response analysis which was based upon intention to treat.

Table 2 Pretreatment characteristics of the 23 study patients

Age (years)	
Mean	49
Range	32–65
Estrogen receptor status (no. of patients)	
Positive	12
Negative	9
Unknown	2
ECOG Performance status	
0–1	23
Adjuvant chemotherapy	
Yes	7
No	16
Adjuvant hormonal therapy	
Yes	6
No	17
Hormonal therapy for metastatic disease	
Yes	5
No	18
Radiation therapy	
Yes	9
No	14
Dominant site of disease	
Local	11
Visceral	9
Bone	3
Number of sites of disease	
0 (no evidence of disease)	1
1	10
2	7
Disease-free interval[a] (months)	
Mean	46
Range	4–141

[a] Disease-free interval from the completion of surgery +/− adjuvant chemotherapy and radiation therapy to the diagnosis of metastatic disease, for the 16 patients who initially presented with localized disease

Toxicity

A total of 98 courses of treatment was administered. The number of courses per patient ranged from two to eight with a median of four. The maximum vinorelbine dose that could be safely administered in this combination was 25 mg/m^2. At this dose (V25/D40/M100) one of five patients developed grade 4 nonhematologic toxicity, consisting of nausea and vomiting that began on day 2 of course 2 and required an overnight admission to the hospital. There were no cases of hematologic DLT at this dose level. In contrast, at dose level 3 (V30/D40/M100) there were two cases of dose-limiting neutropenia, one occurrence of grade 3 nausea and vomiting, and one occurrence of grade 3 fatigue with the first course of treatment among the four patients initially enrolled at this dose level. Subsequently, two further patients were enrolled at this dose level, and they developed grade 3 arm pain and grade 3 malaise, respectively, with the first course of chemotherapy.

After determination of the MTD for vinorelbine, attempts were made to escalate the doxorubicin dose. The MTD for doxorubicin was 40 mg/m^2. All patients treated at dose level 4 (V25/D50/M100) and 5 (V25/D60/M100) developed dose-limiting neutropenia. In addition, there were two occurrences of dose-limiting abdominal pain among the four new patients treated at level four, as well as two occurrences of dose-limiting nausea and vomiting and one occurrence of dose-limiting stomatitis

among the four new patients treated at level 5. Thus, the MTD of this combination regimen was the level 2 dose V25/D40/M100. Without restricting the analysis to new patients and their dose level of entry, there were no occurrences of DLT among 19 courses administered at level 1, three occurrences of DLT among 14 courses administered at level 2, nine occurrences of DLT among 30 courses administered at level 3, ten occurrences of DLT among 22 courses administered at level 4 and eight occurrences of DLT among 9 courses administered at level 5.

There were no treatment-related deaths. Commonly observed grade 1 and 2 nonhematologic toxicities were arm pain, nausea and vomiting, stomatitis, constipation and fatigue. Grade 3 and 4 hematologic toxicities observed at each level are listed in Table 3. Dose-limiting anemia or thrombocytopenia was not observed at any dose level. Although grade 4 neutropenia was a relatively common toxicity, occurring in 43% of all courses (91% of courses at dose level 4 and 67% of courses at dose level 5), it was generally brief and of dose-limiting duration in only 18% of courses. Neutropenic fever, which may be a better indicator of toxicity than grade 4 neutropenia, occurred in only 6 of 94 courses (6%) of chemotherapy administered. No patient developed sepsis. The MTD did not change when neutropenic fever was substituted for grade 4 neutropenia as a DLT.

Dose reductions

Dose reductions were required for three patients. One patient enrolled at dose level 3 (V30/D40/M100) experienced dose-limiting grade 4 neutropenia with one course of chemotherapy. One patient enrolled at dose level 5 (V25/D60/M100) experienced dose-limiting grade 3 stomatitis and nausea and vomiting with the second course of treatment and was subsequently treated at level 4 (V25/D50/M100) for her next two courses of chemotherapy. A second patient initially treated at dose level 5 developed a neutropenic fever with the first course and, although this was not considered a dose-limiting toxicity, she was subsequently treated at dose level 4. She developed dose-limiting neutropenia with her fourth course of treatment and her dose was then lowered to level 2 (V25/D40/M100).

Table 3 NCI grade 3 and 4 hematologic toxicity per dose level

	Dose level 1	Dose level 2	Dose level 3	Dose level 4	Dose level 5
No. of courses	19	14	30	22	9
No. of courses with					
Anemia					
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Leukopenia					
Grade 3	6	5	3	16	4
Grade 4	0	0	1	0	0
Neutropenia					
Grade 3	7	4	8	0	2
Grade 4	3	8	3	21	6
Thrombocytopenia					
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0

Response to treatment

There were 22 of 23 patients evaluable for response to treatment. In total there were three complete responses (CR), five partial responses (PR), two with evaluable disease only who showed improvement, five with stable disease and eight with progressive disease (PD). In the 20 patients with measureable disease the CR rate was 15% (95% CI, 3% to 38%), the PR rate was 25% (95% CI, 9% to 49%) and the OR rate was 40% (95% CI, 19% to 64%). Seven patients received high-dose chemotherapy within 2 months of treatment on the study. Another patient received high-dose chemotherapy at a later date. The estimated median survival from the start of chemotherapy using the Kaplan-Meier method was 25 months.

Discussion

Prior to the emergence of the taxanes, the anthracyclines were considered to be the most active chemotherapeutic agents for the treatment of breast cancer. We had previously observed an 85% response rate in women with metastatic breast cancer using a new 16-week, dose-intense regimen of cyclophosphamide, doxorubicin, vincristine, 5-fluorouracil, methotrexate, and leucovorin rescue [2]. In light of its impressive single-agent activity in breast cancer and relatively mild toxicity profile, vinorelbine was substituted for vincristine in a subsequent pilot study. Grade 3 mucositis, however, proved to be a DLT at a dose of 20 mg/m^2 vinorelbine. The present study was performed to determine if vinorelbine could safely be administered on a 3-weekly schedule with doxorubicin, methotrexate and leucovorin, once cyclophosphamide and 5-fluorouracil were omitted. As there were no alkylating agents in this regimen, it was useful for treatment of patients in preparation for high-dose chemotherapy.

The combination of vinorelbine at 25 mg/m^2, doxorubicin at 40 mg/m^2, and methotrexate at 100 mg/m^2 with leucovorin rescue, administered every 21 days, was the MTD. At this dose level toxicity was acceptable, with no hematologic DLT and only one episode of grade 4 nausea and vomiting as nonhematologic DLT in one of four new patients entered at this level (total of five patients treated at this level). In contrast to our previous study of vinorelbine in combination with 5-fluorouracil, doxorubicin, methotrexate, and leucovorin, dose-limiting mucositis was observed in only 1 of 98 courses of

chemotherapy in the present study, presumably due to the omission of 5-FU.

Prohibitive toxicity was experienced with 50 mg/m^2 doxorubicin when it was combined with 25 mg/m^2 vinorelbine, 100 mg/m^2 methotrexate, and leucovorin. Several investigators have administered vinorelbine at 25 mg/m^2 on days 1 and 8 and doxorubicin at 50 mg/m^2 on day 1, with the cycle repeated every 3 weeks [7, 11, 16]. An OR rate of 74% (95% CI, 65% to 85%) is the highest reported for this combination [16]. Toxicities were similar to those reported here, in that neutropenia was dose limiting and 3% of chemotherapy cycles resulted in febrile neutropenia. Cardiotoxicity of grade 2 to 4, however, was noted in 10% of those patients. In the current study, cardiotoxicity was not noted at any dose level, but results of gated blood pool imaging studies or echocardiography following treatment were available in only nine patients, all of whom had ejection fractions from 47% to 76%. Escalation of the vinorelbine dose to levels used in other studies of vinorelbine with doxorubicin alone was also not feasible, primarily because of dose-limiting neutropenia, nausea, arm pain and malaise.

Both vinorelbine and methotrexate are metabolized primarily through the hepatobiliary system. Preclinical studies of the effect of vindesine on methotrexate metabolism have demonstrated that increasing vindesine concentrations results in reduced hepatocyte uptake and metabolism of methotrexate [4, 5]. The effects of vinorelbine on methotrexate metabolism and methotrexate on vinorelbine metabolism are not known, but competition between these two drugs for hepatic uptake and metabolism is possible. Escalation of the vinorelbine dose in the present study may have been limited by the presence of methotrexate, which was administered at a higher dose than in other combination studies of vinorelbine.

As with most preliminary toxicity trials, ours was a small study. DLT is determined using a small number of patients and results can vary due to patient characteristics. At the MTD and the single dose level below it, we observed one CR, one PR and six patients with PD. For the 20 patients with measurable disease, the CR rate was 15% (95% CI, 3% to 38%) and the PR rate was 25% (95% CI, 9% to 49%), resulting in an OR of 40% (95% CI, 19% to 64%). This OR rate appears to be lower than the 57–74% OR rates previously obtained in phase II studies of combinations of vinorelbine and doxorubicin and is similar to results achieved with single-agent vinorelbine or doxorubicin [7, 11, 16]. Patients in the current study were not of worse performance status and did not have more sites of disease than patients in studies with higher response rates to doxorubicin and vinorelbine. Although the present study did not require a specific time interval between adjuvant therapy and relapse of disease, only one patient relapsed within 1 year of receiving adjuvant therapy. The combination of vinorelbine, doxorubicin, methotrexate and leucovorin could be evaluated further with a lower methotrexate dose to allow more aggressive dose escalation of vinorelbine and doxorubicin.

More promising results may be obtained from studies of the combination of vinorelbine with the taxanes. Preclinical data in mice implanted with subcutaneous tumors have demonstrated synergy between vinorelbine and docetaxel [3]. In addition, it appeared that 80–100% of the MTDs of the individual drugs can be safely administered in combination. These findings led to the initiation of a phase I study of docetaxel and vinorelbine in women with metastatic breast cancer [9]. This study concluded that the recommended dose of this drug combination in phase II studies should be 75–85 mg/m^2 docetaxel on day 1 and 20 mg/m^2 vinorelbine on days 1 and 5, every 3 weeks. OR rates of 80% and 67% were achieved using 85 mg/m^2 and 75 mg/m^2 docetaxel, respectively. Further studies of vinorelbine directed towards its combination with the taxanes may lead to highly effective treatment regimens for women with anthracycline-resistant disease.

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