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ORIGINAL ARTICLE

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Reversibility of liver failure secondary to metastatic breast cancer by vinorelbine and cisplatin chemotherapy

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Abstract *Purpose*: The development of liver metastases from breast cancer is associated with a very poor prognosis, estimated at 4 months median survival. Since treatment with many chemotherapeutic agents is relatively contraindicated, we assessed the safety, tolerability and potential efficacy of combination chemotherapy with vinorelbine and cisplatin (ViP). *Method*: Pilot study in 11 patients with histologically confirmed breast carcinoma, radiological evidence of liver metastases and serum bilirubin greater than 1.5 times the upper limit of normal. Patients received up to six cycles of cisplatin (75 mg/m^2) every 21 days and vinorelbine (20 mg/m^2) on days 1 and 8 of every 21-day cycle. Measurement of liver lesions was performed on CT scan every 8 weeks into treatment. *Results*: The most frequently reported adverse event was myelosuppression. Other adverse effects included nausea, vomiting and mild neurotoxicity. Two patients died after one treatment with ViP, one of whom suffered an intracerebral haemorrhage that was possibly treatment-related. Improvement in liver function tests was observed in 10 patients, and mean time to normalization of bilirubin levels was 36 days. Partial responses were documented radiologically in 7 out of 11 patients treated. Median overall survival from trial entry was 6.5 months (range 11–364 days), with one patient alive 13 months from trial entry. *Conclusion*: Normalization of liver function is possible with ViP treatment of metastatic breast cancer, offering the potential to prolong survival. Phase II clinical trials of this regimen in this patient group should include measurement of quality of life in order to assess risk versus benefit.

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Introduction

The development of liver metastases from breast cancer is associated with an appalling prognosis. In one retrospective study of 912 patients with breast cancer, 47 developed liver metastases and in this subgroup the median survival was 4 months, or shorter in the presence of jaundice [1]. It is well recognized that visceral metastases from breast cancer are generally less responsive to chemotherapy than metastases in soft tissue or bone [2]. In a patient with liver metastases from breast cancer, treatment is aimed at improving symptoms and perhaps lengthening life.

The two most active classes of cytotoxic agent for the treatment of breast cancer are currently anthracyclines and taxanes. Since taxanes are eliminated primarily as inactive metabolites in bile and feces, current recommendations advise against the use of taxanes in patients whose serum bilirubin level is above the upper limit of normal [3, 4]. Significant dose reductions are advocated for patients with normal serum bilirubin levels whose liver function tests are more than 1.5 times the upper limit of normal [3, 4]. Dose modification of anthracyclines is also necessary in patients with hepatic dysfunction [4].

Vinorelbine is a second-generation semisynthetic vinca alkaloid that exhibits clinical activity in the treatment of lung cancer, breast cancer and lymphoma. In 1994, the US Food and Drug Administration approved its use in first-line treatment of non-small-cell lung cancer. In patients with this disease, response rates can be approximately doubled by combination treatment with cisplatin [5]. Clearance of cisplatin depends on irreversible tissue/protein binding and renal excretion, and is not influenced by hepatic function [4]. Similarly, mild or moderate liver impairment does not appear to necessitate

a reduction in the dose of vinorelbine administered [6], despite hepatic metabolism constituting its main elimination pathway. In a study of 29 patients with advanced breast cancer receiving 30 mg/m^2 of vinorelbine by short intravenous infusion, clearance rate of the parent drug correlated with certain liver function tests, including a weak correlation with serum bilirubin level, and the clearance rate of the drug was significantly impaired only in patients with more than 75% of normal liver replaced by tumour, by radiological estimates [6].

In order to assess the safety, tolerability and potential efficacy of combination chemotherapy with vinorelbine and cisplatin (ViP) in patients with liver failure due to metastatic breast cancer, we performed a pilot study. The results provide evidence in favour of formal phase II development of this treatment regimen in this subject group.

Methods

Patients were recruited at the University Hospitals of Leicester NHS Trust. Written informed consent was obtained from all patients in accordance with local guidelines. Patients were considered eligible if they had histologically confirmed breast carcinoma with computed tomographic (CT) evidence of liver metastases and serum bilirubin greater than 1.5 times the upper limit of normal as defined by the hospital laboratory. Patients were also required to have: WHO performance score 0, 1 or 2; absolute neutrophil count $>1.5\times10^9$/l and platelet count $>100\times10^9$/l at screening; normal renal function; and minimum life expectancy of 8 weeks. Patients who were receiving any form of oestrogen receptor-modulating therapy or who had received radiotherapy or chemotherapy in the previous 4 weeks were not eligible. All patients were required to have CT or ultrasound scanning to exclude biliary tract obstruction within 4 weeks of commencement of chemotherapy.

Patients received 75 mg/m^2 of cisplatin every 21 days and 20 mg/m^{2}of vinorelbine on days 1 and 8 of every 21-day cycle. Doses were based on published phase I/II studies of ViP chemotherapy, in which cisplatin doses ranged from 60 to 100 mg/m^2 every 21 days and the doses of vinorelbine ranged from 20 to 35 mg/m^2 on days 1 and 8 of every 21-day cycle [7, 8, 9, 10, 11, 12]. The doses selected were at the lower end of these ranges on account of the documented potential for severe myelosuppression. The dose of vinorelbine was compatible with UK pharmacy guidelines for patients with >75% of the liver involved by tumour on CT [13]. Following prehydration, intravenous cisplatin was administered in 1000 ml 0.9% w/v sodium chloride solution over 2 h via a peripheral venous cannula, immediately followed by a 25-ml saline flush and then the dose of vinorelbine dissolved in 20 ml 0.9% w/v sodium chloride solution over 10 min. Physical examination, vital signs, body surface area calculation, biochemistry, haematology and adverse event assessments were performed prior to each dose of cisplatin. The use of myeloid colony-stimulatory factors was not permitted. Measurement of liver lesions was performed using RECIST criteria on CT scans every 8 weeks into treatment [14]. Patients continued to receive treatment to a maximum of six cycles or until they developed clinical or radiological evidence of progressive disease. Adverse events were graded by US NCI common toxicity criteria (version 2.0).

Results

Eleven patients were recruited, all female. Patient characteristics are shown in Table 1. Liver function tests at baseline and during treatment are shown in Fig. 1. In total, 42 cycles of treatment were administered (median per patient four cycles, range one to six cycles). Ten cycles of chemotherapy were delayed by 1 week. There were no dose modifications.

Table 1 Patient characteristics at baseline

	Arithmetic mean (range)	Number of patients ($n=11$)
Age (years)	60 (33–85)	
WHO performance status		
0		2
1		6
2		3
Sites of other metastases		
Lung		3
Bone		5
Soft tissues		2
Other		1
Liver volume replaced by cancer (%)[a]	16 (10–57)	
Oestrogen receptor-positive		6
Progesterone receptor-positive		5
HER-2 receptor-positive[b]		4
Prior chemotherapy[c]		
Anthracycline regimen (adjuvant)		7
Anthracycline regimen		4
Taxane		7
Other		2
Trastuzumab		4
Concomitant medications[d]		
Enzyme inhibitors		5
Enzyme inducers		2

[a]Estimated by radiologist from baseline CT scan
[b]Status not documented in four patients
[c]With palliative intent unless stated otherwise
[d]For the pharmacological relevance of cytochrome p450 enzymes, see reference 6

The most frequently reported adverse event was myelosuppression. Grade III neutropenia was recorded in four patients and grade IV neutropenia in four other patients. Grade II thrombocytopenia was noted in two patients and grade III thrombocytopenia in one patient. No platelet transfusions were deemed necessary. Six patients suffered from grade II anaemia requiring blood transfusion. Grade III vomiting occurred in one patient, and grade II in three patients (there were no in-patient admissions for nausea or vomiting). Grade I/II neurotoxicity was noted in two patients, both of whom had previously received taxane chemotherapy for metastatic breast cancer. Clinically relevant nephrotoxicity and cardiotoxicity did not occur in any patient, nor significant alopecia. Liver cirrhosis was noted on CT scan at 16 weeks into treatment in one patient who experienced a partial response with normalization of liver function tests.

Two patients died after one treatment with ViP. Both patients developed grade IV neutropenic sepsis and grade II thrombocytopenia, which responded well to supportive management. One patient suffered an intracerebral haemorrhage 11 days into the first cycle of

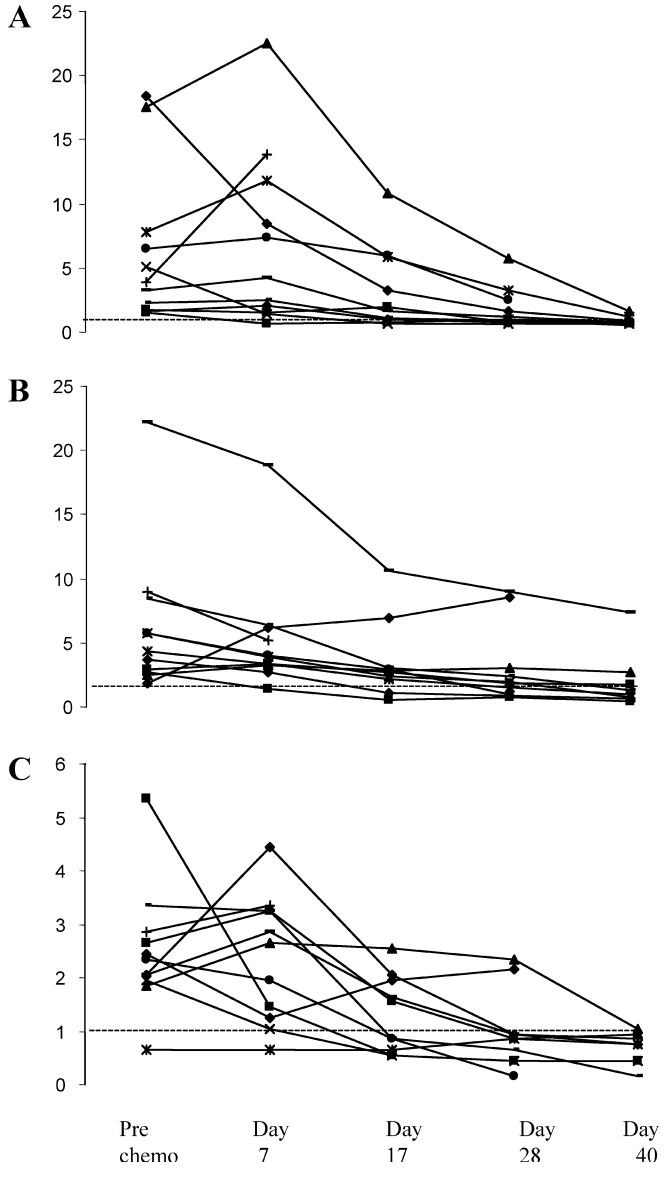

Fig. 1A–C Changes in liver function tests from start of treatment. Serum was taken up to 7 days pretreatment, and on days 7, 17, 28 and 40 from the first day of the first cycle of ViP chemotherapy. Values on the *y*-axes represent multiples of the upper limit of normal (ULN) as defined by the Chemical Pathology Department of the University Hospitals of Leicester; a value of 1.0 (*horizontal broken lines*) being equal to the ULN. **A** Total bilirubin (ULN 17 μmol/l), **B** alkaline phosphatase (ULN 130 U/l), **C** alanine transaminase levels (ULN 53 U/l). Each line represents an individual patient, showing a transient rise in all three indices in some patients on day 7, which was not representative of subsequent response

treatment, and the other patient continued to deteriorate generally and died 5 weeks after treatment.

As shown in Fig. 1, ten patients treated with ViP showed improvement in liver function tests. Mean times to normalization (as defined by our hospital laboratory—see Fig. 1 for absolute values) of serum bilirubin, alanine aminotransferase and alkaline phosphatase were 36, 19 and 51 days respectively (data from nine patients who received more than one cycle, except for alkaline phosphatase which normalized in six patients).

CT scans performed after 8 weeks of treatment showed a partial response in measurement of target liver lesions in five patients and stable disease in two patients. After six cycles of treatment, CT scanning showed a partial response in the two patients found to have stable disease on the first scan, and a continued partial response in three other patients. In total, partial responses were documented in 7 out of 11 patients treated. Response to treatment did not appear to be related to prior history with other chemotherapeutic agents.

One patient remained alive at the time of writing, 13 months after the first treatment with ViP. Median overall survival was 182+ days (range 11–364 days).

Discussion

The aim of this pilot study was to assess the safety of palliative chemotherapy in relatively young patients with severe hepatic dysfunction secondary to metastatic breast cancer. The results suggest that treatment with ViP is tolerable and relatively safe in this patient group, despite their liver failure. One death in the trial may possibly have been treatment-related, although the level of thrombocytopenia (see above) would not normally be considered sufficient to cause intracerebral haemorrhage. The incidence and severity of myelosuppression was equivalent to that observed in phase II studies of ViP in patients with metastatic breast cancer who did not have impairment of liver function [7, 8, 9, 10, 11, 12].

Moreover, the biochemical and radiological results suggest that the regimen tested may be highly efficacious in the treatment of patients with liver failure due to metastatic breast cancer. Five phase II studies of ViP chemotherapy in patients with metastatic breast cancer and normal hepatic function have documented objective response rates of 25–61% (arithmetic mean 46%), although doses and regimens varied between studies [7, 8, 9, 10, 11]. This efficacy is particularly valuable in the subject group used in the study presented here, since normalization of liver function may allow patients to proceed to treatment with other cytotoxic agents such as taxanes, which may significantly prolong survival and improve quality of life. Indeed, response rates in measurement of liver lesions for docetaxel as first-line or second-line treatment of metastatic breast cancer is similar to measurement of lesions in other organs, assuming liver impairment does not necessitate dose reduction [2].

The UK National Institute for Clinical Excellence (NICE) has stated that the routine use of vinorelbine in combination with other chemotherapy drugs cannot be recommended on the basis of evidence currently available and that it should therefore be used as a single agent [14]. Documented response rates of breast cancer to single-agent treatment with vinorelbine or cisplatin are

15–50% or 5–15%, respectively [4]. Response rates to vinorelbine combination therapy as second-line treatment for breast cancer are quoted in the NICE report as ranging from 25 to 74%, although these data include combinations with taxanes or 5-fluorouracil [14]. In the palliative treatment of non-small-cell lung cancer, treatment with ViP appears to be more cost-effective than treatment with vinorelbine alone since response rates are considerably higher [15]. As stated in the NICE report, such data are not currently available for the treatment of metastatic breast cancer, although the high response rates demonstrated with ViP in this disease in some studies would suggest that pharmacological synergy may exist in vivo [8, 10].

Unfortunately, it was not feasible to incorporate measures of quality of life into this pilot study. Larger studies of this regimen in this patient group should include such measures in an attempt to assess the risk-benefit ratio for this palliative treatment. Since the patients who appeared to respond biochemically to the first cycle of chemotherapy appeared to do well overall (see Fig. 1), predictors of response should also be studied in future trials.

Patients with liver failure due to metastatic breast cancer are a group with an appalling prognosis in whom the decision to treat with chemotherapy is a difficult management decision. Since taxanes, anthracyclines and mitomycin C are relatively contraindicated in patients with liver impairment, treatment with single-agent epirubicin [16], oxaliplatin and 5-fluorouracil [17], capecitabine [18] or ViP may be considered. The toxicity, efficacy and palliative benefit of ViP should be studied in formal phase II trials, perhaps in comparison to platinum therapy alone, in order to obtain useful information for patients in this category upon which treatment decisions can be based.

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