Phase I Study of Vinorelbine and Paclitaxel by 3-Hour Simultaneous Infusion with and without Granulocyte Colony-Stimulating Factor Support in Metastatic Breast Carcinoma

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BACKGROUND. The purpose of the study was to determine the maximum tolerated dose (MTD) of vinorelbine and paclitaxel given concomitantly in patients with advanced breast carcinoma, the toxicity of this combination, and whether the addition of granulocyte colony-stimulating factor (G-CSF) would allow administration of higher doses of the combination.

METHODS. Between January 1994 and January 1995, 38 patients were entered on this study. All patients received vinorelbine and paclitaxel administered simultaneously over 3 hours and repeated every 21 days as frontline therapy for metastatic breast carcinoma. Twenty-five patients (Group 1) did not receive prophylactic G-CSF, and 13 patients (Group 2) received prophylactic G-CSF. Toxic effects were documented prospectively using the National Cancer Institute grading system.

RESULTS. One hundred eighty-seven (Group 1) and 111 (Group 2) cycles were administered. For Group 1, Grade 3–4 granulocytopenia was encountered in 72% of the cycles and neutropenic fever in 30% of the cycles. For Group 2, Grade 3–4 granulocytopenia and neutropenic fever were encountered in 23% and 4% of the cycles, respectively. Grade 3–4 fatigue and myalgia, respectively, were encountered in 11% and 3% of the cycles in Group 1, whereas they were reported in 12% and 1% of the cycles in Group 2. The MTD of this combination without prophylactic G-CSF was 25 mg/m^2 of vinorelbine and 150 mg/m^2 of paclitaxel, the dose-limiting toxicity (DLT) being neutropenic fever and myalgia. The MTD of this combination with G-CSF was 36 mg/m^2 of vinorelbine and 150 mg/m^2 of paclitaxel, the DLT being myalgia and fatigue.

CONCLUSIONS. The authors conclude that vinorelbine and paclitaxel can be safely administered concomitantly and are well tolerated. Phase II studies are recommended to test the efficacy of this schedule. ***Cancer*** **2001;91:664–71.**

KEYWORDS: maximum tolerated dose, toxicity, advanced breast carcinoma, vinorelbine, paclitaxel.

Vinorelbine, a semisynthetic vinca alkaloid, is derived from a hydroxy substitution of the catharanthine ring of the vinblastine molecule. By inhibiting microtubule assembly, vinorelbine blocks the formation of the mitotic spindle apparatus at the metaphase, thus preventing cell division. Its selective affinity for the mitototic tubulin and tubulin-associated proteins and the relative sparing of the axonal microtubules makes it a less neurotoxic vinca alkaloid.[1] Vinorelbine is an active agent in various solid tumors, including breast carcinoma.[2] In previously untreated patients with metastatic breast carcinoma,

vinorelbine given intravenously at 30 mg/m^2/week showed an objective response rate of 40–60%[3–10] and as salvage therapy, 16–64%.[11–16] The dose-limiting toxic effect of weekly vinorelbine is neutropenia. Nonhematologic toxic effects are usually mild and include neurotoxicity, constipation, pain at the injection site, phlebitis, nausea, and asthenia. Vinorelbine also has demonstrated significant antitumor activity against breast carcinoma when combined with other agents such as doxorubicin,[17–19] epirubicin,[20,21] 5-fluorouracil (5-FU),[22–24] mitomycin C,[25–29] cisplatin,[30,31] and carboplatin.[32]

Paclitaxel, conversely, promotes and stabilizes polymerized tubulin into nonfunctional microtubule bundles and therefore blocks the cells in the G2/M-phase of the cell cycle. It has proven activity in various solid tumors, including breast carcinoma. In previously untreated metastatic breast carcinoma,[33–38] the response rate to paclitaxel is 30– 60%, and it is 21–32% in patients with extensive prior therapy,[39–41] including those who are resistant to anthracyclines. Many studies also have demonstrated significant activity of paclitaxel when combined with other agents including doxorubicin,[42–50] cisplatin,[51–53] carboplatin,[54–56] and 5-FU.[57,58] Many of the dose-limiting toxic effects of these combinations are due to the sequence of administration and/or the doses used in the various combinations. For example, the dose-limiting toxic effects of paclitaxel and doxorubicin are hematologic, cardiac, and mucositis;[42,43,59] those of paclitaxel and cisplatin are hematologic and neurosensory,[51–53] and for paclitaxel and 5-FU they are mucositis, diarrhea, neuropathy, and hematologic toxicity.[57,58]

Anthracycline–cyclophosphamide-based regimens are the gold standard, frontline therapy for metastatic breast carcinoma; the overall response (OR) rate is 45– 75%, and the complete response (CR) rate is 10–20%.[60] Development of a relatively non–cross-resistant regimen may help to improve the response rates and possibly the survival rate. The combination of paclitaxel and vinorelbine, if it proves to be tolerable and effective, may possibly serve as a non–cross-resistant regimen used in conjunction with an anthracycline–cyclophosphamide-based regimen in an attempt to improve the natural history of metastatic breast carcinoma.

Knick et al.[61] studied the in vivo effect of combining vinorelbine and paclitaxel. The combination resulted in a significantly greater proportion of cell kill of transplanted p388 murine leukemia cells than either agent alone. This study also has shown that there was no added toxicity by combining these two drugs; that the order of sequencing of these drugs did not influence the toxicity or the cure rate; and that survival was not significantly different when both drugs were delivered simultaneously or were separated by a 1-hour interval. On the basis of these data, this Phase I study was initiated. The two drugs were administered simultaneously to determine the tolerability and toxicity, including myelosuppression and neurotoxicity, of this drug combination. After the maximal tolerated dose (MTD) of this combination was determined, granulocyte colony-stimulating factor (G-CSF) was introduced in an attempt to dose-intensify the combination. It was hypothesized that a higher dose intensity would enhance the response rates.

METHODS

Patients were considered eligible if they had microscopically confirmed carcinoma of the breast, with no prior chemotherapy for their metastatic disease. Hormonal therapy or adjuvant chemotherapy was admissible. Patients who were receiving hormonal therapy for metastatic disease were required to wait 4 weeks after completion of the last dose of hormonal treatment before entering this study; no waiting period was required for patients with rapidly progressive visceral disease. All patients were required to have bidimensionally measurable disease, performance status of 0–2, and a life expectancy greater than 16 weeks. Laboratory requirements for eligibility included an absolute granulocyte count greater than 1500 cells/mm^3 and a platelet count greater than 100,000 cells/mm^3, a serum creatinine less than 2.5 mg/dL, a serum total bilirubin less than 1.3 mg/dL, and a serum glutamic pyruvic transaminase less than 3 times the upper limit of normal. Patients were excluded if they were considered medically unstable or had uncontrolled cardiac disease, a history of congestive heart failure, or unstable angina or arrhythmia that required medications, were pregnant or lactating, or were not using adequate contraception. Patients who had metastatic disease to the central nervous system or a history of other malignancy within the past 5 years, except for basal cell carcinoma of the skin or carcinoma in situ of the cervix, were excluded from this study. Patients with preexisting clinically significant peripheral neuropathy were excluded except when it was considered to be resulting from the cancer process. All patients had to sign an Institutional Research Board–approved informed consent before registration on the study.

Treatment Plan

Both drugs were administered via a double-lumen central venous catheter (CVC): vinorelbine was mixed with 20–25 dL of normal saline or 5% dextrose in water (D_5W), to a final dilution of 1:4 and then added to a 100-mL bag of normal saline or D_5W. Vinorelbine was

TABLE 1
Dose Modifications for Patients Receiving Vinorelbine and Paclitaxel Without G-CSF Support[a]

Level	Vinorelbine (mg/m^2)	Paclitaxel (mg/m^2)	No. of patients
−4	25	150	3
−3	30	150	3
−2	25	175	3
−1	30	175	3
0	36	175	3

G-CSF: granulocyte colony-stimulating factor.
[a] Cycle repeated every 21 days.

TABLE 2
Dose Modifications for Patients Receiving Vinorelbine and Paclitaxel with G-CSF Support[a,b]

Level	Vinorelbine (mg/m^2)	Paclitaxel (mg/m^2)	No. of patients
−1	25	150	3
0	30	150	3
1	36	150	3
2	42	150	3
3	46	150	3

G-CSF: granulocyte colony-stimulating factor.
[a] Cycle repeated every 21 days.
[b] G-CSF 5 μg/kg subcutaneously given on Days 3 through 8 or until absolute granulocyte count $> 10{,}000$.

infused over 3 hours. Concomitantly, paclitaxel was also infused over 3 hours by using the second branch of the CVC. Patients were premedicated 14 and 7 hours before the paclitaxel infusion with oral dexamethasone 20 mg in addition to diphenylhydramine 50 mg and cimetadine 300 mg, both given intravenously 60 minutes before paclitaxel infusion. Patients also received antiemetic therapy. The starting doses of the study drug combination were paclitaxel 175 mg/m^2 and vinorelbine 36 mg/m^2. Dose modification schema for patients receiving this combination without or with G-CSF are shown in Tables 1 and 2, respectively.

Statistical Considerations

This Phase I study aimed to determine the MTD of vinorelbine and paclitaxel given concomitantly by 3-hour infusions without and with G-CSF support. We used the two-stage Simon model to determine the MTD. The total number of patients needed was a minimum of three at each dose level and six at the recommended dose level. The MTD was defined as the highest dose level at which less than 50% of the patients (a minimum of 6) experienced Grade 3 or higher toxicity. Once the MTD was determined, G-CSF support was added prophylactically to dose-intensify this regimen and to determine a new MTD for this combination.

TABLE 3
Characteristics of Group 1 (25 Patients Treated with Vinorelbine and Paclitaxel without G-CSF Support) and Group 2 (13 Patients Treated with Vinorelbine and Paclitaxel with G-CSF Support)

Characteristic	Group 1 (n [%])	Group 2 (n [%])
Patients entered	25	13
Patients assessable	25 (100)	13 (100)
Median age (yrs, range)	47 (34–72)	55 (36–73)
Female gender	25 (100)	13 (100)
Performance status		
0–1	24 (96)	8 (62)
2	1 (4)	5 (39)
Histology		
Invasive ductal carcinoma	23 (92)	13 (100)
Invasive lobular carcinoma	2 (8)	0
Prior chemotherapy		
Chemotherapy naive	5 (20)	7 (54)
Adjuvant chemotherapy	20 (80)	6 (46)
Prior anthracycline exposure	17 (68)	5 (38)
Tumor burden		
1 metastatic site	12 (48)	5 (38)
2 metastatic sites	7 (28)	3 (23)
≥ 3 metastatic sites	6 (24)	5 (38)
Visceral metastasis	16 (64)	9 (69)

G-CSF: granulocyte colony-stimulating factor.

RESULTS

Between January 1994 and January 1995, 38 patients were entered on this study. Twenty-five patients received vinorelbine and paclitaxel without prophylactic use of G-CSF (Group 1), and 13 patients received the study drugs plus prophylactic G-CSF support (Group 2). Patient characteristics of both groups are listed in Table 3. One hundred eighty-seven (Group 1) and 111 (Group 2) cycles were administered for both groups. Hematologic toxicity (National Cancer Institute Grade 1–4) in both groups is shown in Table 4. For Group 1, Grade 3–4 granulocytopenia was encountered in 135 (72%) cycles and neutropenic fever in 30 (16%) cycles. For Group 2, Grade 3–4 granulocytopenia was encountered in 25 (23%) cycles, and neutropenic fever in 4 (4%) cycles, none of whom needed inpatient care. Nonneutropenic fever, however, was encountered in four patients (four cycles) of Group 2.

The nonhematologic toxicities for Group 1 are listed in Table 5. Besides alopecia (observed in 100% of the patients), fatigue was the most common nonhe-

TABLE 4
Hematologic Toxicity in Patients Receiving Chemotherapy without and with G-CSF Support

Toxicity	Without G-CSF (n = 187 cycles [%])	With G-CSF (n = 111 cycles [%])
Granulocytopenia		
Grade 1–2	3 (2)	1 (1)
Grade 3–4	135 (72)	25 (23)
Neutropenic fever		
Grade 1–2	16 (9)	3 (3)
Grade 3–4	14 (7)	1 (1)
No. of hospitalizations	17 (9)	0

G-CSF: granulocyte colony-stimulating factor.

TABLE 5
Nonhematologic Toxicities in Group 1 (Patients Receiving Chemotherapy without G-CSF) and Group 2 (Patients Receiving Chemotherapy with G-CSF Support)

	Group 1 (n = 187 cycles)		Group 2 (n = 111 cycles)	
Toxicity	Grade 1–2 (%)	Grade 3–4 (%)	Grade 1–2 (%)	Grade 3–4 (%)
Sensory	151 (81)	7 (4)	73 (66)	7 (6)
Myalgia	131 (70)	6 (3)	77 (69)	1 (1)
Fatigue	127 (68)	21 (11)	83 (75)	13 (12)
Pelvic pain	0	3 (2)	0	0
Nausea/vomiting	91 (49)	0	30 (27)	0
Stomatitis	44 (24)	1 (1)	11 (10)	0
Diarrhea	29 (16)	2 (1)	16 (14)	0
Constipation	28 (15)	0	18 (16)	0
Mood changes	17 (9)	0	0	0
Bone pain	16 (9)	1 (1)	11 (10)	1 (1)
Conjunctivitis	2 (1)	0	0	0

G-CSF: granulocyte colony-stimulating factor.

matologic Grade 3–4 toxicity encountered in 21 (11%) cycles. Grade 3–4 myalgia was encountered in six (3%) cycles. Grade 3–4 peripheral neuropathy or gastrointestinal symptoms, such as diarrhea and stomatitis, were not common, observed in 4% and 2% of the cycles, respectively. The dose-limiting toxic effects therefore were neutropenic fever and myalgia. Two patients at dose level (DL) 0 and 1 at DL −1 developed Grade 3–4 pelvic pain. In addition, two of four patients developed neutropenic fever at DL −1. However, no pelvic pain was encountered at DL −2. Because paclitaxel is more neurotoxic than vinorelbine, we therefore amended the protocol to reduce the dose of paclitaxel to 150 mg/m^2 and proceeded to determine the associated MTD of vinorelbine.

Once the MTD of paclitaxel and vinorelbine was reached, prophylactic G-CSF support was added to dose-intensify vinorelbine. Patients were started on vinorelbine 30 mg/m^2 and paclitaxel 150 mg/m^2 infused simultaneously over 3 hours. The cycle was repeated every 21 days. Patients received subcutaneous injections of G-CSF 5 μg/kg on Days 3 through 8 or to a total leukocyte count greater than 10,000/mm^3. The doses of G-CSF were rounded to 300 or 480 μg total dose. Thirteen patients were entered. Their characteristics are shown in Table 3. A total of 111 cycles was administered. Hematologic toxic effects are listed in Table 4. Grade 3–4 granulocytopenia was encountered in 23% of the cycles and neutropenic fever in 4% of the cycles, none of whom required hospitalization. Nonneutropenic fever was also observed in four cycles. Nonhematologic toxic effects in Group 2 are shown in Table 5. Besides alopecia, Grade 3–4 fatigue was the most common nonhematologic toxic effect encountered in 13 (12%) cycles. Grade 3–4 peripheral neuropathy was not common, occurring in 6% of the cycles. The dose-limiting toxic effects were nonhematologic: fatigue and myalgia.

The MTD of this combination administered simultaneously over 3 hours every 21 days without prophylactic G-CSF was 25 mg/m^2 vinorelbine and 150 mg/m^2 paclitaxel, and with G-CSF, 36 mg/m^2 vinorelbine and 150 mg/m^2 paclitaxel.

All patients were assessable for response. In Group 1, 40% (1 CR, 9 partial responses [PRs]) of the patients responded, and 12% (3 patients) had disease progression; all others had stable disease. The median time to progression for Group 1 was 17 weeks (range, 6–56 weeks). In Group 2, 61% (2 CRs, 6 PRs) of the patients responded, and 15% (2 patients) had disease progression; all others had stable disease. The median time to progression for Group 2 was 31 weeks (range, 9–41 weeks; Table 6).

DISCUSSION

Prevention of depolymerization of microtubules by taxanes, or its polymerization by vinca alkaloids (vincristine and vinblastine), causes phosphorylation of *bcl-2* and cell death (apoptosis).[62] Paclitaxel-induced apoptosis may be p53-dependent;[63,64] tumors that lack *p53* or have a mutant form of the gene are resistant.[65,66] The apoptotic activity of vinorelbine appears to be p53-independent.[67] Cellular resistance to vinorelbine, as with other vinca alkaloids, may be caused by *p*-glycoprotein–mediated multidrug resistance (MDR) mechanisms.[68] Other non-MDR mechanisms of resistance also were observed.[69] Resistance to paclitaxel also can be mediated by *p*-glycoprotein and the MDR phenotype or by specific mutations in tubulin that interfere with the mechanism of microtubule stabilization. In breast carcinoma cell line models MCF-7 and MDA-MB-231, when paclitaxel and vinorelbine were added simultaneously at an optimal

TABLE 6
Responses and Time to Progression of Patients Treated without and with G-CSF Support

Group	CR (%)	PR (%)	SD (%)	PD (%)	TTP (wks, range)
Without G-CSF (n = 25)	1 (4)	9 (36)	12 (48)	3 (12)	17 (6–56)
With G-CSF (n = 13)	2 (15)	6 (46)	3 (23)	2 (15)	31 (9–41)

G-CSF: granulocyte colony-stimulating factor; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; TTP: time to progression.

molar ratio of 0.1:10, an additive effect was noticed (John A. Hohneker, M.D., GlaxoWellcome Laboratories, personal communication). The additive effects produced by the simultaneous administration of these two drugs[61,70] supports the rationale of combining them in the treatment of breast carcinoma.

Phase I studies demonstrated the safe administration of vinorelbine and paclitaxel sequentially. Budman et al.[71] gave patients with metastatic breast carcinoma vinorelbine daily for 3 days followed by paclitaxel on Day 3. All patients above the initial dose level received G-CSF prophylactically. The dose-limiting toxicities were myalgia and fatigue, and the recommended Phase II doses were 13 mg/m^2/day for 3 days for vinorelbine and 175 mg/m^2, by 3-hour infusion, for paclitaxel. For Phase II studies, Culine et al.[72] recommended the sequential administration of paclitaxel 155 mg/m^2 and vinorelbine 25 mg/m^2 on Day 1, every 21 days. In this Phase I study, the dose-limiting toxicity was neutropenic fever. Tortoriello et al.,[73] however, recommended paclitaxel 210 mg/m^2 by 3-hour infusion and vinorelbine 30 mg/m^2 over 15 minutes, repeated every 21 days. Peripheral neuropathy and neutropenia were dose-limiting toxicities. The overall response rate, however, was 38% (9% CR).

Several Phase II studies combining vinorelbine and paclitaxel have been conducted. Martin et al.[74] administered paclitaxel 135 mg/m^2 intravenously over 1 hour followed by vinorelbine 30 mg/m^2 intravenously over 10 minutes every 3 weeks to patients with metastatic breast carcinoma. The overall response rate was 54%. Grade 3–4 neutropenia was observed in 29% of the cycles, neutropenic fever in 18%, and Grade 3 peripheral neuropathy in 2.5%. In another study,[75] vinorelbine 30 mg/m^2 20-minute infusion given on Days 1 and 8 to patients with metastatic breast carcinoma and paclitaxel 135 mg/m^2 given over 3 hours, starting 1 hour after vinorelbine, on Day 1 and repeated every 28 days resulted in an overall response rate of 60%. The dose-limiting toxic effect was myelosuppression. No Grade 3–4 peripheral neurotoxicity was observed. In a Phase I–II study, Ellis et al.[76] administered paclitaxel by 96-hour infusion and vinorelbine intravenously on Days 8 and 15, with prophylactic G-CSF support and repeated every 3 weeks, as a second-line therapy in doxorubicin-treated patients. The overall response rate was 50% (CR, 22%). The dose-limiting toxicity was Grade 4 neutropenia. In addition, in a Phase II study, Vici et al.[77] treated 41 examinable patients with metastatic breast carcinoma with the combination of vinorelbine 25 mg/m^2 and paclitaxel 150 mg/m^2 by simultaneous intravenous 3-hour infusion, with cycles repeated every 3 weeks. Granulocyte colony-stimulating factor, 300 μg subcutaneously, was given on Days 7–12 to the first 10 patients only because severe neutropenia was uncommon. Grade 4 neutropenia or neutropenic fever was encountered in 21% and 7% of the patients, respectively. The overall response rate was 49% (CR, 5%).

This study sought to determine whether vinorelbine and paclitaxel could be given simultaneously and still be well tolerated by the patients. The recommended dose for this combination without the use of G-CSF was 25 mg/m^2 of vinorelbine and 150 mg/m^2 of paclitaxel given simultaneously over 3 hours every 21 days. The dose-limiting toxicity was neutropenic fever and myalgia. Of note, all the patients who experienced Grade 3–4 pelvic pain received paclitaxel at 175 mg/m^2. Upon reducing the paclitaxel dose to 150 mg/m^2 and throughout the study thereafter, no incidence of pelvic pain was encountered, allowing the increase of the vinorelbine dose. The addition of G-CSF prophylactically to dose-intensify vinorelbine helped in achieving a new MTD: vinorelbine 36 mg/m^2 and paclitaxel 150 mg/m^2 given simultaneously over 3 hours every 21 days. The dose-limiting toxic effects were fatigue and myalgia.

It is concluded that the combination of vinorelbine and paclitaxel without or with G-CSF is a well tolerated regimen at the recommended doses and is biologically active in patients with metastatic breast carcinoma, whereas the synergistic effect was not apparent in this study. Phase I studies, however, are not intended to assess responses. Therefore, Phase II studies are warranted to assess the response rates and to explore the probable synergistic activity of combined vinorelbine and paclitaxel as suggested by in vivo studies.

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