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Treatment of patients with liver metastases

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The presence of liver metastases is considered a very poor prognostic factor for patients with metastatic breast cancer. Liver metastases are generally considered to be less responsive to chemotherapy than metastases in other sites, and patients with liver lesions have a shorter survival duration than patients with other sites of disease. The results from five multicentre phase II studies of docetaxel (Taxotere®) as a first-line treatment for metastatic breast cancer have been analysed with regard to the presence or absence of liver lesions, which were found in 39% of the 209 patients involved. Response rates to docetaxel, 100 or 75 mg/m², were maintained in the presence of liver lesions and the median survival across all five studies was 16.4 months for all patients and 14.7 months for patients with liver lesions. Similarly, when results from 129 patients given docetaxel as a second-line treatment were analysed, the response rates and survival durations were not reduced in the 57% of patients who had liver lesions. These results indicate that the presence of liver metastases does not reduce the probability or duration of response to docetaxel as a first- or second-line treatment for advanced breast cancer.

Keywords: Metastatic breast cancer, docetaxel (Taxotere®), liver metastases.

Introduction

Advanced breast cancer is a fatal disease, and treatment remains palliative in intent, but the prognosis for individual patients will vary according to well defined factors such as the presence of liver metastases. A high percentage of patients develop liver metastases at some point during the course of their disease and the presence of liver metastases is considered a very poor prognostic factor, reducing the average survival time from 10–24 months to 6 months from diagnosis.

The mainstay of treatment for hepatic involvement is chemotherapy. Hormonal treatments are rarely effective against liver metastases, which tend to be hormone receptor-negative. In the past, chemotherapy has been generally considered to be less effective against hepatic metastases than against metastases in lung, bone or other non-visceral sites.

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Responses of liver metastases to established chemotherapeutic agents

The percentage of patients with detectable liver metastases varies amongst studies, and the numbers are often small, making response rates in liver metastases difficult to compare between studies. In studies of first-line chemotherapy for metastatic breast cancer, doxorubicin has been reported to be active against liver metastases with a hepatic response rate of 60%, but the number of patients involved was only five [1]. Similarly, first-line epirubicin has also demonstrated activity against liver disease, with hepatic response rates of 40–80%, but these studies also involved only 5–10 patients [2]. In a larger study of patients with hepatic involvement [3] epirubicin treatment resulted in a response rate of 30% amongst 36 patients. The anthracenedione, mitoxantrone, has shown a lower first-line response rate against liver metastases, with a 16% response amongst 19 patients [4]. Edatrexate has shown a response rate of 34% (32 patients) [5] and carboplatin, a response rate of 20% (5 patients) [6] against visceral metastases. The response rate to vinorelbine has been reported to be 23% (39 patients) [7] and 28% (50 patients) [8], in liver metastases.

The response rates to chemotherapy decline with increasing numbers of regimens administered, and the second-line response rate to vinorelbine in patients previously treated with anthracyclines has been reported to be only 8% against liver metastases, and 16% overall [9]. The taxoid drug, paclitaxel (Taxol®), has shown a 45% response rate against liver metastases in anthracycline-resistant patients when infused over a 96-h period at a dose of 140 mg/m² [10], but only a 20% response rate against visceral metastases when infused over a 24-h period at doses of 135–150 mg/m² [11].

Combination chemotherapy usually produces better response rates than single agent therapy, and the response rates for first-line therapy with various combinations are summarized in Table 1. Response rates were not conspicuously reduced in patients with liver metastases, with the possible exception of fluorouracil-epirubicin-cyclophosphamide (FEC) treatment, and the response durations were 9–12 months with all combination chemotherapies.

Table 1. Combination chemotherapy as first-line treatment for metastatic breast cancer: response of liver metastases

Regimen	Number of patients	Response rate (%)
FEC [12]	117 (overall)	50
	38 (liver)	38
FAC [12]	113 (overall)	52
	32 (liver)	41
Vinorelbine + doxorubicin [13]	89 (overall)	74
	30 (liver)	50
Vinorelbine + 5-fluorouracil [14]	63 (overall)	67
	20 (liver)	60
Vinorelbine + mitoxantrone [15]	32 (overall)	56
	7 (liver)	50

FEC, fluorouracil-epirubicin-cyclophosphamide; FAC, fluorouracil-adriamycin-cyclophosphamide.

Responses of liver metastases to docetaxel therapy

Docetaxel (Taxotere®) has been investigated as a single agent in five phase II studies of first-line treatment of metastatic breast cancer. These studies involved a total of 209 patients, 188 of whom were evaluable for response. Liver lesions were confirmed in 73 (39%) evaluable patients. More than three organs were involved in metastatic disease in 38% of evaluable patients.

Response rates, which are summarized in Table 2, are grouped according to the starting dose of docetaxel, since some patients were treated at the reduced initial dose of 75 mg/m^2. Overall response rates, and hepatic response rates, were generally higher in patients given the recommended starting dose of 100 mg/m^2 than in those given the lower starting dose. The mean overall response rate for patients given the lower dose was 48%, and the hepatic response rate was 45%. When the recommended dose of 100 mg/m^2 was given, the mean overall response rate was 61%, and the hepatic response rate was 60%. The median response duration for the five phase II studies was 8.3 months in the overall patient population, and 7.2 months in patients with hepatic metastases. The median survival across all the studies was 16.4 months in the overall patient population, and 14.7 months in patients with liver metastases.

These results indicate that the presence of liver metastases does not reduce the probability or duration of response to docetaxel as a first-line treatment for metastatic breast cancer.

Overall response rates are usually lower in second-line treatments than in first-line treatments for metastatic disease, and the response to docetaxel, in patients with and without detectable liver metastases,

Table 2. Docetaxel therapy as first-line treatment for metastatic breast cancer: responses of liver metastases

Dose of docetaxel	Study	Number of evaluable patients	Response rate (%)
75 mg/m^2	NCIC [16]	15 (overall)	40
		11 (liver)	45
	EORTC	31 (overall)	52
	CSG2 [17]	9 (liver)	44
	Total	46 (overall)	48
		20 (liver)	45
100 mg/m^2	MSKCC [18]	34 (overall)	56
		10 (liver)	50
	NCIC [16]	32 (overall)	56
		14 (liver)	57
	EORTC	31 (overall)	68
	CSG1 [19]	16 (liver)	75
	EORTC	37 (overall)	68
	CSG3 [20]	13 (liver)	77
	Total	142 (overall)	61
		53 (liver)	60

NCIC, National Cancer Institute of Canada; MSKCC, Memorial Sloan-Kettering Cancer Center; EORTC, European Organization for Research and Treatment of Cancer; CSG, Clinical Screening Group.

has been studied in second-line treatment in several multicentre studies, all of which used an initial dose of docetaxel of 100 mg/m^2 [21–23]. One of these studies [23] recruited patients with metastatic breast cancer who had already received at least one chemotherapy regimen whereas the other three studies recruited only patients with evidence of anthracycline-resistant metastatic disease.

Out of 129 evaluable patients from these studies, 73 (57%) had liver metastases, 84% of these had multiple liver lesions and 52% had three or more organs involved in their disease. The responses to docetaxel, 100 mg/m^2, as second-line treatment are summarized in Table 3. The patients are divided into those who had not shown evidence of resistance to anthracyclines, and those whose disease was defined as anthracycline-resistant or anthracycline-refractory. The overall (61%) and hepatic (60%) response rates were higher in patients who had not shown evidence of anthracycline resistance than in patients who had anthracycline-resistant or refractory disease (47%, and 36%, for overall and hepatic response rates, respectively). The median response duration was 7.8 months for patients with liver metastases, and the median survival was 9 months. In the overall patient population, the response duration was 8.7 months for patients who did not show anthracycline-resistant disease, with a median survival of 11.5 months; and 6 months for patients with anthracycline-resistant or refractory disease, with a median survival of 10.4 months.

Table 3. Docetaxel therapy as second-line treatment for metastatic breast cancer: responses of liver metastases

Study	Number of evaluable patients	Response rate (%)
Not anthracycline-resistant		
EORTC–ECTG [23]	23 (overall)	61
	13 (liver)	85
Anthracycline-resistant		
MDA [22]	34 (overall)	53
	16 (liver)	44
UTSA [21]	35 (overall)	57
	12 (liver)	33
European multi-centre [24]	38 (overall)	32
	15 (liver)	14

MDA, MD Anderson Cancer Center; UTSA, University of Texas Health Science Center at San Antonio; EORTC-ECTG, European Organization for Research and Treatment of Cancer Early Clinical Trials Group.

Conclusion

These results indicate that the presence of liver metastases does not reduce the probability or duration of response to docetaxel in second-line treatment of patients with metastatic breast cancer.

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