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Two weekly vinorelbine: administration in patients who have received at least two prior chemotherapy regimes for advanced breast cancer

D.I. Udom, D.M. Vigushin, H. Linardou, H. Graham, C. Palmieri, R.C. Coombes*

Department of Cancer Medicine, Division of Medicine, Imperial College School of Medicine, Charing Cross Hospital, London W6 8RF, UK

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Abstract

This study examined the response to and toxicity of two weekly vinorelbine administrations in patients with at least two prior chemotherapeutic treatments for advanced breast cancer. This single centre study enrolled 20 patients, 19 of whom had received prior taxane treatment for advanced breast cancer. Taxane treatment was in the form of docetaxel for all but 1 patient who had received paclitaxel. All patients had received two or more prior chemotherapeutic regimes for advanced breast carcinoma, including anthracyclines (epirubicin) in 19 patients. Vinorelbine 25 mg/m^2 two weekly was given for 6 months, until disease progression or toxicity precluded further treatment. 5 earlier studied patients started vinorelbine at 25 mg/m^2/week; all changed to the two weekly schedule, limiting the incidence and severity of neutropenia. 7 partial responses (PRs) out of 20 assessable patients (35% overall response rate, 95% confidence interval 15–59%) were noted, all PRs occurring in taxane pretreated patients. The median duration of response was 4 months whilst the median time to progression was 2.75 months. Overall, there were 7 neutropenic events (35%) of 2 week median duration, spanning common toxicity criteria (CTC) grades 1–3 in severity. 5 neutropenia cases (25%) occurred in patients whilst on two weekly vinorelbine. 2 cases (10%) required granulocyte colony stimulating factor support, 1 having had febrile neutropenia (52%). One case of thrombocytopenia, neurotoxicity and nausea (each CTC grade 1) were recorded. Although this study involves a small number of cases, these preliminary results suggest that two weekly vinorelbine is effective in heavily pretreated (including taxane pretreated) advanced breast carcinoma. Response is comparable with that of traditionally used weekly regimes, with markedly less toxicity.

Keywords: Vinorelbine; Breast cancer; Metastatic disease; Chemotherapy; Palliation; Systemic therapy

1. Introduction

Metastatic breast cancer poses a challenging therapeutic dilemma; conventional treatment schedules result in disappointingly short periods of disease remission, with adverse effects being the rule rather than the exception. Much research is focused on the discovery of agents that produce a significant clinical response even in the face of heavy pretreatment, and preferably with minimally debilitating side-effects.

Vinorelbine (5′ noranhydrovinblastine) is a semi-synthetic analogue of vinblastine, a member of the *catharanthus* vinca alkaloid family. It exerts its antineoplastic effect by molecular binding to tubulin, forming a tubulin dimer and hence preventing its polymerisation at the G2 and M phases of the tumour cell cycle; this leads to mitotic arrest at metaphase, cytostasis and cell death [1,2]. It preferentially binds mitotic over axonal microtubules (except at high concentrations), making it less neurotoxic than other vinca alkaloids [1]. Its microtubular binding sites differ from those of the taxanes, a property that makes it useful in tumour cells resistant to this drug type [2,3].

The antitumour activity of vinorelbine has been well documented against a large number of experimental murine and human tumours, including human tumour xenografts in nude mice [4]; synergistic activity has also been demonstrated with docetaxel [5] and in a more recent study, medroxyprogesterone acetate [6]. Phase I

* Correspondence to R.C. Coombes.
E-mail address: c.coombes@ic.ac.uk (R.C. Coombes).

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and II trials have demonstrated a clear-cut clinical response to weekly intravenous (i.v.) vinorelbine, either alone or as combination chemotherapy, in both pretreated and non-treated cases of metastatic breast cancer, with generally acceptable side-effects. A clinical response rates of 16–60% was seen with vinorelbine as a single agent, 28–77% in combination chemotherapy [7–12]. Its dose-limiting toxicity is neutropenia, which is short-lived and non-cumulative [13], with neurotoxicity being mild at the maximum tolerated dose [14]. Promising studies evaluating the place of oral vinorelbine in cancer management are still ongoing [15–17].

Previously published research protocols utilised a weekly regime of vinorelbine when administered as monotherapy and many of these patients require GCSF support; very few of these studies have looked at vinorelbine as salvage treatment, especially in taxane-resistant MBC. We, therefore, undertook a single centre study, evaluating predominantly two weekly vinorelbine administration in this advanced setting.

2. Patients and methods

2.1. Patient selection

The patients entered into this study attended the Department of Medical Oncology, Charing Cross Hospital, London, between 8 September 1997 and 12 October 1998. All patients with advanced breast cancer who had received two or more prior chemotherapeutic regimes, including those who had been treated with a taxane (paclitaxel or docetaxel), with or without hormonal manipulation were included. All patients gave informed written consent to receiving vinorelbine treatment. Oestrogen and progesterone receptor status, WHO performance status, types of metastasis and the number of previous treatment modalities were ascertained where possible — these, along with other demographic data are summarised in Table 1.

2.2. Treatment

All patients received i.v. vinorelbine at a dose of 25 mg/m^2 in 250 ml of normal saline over 1 h, administered two weekly (every 2 weeks). 5 patients (earlier accrued cases) changed from a weekly to a fortnightly schedule, to reduce the unacceptably high incidence of neutropenia. Dose reductions of 15–33% were instituted in patients at high risk of bone marrow suppression, i.e. those with neutropenia and/or thrombocytopenia on vinorelbine administration despite 2 weekly regime, poor marrow reserve from previous high-dose chemotherapy, severe prolonged neutropenia with previous chemotherapies, poor WHO performance status (3–4), or various combinations of these poor prognosticators. One patient had a 50% dose reduction due to a combination of poor marrow reserve, severe bone marrow suppression with previous chemotherapy and a poor WHO performance status. The duration of vinorelbine treatment was either for 6 months, until observed disease progression, or until toxicity precluded further treatment.

2.3. Assessment of response

Baseline measurements of metastatic lesions were evaluated by clinical examination and radiographic imaging techniques, prior to the commencement of vinorelbine therapy. Evaluations were made pretreatment, midtreatment (i.e. after at least 4 weeks of vinorelbine treatment), and at the end of therapy. Response was evaluated using Standard Union Internationale Contre le Cancer (UICC) response criteria [18]. Complete response (CR) was defined as resolution of all detectable disease for at least 4 weeks; partial response (PR) as $\geq$50% reduction in tumour size, as determined by two measurements of tumour diameter, or the product of two perpendicular diameters where applicable, at least 4 weeks apart. No change (NC) was defined as $<$50% tumour regression or $<$25% progression, and progressive disease (PD) as $\geq$25% increase in tumour measurements. Response duration was defined as the time from the date of vinorelbine treatment commence-

Table 1
Patient characteristics

n of patients treated	20
Assessable for response	20
Assessable for toxicity	20
Age	
Median (range)	47 (23–71) years
WHO Performance status	
0	3
1	2
2	7
3	5
4	0
Unknown	3
Oestrogen and progesterone receptor status	
Positive	8
Negative	9
Unknown	3
Sites of disease	
Loco-regional	11
Bone	9
Visceral	14
No. of disease sites	
1	7
2	10
$>$2	3
No. of treatments (previous)	
2	12
3	5
4	3
Hormonal treatment	17

ment to the documented date of progression for responding patients. Time to progression (TTP) was defined as the time from the date of vinorelbine treatment commencement to the documented date of progression for all patients.

2.4. Toxicity

Toxicity was evaluated utilising the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) [18].

3. Results

3.1. Patient characteristics

20 patients aged 23–71 years (median age 47 years) were studied (Table 1). 19 patients had received prior taxane chemotherapy for metastatic and/or locally advanced disease; this was in the form of docetaxel for all but 1 patient who had received paclitaxel. The same number had been treated with an anthracycline (epirubicin)-containing regime in this setting. 3 patients (pts 5, 14, 17; see Table 2) were evaluated as having locally advanced disease with anthracycline resistance, having had early metastasis (within 18 months or less) after a high-dose, anthracycline-containing adjuvant regime modified from that of Antman and colleagues [19] — 5-fluorouracil 600 mg/m^2, epirubicin 50 mg/m^2 and cyclophosphamide 600 mg/m^2 every 4 weeks on a day 1 and 8 schedule, omitting epirubicin on day 8 for a total of three cycles, followed by cyclophosphamide 1.5 mg/m^2, thiotepa 125 mg/m^2 and carboplatin 200 mg/m^2 daily for 4 days, with peripheral stem cell collection and reinfusion pre- and postcarboplatin, thiotepa and high-dose cyclophosphamide therapy, respectively (FEC–CCT regime); these patients were not retreated with anthracyclines for metastatic disease. Anthracycline resistance, therefore, was defined either as early metastasis following adjuvant high-dose treatment with an epirubicin-containing regime or no response to an epirubicin-containing regime administered for locally advanced/metastatic disease.

The number of prior chemotherapeutic treatments ranged from 2 to 4 (median 2, mean 3). 15 patients received two weekly vinorelbine over the entire course of treatment. 5 patients were changed to a two weekly vinorelbine schedule after 2, 4, 5, 14 and 15 weekly

Table 2
Previous chemotherapy and response of vinorelbine treated cases

Patient	Age (years)	Adjuvant chemotherapy	Chemotherapy for metastatic/locally advanced disease								Response to vinorelbine and duration (months)
			First-line	R	Second-line	R	Third-line	R	Fourth-line	R	
1	23	FEC	FEC	PD	DOC	PD					PD
2	35	CMF	MMM[a]	PD	FEC	PD	DOC	PR			PD
3	37	NIL	PAC[a]	PR	MM	PD	FEC	PR	DOC	PD	PD
4	38	NIL	FEC[a]	NC	DOC	PD					PR (2 1/2)
5	39	FEC + CTT	DOC	PD							PD
6	40	CMF	FEC + CCT	CR, PR	DOC	PD					PD
7	40	NIL	ECF[a]	NC	DOC	PD					PR (5 1/2)
8	40	NIL	ECF[a]	PR	MM	NA	FEC	NC	DOC	PR	PD
9	40	NIL	MMM/MM[a]	PR	FEC	PR	FEC	PR	DOC	PR	NC[b] (2)
10	42	FEC	FEC	PR	DOC	PR					PR[b] (4)
11	45	FEC	CMF	PD	PAC	PR					PR (3)
12	46	FEC	DOC	PD	MMM/MM	PD					NA
13	55	CMF	FEC	PR	DOC	NC					PD
14	57	FEC + CCT	DOC	NC							NC (2)
15	57	NIL	CMF	PR	MMM	PD	DOC	PR			PR (7)
16	59	NIL	CMF	PR	DOC	NC	EPI	NC			NC[b] (2 1/2)
17	62	FEC + CCT	DOC	NC							PR[b] (2 1/2)
18	63	NIL	CMF	NC	EPI	PR					PD
19	68	NIL	CMF	PR	EPI	PD	DOC	PD			PD
20	71	NIL	CMF	NC	EPI	PR	DOC	PR			PR[b] 1/2

[a] Neoadjuvant therapy.
[b] Still on vinorelbine therapy.

NA, not assessable by UICC criteria; CMF, cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, 5-fluorouracil 600 mg/m^2 4 weekly on a day 1 and 8 schedule, omitting methotrexate from day 8; FEC, 5-fluorouracil 600 mg/m^2, epirubicin 50 mg/m^2 and cyclophosphamide 600 mg/m^2 4 weekly on a day 1 and 8 schedule, omitting epirubicin from day 8; EPI, epirubicin 75 mg/m^2 3 weekly; DOC, docetaxel 100 mg/m^2 3 weekly; PAC, paclitaxel 175 mg/m^2 3 weekly; MMM, mitoxantrone 6.5 mg/m^2, methotrexate 30 mg/m^2 and mitomycin C 6.5 mg/m^2 3 weekly; MM, MMM minus mitomycin C; MMM/MM, MMM alternating with MM 3 weekly; FEC–CCT, FEC×3 cycles followed by cyclophosphamide 1.5 mg/m^2 and carboplatin 200 mg/m^2 thiotepa 125 mg/m^2 daily for 4 days with peripheral stem cell collection and reinfusion pre- and postCCT therapy, respectively; NIL, no treatment; R, response.

courses of vinorelbine administration; they received fortnightly treatments for a total of 4, 10, 12, 4 and 4 weeks, respectively. None of the patients studied received palliative radiotherapy to a site of assessed metastatic or locally advanced disease immediately prior to, or during the period of vinorelbine administration.

3.2. Response

There were 4 PRs out of 15 assessable patients treated exclusively with fortnightly vinorelbine (27%), and 3 cases of NC (20%). 3 PRs (60%) and no NCs were recorded in the 5 patients initially treated with weekly vinorelbine; these partial responses continued for 12, 4 and 4 weeks after changing to the two weekly regime. In all, 7 PRs (35% overall response rate: 95% confidence interval 15–59%) and 3 NCs (15%) were seen in the 20 patients with assessable disease for between 2 and 7 months (Tables 2 and 3). One case had non-assessable disease using UICC criteria, although clinical notes indicated a marked reduction in brawny lymphoedema of the arm, and significant symptomatic relief on vinorelbine therapy. This patient had been refractory to previously administered taxane and anthracycline chemotherapy. No CRs were noted.

In specific sub-analysis of taxane pretreated patients (Tables 2 and 3), 4 PRs (29%) and 3 NCs (21%) were observed in the exclusively two weekly treated group ($n=14$). There were 3 PRs (60%) and no NCs in those cases started on weekly vinorelbine, making a total of 7 PRs (37%) and 3 NCs (16%) in all taxane-pretreated patients ($n=19$). The corresponding figures for the anthracycline-pretreated cases ($n=19$) were 6 PRs and 3 NCs (32% and 16% respectively), of which 4 PRs (29%) and 3 NCs (21%) occurred in patients ($n=14$) on two weekly vinorelbine for the entire course of their treatment. 8 patients overall had taxane resistant disease. 2 PRs (25%) on vinorelbine were recorded in this subgroup; 1 of these patients continued to respond for up to 12 weeks after changing to a two weekly schedule of vinorelbine administration, with the other treated on the fortnightly regime from the start. A similar sub-analysis yielded 2 partial responders out of 8 anthracycline refractory patients (25% response rate). NC was not seen in either taxane- or anthracycline-resistant subgroups.

Of the 3 patients studied who had early metastasis on the high-dose (FEC–CCT) regime, 1 achieved a PR, another disease stabilisation and the third failed to respond on vinorelbine therapy. This last patient had been refractory to all previously administered chemotherapeutic regimes. In all, 3 patients were universally resistant to all prior treatments (pts 1, 5, 12); none of these patients had an assessable response to vinorelbine.

Regarding sites of disease involvement, 4 of 11 patients with loco-regional disease (36%), 5 of 14 with visceral disease (36%) and 2 of 9 patients with bony metastases (22%) had a partial response to vinorelbine therapy; 1 (9%), 3 (21%) and 2 (22%) of these cases had NC, respectively. 4 PRs (57%) and 1 NC (14%) were noted in 7 patients who had a single site of tumour involvement. In the 13 patients with two or more sites of disease involvement, there were 3 PRs (23%) and 2 NCs (15%).

Overall response duration ranged from 2.5 to 7 months (median 4 months, mean 4.3 months). In the exclusively two weekly treatment group, response duration ranged from 2.5 to 5.5 months (median 3.3 months, mean 3.6 months) 3 PRs and 2 NCs were still receiving vinorelbine treatment at the time of this analysis. TTP ranged from 0.5 to 7 months (median 2.75, mean 3.075 months).

3.3. Toxicity

There were seven neutropenic events (35%) spanning CTC grades 1–3 in severity. 4 of these were in the exclusively two weekly treatment group (toxicity rate 27%). The remaining neutropenic episodes occurred in the 5 patients started on weekly vinorelbine, low counts developing in all cases whilst still on weekly treatments. Only 1 case of neutropenia overlapped from the weekly to the two weekly vinorelbine schedule; this patient had been pretreated with FEC–CCT and docetaxel regimes and was the most protracted, lasting a total of 5 weeks. Overall, neutropenia duration ranged from 1 to 5 weeks (median 2 weeks, mean 2.1 weeks), with all but one case having neutropenia for 2 weeks or less. Only 2 patients required GCSF support. Only a single patient had short lived febrile neutropenia and required GCSF. She was from the exclusive two weekly vinorelbine group; the

Table 3
Summary of response and disease stabilisation on vinorelbine treatment is relative to prior chemotherapy

	All patients ($n=20$)	Taxane pretreated ($n=19$)	Anthracycline pretreated ($n=19$)	Taxane resistant ($n=8$)	Anthracycline resistant ($n=8$)	Pan-resistant to previous chemotherapy ($n=3$)
n of responses (%)	7 (35)	7 (37)	6 (32)	2 (25)	2 (25)	0 (0)
n of disease stabilisations (%)	3 (15)	3 (16)	3 (16)	0 (0)	0 (0)	0 (0)

Table 4
Summary of neutropenic events on vinorelbine treatment

	All patients	Weekly vinorelbine	Two weekly vinorelbine	Prior FEC–CCT chemotherapy
n of patients	20	5	20	4
n of neutropenic cases (%)	7 (35)	3 (60)	5 (25)[a]	3 (75)

[a] One case of neutropenia overlap from weekly to two weekly vinorelbine administration.

other patient requiring GCSF was our most protracted neutropenic patient, already discussed above. Table 4 summarises neutropenia according to the various subgroups.

Other toxic events were mild, with 6 local venous reactions (30%) (3 cases of painless erythema along the venous site of vinorelbine administration, in addition to 3 cases of CTC grade 2 thrombophlebitis), and 1 case respectively of thrombocytopenia, neurotoxicity and nausea (15%) (each CTC Grade 1). Overall, none of the toxicities was life-threatening, nor did any treatments have to be discontinued on account of adverse effects.

9 patients (45%) had vinorelbine dose modifications, with 4 PRs (44%) and 2 NCs (22%) in this group. Only 2 patients (10%) developed neutropenia following initial dose reductions — one had the longest duration of neutropenia, and the other CTC grade 1 neutropenia, of 1 week duration, that did not necessitate further dose schedule adjustments.

4. Discussion

In recent years, several clinical trials have demonstrated the activity of single-agent vinorelbine in advanced breast carcinoma, showing its efficacy as first-line and more recently, second- and third-line treatment for advanced disease [7–12]. Our study examined the response to single-agent vinorelbine in a select group of patients, all of whom had received at least two prior chemotherapeutic regimes for advanced breast cancer, or had received recent intensive therapy. All cases but 1 had received taxanes. Livingston and colleagues [20] examined vinorelbine activity in taxane pretreated patients in this advanced setting, the only other study to do so. In their study, vinorelbine was given weekly with concurrent GCSF to deliver higher dose intensity; comparatively more non-neutrophil related toxic effects were observed [20]. Our analysis evaluated the response to predominantly two weekly vinorelbine administration in taxane pretreated patients, without G-CSF in the treatment protocol.

The total number of patients studied is relatively small; nevertheless, several interesting trends emerged during data analysis. The overall response rate of 35% is comparable with prior vinorelbine salvage therapy studies — 16 to 40% from pooled data [7–9,20–23]. The response duration that we obtained was also similar with a median of 4 months, with 3 PRs and 2 NCs still on vinorelbine treatment. This was an encouraging response, given that a significant number of our patients had received three or more chemotherapy treatments prior to vinorelbine therapy. The two weekly dosing schedule was generally less toxic and more convenient to administer, implying though not confirming comparable efficacy, even when individually determined dose reductions were instituted.

Indeed, more than half the partial responders, and all the cases of stable disease were patients started on the two weekly treatment protocol (see Table 3) with 4 PR (57%) and 2 NC (67%) occurring in patients with treatment modifications. A probable explanation is the more regular vinorelbine delivery: two weekly administration with or without individualised treatment reductions enables a smooth, uninterrupted schedule of treatment in almost all affected cases, albeit at a lower dose than is customarily used. The two weekly vinorelbine schedule, with dose reductions based on specifically predetermined poor prognostic indicators is, therefore, probably the chosen method of vinorelbine administration with patient, administrative and cost benefits.

Several studies using other chemotherapeutic agents in the salvage therapy of advanced breast cancer show response rates similar to those of vinorelbine, but worse toxicity profiles [24]. Our analysis supports vinorelbine as one of the least toxic agents in this setting. No CTC grade 4 toxicities were observed, and haematological adverse effects were easy to reverse. It is somewhat surprising that granulocyte toxicity was more severe, and more common, in the report by Livingston and colleagues [20] with grade 3 to 4 neutropenia reported in 58% of patients. We noticed this trend in our earlier studied cases, which prompted a change to the less toxic two weekly regime, so reducing the frequency of neutropenia by almost half (35%); although a randomised comparative analysis was not done, we believe this to be due to our treatment protocol.

25% of our taxane-resistant patients responded to vinorelbine. This lends clinical support to preclinical studies that show good vinorelbine activity in taxane-resistant tumour cell lines [3], and may provide a rationale for the sequence of administration of these two agents in advanced breast cancer treatment. A similar phenomenon has been observed in anthracycline refractory patients, confirming earlier studies [8,21,25]. 3 patients who were resistant to previous chemotherapeutic regimes were also resistant to vinorelbine, except for 1 case where clinical improvement could not be assessed using UICC criteria.

In summary, vinorelbine appears to have notable activity and low toxicity when given on a two weekly schedule, with or without predetermined dose reductions, for locally advanced and metastatic breast malignancy. With this relatively mild treatment regime, it is worthwhile evaluating its usefulness in the first-line treatment of metastatic breast carcinoma, or even as a part of adjuvant treatment postoperatively. Quality of life and survival issues were not addressed here; these may provide the focus of future research, further establishing vinorelbine's role in the management of difficult to treat locally advanced and metastatic breast cancer.

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