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Docetaxel: a new defence in the management of breast cancer

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The results of nine phase II trials of docetaxel in the first- and second-line treatment of patients with advanced breast cancer are summarized. All 316 patients included in this report received docetaxel at a dose of 100 mg/m^2 administered over 1 h every 3 weeks on an outpatient basis. One hundred and fifty-four patients received docetaxel as first-line therapy for advanced disease, half of whom had received prior adjuvant chemotherapy (finished at least 1 year previously). An overall response rate of 59% (95% CI: 51–67) was achieved in these patients, with a median duration of response of 8.3 months and a median time to progression of 4.9 months. Similar results were seen in a subgroup of 68 patients with liver metastases. Among the 162 patients given docetaxel as second-line therapy, 134 had strictly defined anthracycline-resistant disease; 73 had liver metastases. The combined overall response rate for anthracycline-resistant patients in two US studies was 48% (95% CI: 37–59) while that in a multicenter French study was 29% (95% CI: 18–44). The median duration of response in each case was 6.3 and 5.5 months, respectively, with an overall median survival duration of 11 and 10 months, respectively. Among patients with liver metastases, second-line treatment with docetaxel achieved an overall response rate of 32%, a median duration of response of 7.8 months and a median survival duration of 9 months. These results for docetaxel as both first- and second-line therapy are comparable with those achieved with doxorubicin and are particularly promising in patients with liver metastases and anthracycline-resistant disease.

Introduction

Carcinoma of breast is the most common form of cancer in women in the US and the European Community. In 1994 it was estimated that 182,000 new cases of breast cancer would be diagnosed in the US and that 46,000 patients would die from advanced breast cancer.[1] Unfortunately, the adjuvant hormonal therapy and/or chemotherapy for operable breast cancer introduced over the last 20 years has not dramatically altered the natural history of this disease. Despite the development of more effective treatment regimens, in terms of response rates and disease-free survival, the improvements in long-term overall survival have been small.[2] Evaluation of patterns of first relapse indicates that adjuvant therapy with currently used hormonal treatment and chemotherapy has little impact on bone and visceral (including liver) metastases compared to that on local/regional and distant soft tissue sites.[2] This is probably a result of occult chemo- and hormone-insensitive micrometastases present even at the time of diagnosis.[3] Patients with liver metastases have a particularly poor prognosis.

A second major problem is the rapid development of drug resistance in a high proportion of patients. Resistance to doxorubicin is particularly important as it is generally considered to be the most active cytotoxic agent against advanced breast cancer.[4,5] The dramatic reduction in response rates after first-line chemotherapy is evidence of this problem. After failure of hormonal manipulation, first-line combination chemotherapy achieves response rates in the range of 60–70%.[6] In contrast, the response rate to second-line chemotherapy, even with doxorubicin, is only around 30%.[6,7] Nevertheless, this remains higher than the response rates seen with other available drugs (e.g. cyclophosphamide, fluorouracil, mitomycin C, methotrexate and melphalan), with the exception of paclitaxel, one of a separate class of cytotoxic agents, the taxoids.[6] Importantly, the response to paclitaxel does not seem to be markedly influenced by prior treatment with anthracyclines.[8] Docetaxel is a new, semisynthetic taxoid currently undergoing phase II studies in the first- and second-line treatment of breast cancer. In view of the problems with established forms of therapy for advanced disease, it is of particular interest to determine whether this new agent will have

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an impact on the natural history of patients with anthracycline-resistant breast cancer and those with liver metastases. The results of a series of these trials including such patients are presented below.

Methods

A total of 316 patients received docetaxel at a dose of 100 mg/m^2 administered intravenously over 1 h every 3 weeks on an outpatient basis. This population comprised 154 patients who were given docetaxel as first-line treatment for advanced disease in five phase II studies and 162 previously treated patients given docetaxel as second-line therapy in four phase II studies, including 134 who were resistant to anthracyclines. One hundred and forty-one of these patients (45%) presented with liver metastases. Other metastatic sites identified on histo/cytology included bone, skin, lung and nodes. The same entry criteria and methodology were applied in all studies. Most patients had progressive metastatic disease and all had at least one bi-dimensionally measurable lesion. WHO performance status ranged from 0 to 2 and all patients had to have adequate hematological, hepatic and renal function at enrolment. Responses (WHO criteria) were reviewed by an independent panel and analyzed on an intent-to-treat basis.

First-line treatment

Patients

Not all of the 154 patients who received docetaxel as first-line therapy for advanced disease were chemotherapy-naïve as half had received prior adjuvant chemotherapy. However, there had to be an interval of at least 1 year since completing the last adjuvant chemotherapy course in order to enrol in the docetaxel trials. There were 68 patients with liver metastases.

Results

In the 154 patients receiving docetaxel as first-line therapy for advanced breast cancer, an overall response rate (complete response [CR] plus partial response [PR]) of 59% was achieved, with a CR rate of 8.4% (95% CI: 51–67). Table 1 shows the findings for each individual group of investigators and illustrates the remarkable consistency of results observed across all the studies. Median duration of response was 8.3 months overall with a median time to progression of 4.9 months.

Table 1. Response rates in patients receiving docetaxel as first-line therapy for advanced breast cancer in five phase II studies

Institution	Patients *n*	CR *n*	PR *n*	CR+PR *n*
MSKCC	37	2	18	20 (54%)
NCI-C	35	2	17	19 (54%)
EORTC–CSG	34	5	17	22 (65%)
EORTC–CSG	11	2	3	5 (45%)
MSKCC	37	2	23	25 (68%)
Total	154	13 (8.4%)	78 (50.6%)	91 (59%)

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

Table 2. Efficacy of docetaxel in patients with advanced breast cancer and liver metastases: first- and second-line treatment results

	First-line (*n* = 68)	Second-line (*n* = 73)
Response rates		
Overall	54%	32%
Patients with measurable liver lesions	60%	36%
Median duration of response (months)	7.2	7.8
Median survival (months)	14.7	9

Among the 68 patients with liver metastases, an impressive response rate of 54% was recorded. Median duration of response was 7.2 months and median survival 14.7 months (Table 2).

Second-line treatment

Patients

One hundred and sixty-two patients who had previously received treatment for advanced breast cancer (including 134 with anthracycline-resistant disease) were enrolled in four multicenter studies (one in Europe, EORTC–ECTG, which did not focus on an-

Table 3. Characteristics of anthracycline-resistant patients

Institution	MDACC / UTHSC (n = 83)	Europe (Marty) [a] (n = 51)
Median age (years)	52	47
Karnofsky performance status 70–100	90%	88%
Visceral metastases	73%	67%
Liver	42%	43%
≥ 3 organs involved	48%	41%
Primary resistance	59%	59%
Anthracycline	40%	59%
Anthracenedione	19%	0%
Secondary resistance	37%	37%
Anthracycline	32%	37%
Anthracenedione	5%	0%
Not resistant	4%	4%

MDACC, M.D. Anderson Cancer Center, Texas; UTHSC, University of Texas Health and Science Center. [a] European multicenter trial coordinated by Professor Marty, Hôpital St. Louis, Paris, France.

thracycline-resistant patients, and three which specifically enrolled these patients, including poor-risk patients). Seventy-three of the 162 patients had liver metastases. About 50% of the patients had been heavily pretreated with both adjuvant chemotherapy and one or sometimes two chemotherapeutic regimens for metastatic disease.

Four patient subgroups were predefined for anthracycline resistance as follows: (1) patients with progressive disease (PD) as 'best response' on anthracycline therapy for advanced disease; (2) patients who relapsed while on adjuvant anthracycline therapy or within 6–12 months from the end; (3) patients with a CR or PR followed by PD while on anthracycline treatment for advanced disease; and (4) patients with no change followed by PD while receiving anthracycline therapy for advanced disease. Resistance was also defined as primary (refractory) (subgroups 1 and 2) or secondary (subgroups 3 and 4). Table 3 shows the characteristics of the 134 anthracycline-resistant patients.

Results

Response rates, median duration of response and time to progression for the 134 anthracycline-resistant patients are summarized in Table 4. The overall response rate was slightly higher in the two US studies (48.2%) than in the European study (29.4%). However, median durations of response were similar in each study, at around 6 months, as were median time to progression (in the region of 4 months) and median survival duration (10–11 months). Among the 73 patients with liver metastases, the results compared quite favorably with those for patients without liver involvement, with an overall response rate of 32% (36% in patients with measurable lesions), a median duration of response of 7.8 months and a median survival duration of 9 months (see Table 2).

Table 4. Results of docetaxel in anthracycline-resistant breast cancer patients with advanced disease: response rates, duration of response, time to progression, and survival

	MDACC / UTHSC (n = 83)		Europe (Marty) (n = 51)	
Complete response [a]	3	(3.6%)	0	(0%)
Partial response [a]	37	(44.6%)	15	(29.4%)
Complete + partial response [a]	40	(48.2%)	15	(29.4%)
Duration of response (from first infusion) [b]	6.3	(2–18)	5.5	(3+–8)
Time to progression [b]	4.4	(1–18)	3.7	(0.2–9+)
Survival [b]	11	(0.2–25+)	10	(0.2–11+)

[a] n (%); [b] months, median (range).

Table 5. Reasons for discontinuation of docetaxel therapy in 134 anthracycline-resistant patients treated for advanced breast cancer

	Patients n (%)
Toxic death	3 (2)
Neurotoxicity	7 (5)
Fluid retention	6 (5)
Asthenia	2 (1.5)
Infection	2 (1.5)
Combined toxicities	4 (3)
Total	24 (18)

Discontinuation due to toxicity

Of the 134 patients with anthracycline-resistant breast cancer, 24 (18%) discontinued treatment with docetaxel because of toxicity (Table 5).

Discussion

In an attempt to explain why the effects of adjuvant therapy on mortality rates are modest, the Interna-

tional Breast Cancer Study Group (IBCSG) evaluated patterns of first relapse occurring in five separate randomized trials of adjuvant systemic treatments.[2] All 2830 women included in the trials were node-positive and had undergone a total mastectomy and axillary clearance, but none had received radiotherapy. For evaluation of cumulative incidence of first relapse, patients were divided into those who had received 'more-effective' treatments (≥ 6 cycles of cyclophosphamide/methotrexate/fluorouracil/prednisone, with or without tamoxifen, or tamoxifen and prednisone alone) and those who had received 'less-effective' therapy (no treatment or a single cycle of chemotherapy). Three main categories of first site of relapse were defined as: (1) local/regional and distant soft tissue; (2) bone; and (3) viscera.

The more effective treatments were found to produce a 10-year cumulative relapse rate in local/regional and distant soft tissue sites of only 18% compared to 36% on the less-effective treatments (p = 0.0001).[2] In bone and viscera, however, the 10-year cumulative incidence of first relapse was similar on both types of treatment, irrespective of pre- or postmenopausal status and in patients with estrogen-receptor-positive or -negative tumors.[2] It appears, therefore, that currently used regimens of adjuvant chemotherapy have little impact on the occurrence of bone and visceral metastases. This finding is supported by earlier observations that adjuvant systemic treatments are more effective at preventing local and regional recurrences than those resulting from distant metastases.[9] Identification of new agents or therapeutic strategies with improved activity against bone and visceral micrometastases may therefore have a more significant effect on the prognosis of patients with primary breast cancer than that observed to date.

As indicated above, docetaxel as first-line therapy for advanced breast cancer achieves results that are very similar to those achieved in three trials of doxorubicin (at doses of 60–75 mg/m^2 every 3 weeks), in which overall response rates ranged from 50–57%, duration of response from 7.0 to 8.0 months and time to progression from 4.0 to 5.0 months.[4,10,11] These comparable results were achieved despite the fact that all the doxorubicin patients were chemotherapy-naïve while half of the docetaxel patients had previously received adjuvant therapy (including doxorubicin in some cases). Furthermore, the response to docetaxel in the patients with liver metastases was as good as the response seen in those without liver involvement.

In the second-line setting, the overall response rate to single-agent chemotherapy has been poor, with the best results seen in patients receiving doxorubicin or paclitaxel (Table 6).[6] The two subgroups of relapsing breast cancer patients with a particularly poor prognosis are (again) those who develop liver metastases, among whom median survival is only 9–10 months, and those who develop resistance to chemotherapy and particularly to doxorubicin.[6,7] According to the M.D. Anderson database, patients who have become resistant to doxorubicin have a median survival in the region of only 4 months (Hortobágyi, personal communication). The studies of docetaxel as second-line therapy reviewed above have indicated that its activity remains high even in poor-risk patients with resistance to anthracyclines and/or liver metastases. In particular, the high median survival duration justifies the initiation of randomized clinical trials of docetaxel vs other agents with activity in anthracycline-resistant breast cancer, such as paclitaxel. However, the optimum dose and schedule of paclitaxel have yet to be defined.

Table 6. Single-agent activity in the second-line management of patients with metastatic breast cancer

Drug	Years of publication	Patients (n)	CR+PR (%)
Doxorubicin (60–75 mg / m^2)	1974–1985	940	29
Doxorubicin (60–75 mg / m^2)	1985–1994	141	32
Paclitaxel (175 mg / m^2 / 3 h)	1993–1994	235	29
Cyclophosphamide	1959–1968	135	22
Melphalan	1965–1983	45	4
Fluorouracil	1961–1981	116	15
Methotrexate	1952–1981	134	17
Mitomycin C	1976–1985	307	22

Adapted from Henderson IC.[6]

The adverse effects of docetaxel have been problematic, with severe acute hypersensitivity reactions (AHRs), edema and skin toxicities in some cases. Nevertheless, progress is being made in the management of these toxicities. The EORTC Breast Cancer Study Group has convincingly demonstrated that oral pretreatment with a corticosteroid (32 mg methylprednisolone) significantly delays the onset of the fluid retention phenomenon.[12]

Conclusions

Docetaxel appears to be as effective as doxorubicin for the treatment of patients with advanced breast cancer, in both first- and second-line settings. Im-

portantly, its activity appears not to be influenced by prior therapy with anthracyclines or other agents and response rates are just as good in patients with liver metastases as in those without liver involvement. The toxic effects of docetaxel can largely be managed by prophylactic administration of corticosteroids. Randomized clinical trials comparing docetaxel with other agents in the setting of clinical resistance to anthracyclines should now be initiated.

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