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Phase II study of mitoxantrone for liver metastases from breast cancer

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Summary. Mitoxantrone was given to 19 patients with liver metastases from breast cancer and biochemical evidence of liver dysfunction. In all, 2 patients received the drug at a dose of 10 mg/m^2 on days 1 and 2 of the first course of treatment; 1 patient was given 9 mg/m^2 and 17 received 8 mg/m^2. Subsequent courses were given at a dose of 10 mg/m^2. Three patients (16%) showed a partial response, with time to progression of between 3 and 7 months. Toxicity was considerable, with myelosuppression being the major problem.

Introduction

Liver metastases are common in advanced breast cancer and are associated with a poor prognosis [2]. Most patients have biochemical evidence of liver dysfunction at diagnosis of liver metastases and in this group the outlook is even worse (O'Reilly et al., in preparation). Doxorubicin, the most effective single agent in the treatment of advanced breast cancer [7], cannot be given at the conventional dose to these patients because impaired hepatic drug clearance leads to excessive toxicity.

Mitoxantrone is an anthracenedione derivative with known activity in breast cancer [3]. In a multicentre European study of this drug, given at a dose of 14 mg/m^2 as first-line chemotherapy for advanced breast cancer, a response was seen in 12/19 (63%) patients with liver metastases and normal biochemistry; the treatment was well tolerated, with only mild alopecia and gastrointestinal toxicity [4]. This encouraging response rate prompted us to assess the role of mitoxantrone in the treatment of patients with liver dysfunction, in whom the toxicity of treatment should be mild and not detract from the quality of their lives.

Patients and methods

Eligible patients had histologically proven breast cancer and were less than 70 years old. Liver metastases were present in all, diagnosed on the basis of an abnormal liver radionuclide or ultrasonographic scan, with or without hepatomegaly. All patients had a bilirubin count of >20 μmol/l (normal, <17) and/or aspartate transaminase (AST) levels of >70 IU/l (normal, <35) as well as adequate bone marrow function (leucocytes, $>3.0\times10^9$/l; platelets, $>70\times10^9$/l). Two patients had previously undergone chemotherapy for metastatic disease; in neither case was an anthracycline used and in both treatment had been stopped for >4 weeks. Patients with evidence of current or previous cardiac disease were ineligible for the study.

For the first course of treatment, two patients received 10 mg/m^2 mitoxantrone given as an intravenous infusion in 100 ml 5% dextrose over 30 min, one was treated at 9 mg/m^2, and the remainder received 8 mg/m^2 on days 1 and 2. The first course of treatment was given at a relatively high dose to maximise the probability of response, but doses of >8 mg/m^2 resulted in unacceptable toxicity. Treatment was repeated every 21 days at a dose of 10 mg/m^2 on day 1 only. Patients with leucocyte counts of $<4.0\times10^9$/l or platelet counts of $<120\times10^9$/l on day 21 had a 50% dose reduction for that course of treatment; in the event of leucocytes falling to $<2.0\times10^9$/l or platelets, to $<70\times10^9$/l, treatment was postponed until marrow recovery. The maximal cumulative dose of drug was 160 mg/m^2.

Clinical examination and serum biochemistry were repeated before each course of treatment. A liver scan was repeated at 6 weeks unless there was clinical evidence of progression. Response was assessed according to Union International Contra le Cancrum (UICC) criteria [5] and toxicity according to the WHO classification [6].

Results

A total of 19 patients were treated; their characteristics on entry to the study are listed in Table 1. No patient achieved a complete response. A partial response was seen in only 3/19 (16%) patients, with time to progression of 3, 4 and 7 months respectively. The disease remained stable for 3 months in two further patients. Progressive disease was seen in the remaining 14 patients. The median survival for the whole group was 7 weeks. Only one patient is currently alive, 23 months after diagnosis of liver metastases; she did not respond to mitoxantrone and was changed to norethisterone acetate.

Myelosuppression was the major toxicity (Table 2), with significant leucopenia (WHO grade 3 or 4) occurring in seven patients. Six of the seven episodes of leucopenia followed the first course of chemotherapy. Four patients

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Table 1. Patient characteristics on entry to the study

Patients (*n*)	19	
Age: median (range)	60 years (38–70)	
Disease duration (months):		
Median (range)	30	(6–181)
Sites of other metastases:		
Bone	16	
Soft tissue	12	
Lung	10	
Steroid receptor status:		
ER positive	7/8	
PR positive	6/8	
Prior therapy:		
Endocrine therapy	12	
Chemotherapy	2	
Bilirubin (μmol/l):		
Median (range)	13	(6–371)
AST (IU/l):		
Median (range)	152	(83–334)

Table 2. Toxicity

	Patients (*n*)
Myelosuppression:	
WBC $<2.0\times10^9$/l	7
Platelets $<50\times10^9$/l	2
Gastrointestinal toxicity:	
Vomiting >grade 2	5
Stomatitis	3

developed severe infections (one pneumonia, three septicaemias) while leucopenic, and one died. Another patient died of probable pulmonary embolism shortly after the first course of treatment. Two patients, both of whom had received treatment at 10 mg/m^2, had an episode of unexplained breathlessness following the first course of chemotherapy; in each case, the breathlessness resolved with symptomatic treatment. Five patients required treatment for chemotherapy-induced vomiting despite prophylactic metoclopramide.

Discussion

Mitoxantrone, given at maximum tolerable doses, gave a poor response rate in this group of patients (3/19; 16%). This is no better than the response seen in historical controls from this unit with a similar degree of liver dysfunction, who were treated with a combination of cyclophosphamide, methotrexate and 5-fluorouracil (O'Reilly et al., in preparation).

Despite our original aim, toxicity was considerable, with myelosuppression being the major problem. There are conflicting reports as to the effect of hepatic dysfunction on mitoxantrone clearance [1, 8]. Whereas patients with elevated bilirubin secondary to hepatocellular carcinoma tolerate mitoxantrone well, showing no excessive myelosuppression relative to patients with normal liver function [8], the same does not appear to hold true for breast cancer patients [1]. The myelosuppression seen in these patients may reflect the additional effect of bone marrow infiltration; the majority of our patients (Table 1) had both bone and liver metastases.

The treatment of patients with liver dysfunction is difficult, as active agents commonly used in advanced breast cancer are either metabolised in (cyclophosphamide) or cleared by (doxorubicin) the liver. Such patients are often excluded from clinical trials and treated on an empirical basis. Our approach involving initially aggressive treatment with mitoxantrone in an attempt to improve response without undue toxicity was not successful. We are currently assessing a different approach using weekly low-dose epirubicin, which is showing encouraging response rates and low toxicity [9].

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