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ORIGINAL ARTICLE

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A phase II study of the effectiveness of docetaxel (Taxotere) in women with advanced breast cancer previously treated with polychemotherapy

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Abstract *Purpose*: The aim was to study the effectiveness of docetaxel (Taxotere) in patients with advanced breast cancer treated previously with polychemotherapy. *Patients and methods*: Forty-nine patients received docetaxel (100 mg/m^2; 1-h i.v. infusion) and corticosteroid premedication. Forty-one patients who had received previous anthracycline treatment were divided into anthracycline-refractory and anthracycline-resistant (early and late) groups. *Results*: Of 45 evaluable patients, 66.7% had a partial response (PR) and 2.2% a complete response (CR), giving an overall response rate (ORR) of 68.9%. The ORR in anthracycline-refractory patients was 60% versus 82.6% in anthracycline-resistant patients; the difference was not significant. The ORR in early-resistance patients was 62.5% versus 93.4% in late-resistance patients ($0.05 < P < 0.1$). The median response duration and overall survival was 8 months (range, 4–23+ months) and 11.5 months (range, 4–31+ months), respectively, in 39 patients treated previously for metastatic disease. For 295 courses, grade 3/4 neutropenia developed in 28.6% of patients (12.5% of courses) and was febrile in 26.5% of patients (6.1% of courses), including one septic death. Hypersensitivity reactions (HSR) developed in 16.3% of patients, and fluid retention developed in 34.7% of patients (11.9% of courses). *Conclusions*: Docetaxel is an active second-line drug in advanced breast cancer. The time of relapse after cessation of anthracycline treatment may be a significant prognostic factor.

Key words Breast cancer · Anthracycline refractory disease · Docetaxel · Second-line chemotherapy

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Introduction

Second-line chemotherapy has been of limited value in the treatment of recurrent and progressive breast cancer, particularly after anthracycline failure [7, 11]. Recently, however, a new class of antineoplastic agents, the taxanes, has shown considerable activity against refractory breast cancer [9, 13, 16, 19]. The two taxanes currently available, docetaxel (Taxotere, Rhone-Poulenc Rorer, Antony, France) and paclitaxel (Taxol, Bristol-Myers Squibb, Princeton, NJ, USA), have a novel mechanism of action that enhances microtubule polymerization and inhibits microtubule depolymerization [16]. The resultant stable nonfunctional microtubule bundles disrupt mitosis and replication in cancerous cells [13]. Docetaxel is more potent than paclitaxel in stabilizing microtubules, promoting tubulin assembly, and inhibiting microtubule depolymerization [6]. This study investigated the effectiveness of docetaxel in a well-characterized group of patients with advanced breast cancer previously treated with polychemotherapy. In particular, the impact of relapse interval on the response to docetaxel was assessed by analyzing subgroups of patients in whom anthracycline treatment had failed (defined as refractory, early-resistance, or late-resistance patients according to the time of the relapse).

Patients and methods

Patients

Patients aged between 18 and 75 years with a confirmed diagnosis of carcinoma of the breast who had relapsed after previous expo-

sure to combined adjuvant or palliative chemotherapy were eligible. No more than one previous palliative chemotherapeutic regimen was permitted for each patient. A World Health Organization (WHO) performance status of 2 (or less) and a life expectancy of 3 months or more were also required. Other eligibility criteria included an absolute neutrophil count (ANC) of 2000/mm^3 or more, a platelet count of 100,000/mm^3 or more, and normal liver and renal function tests. Patients with brain or leptomeningeal metastases or other malignancies were excluded.

Patients who progressed while receiving anthracycline therapy or showed disease progression less than 2 months after discontinuing treatment were characterized as *anthracycline refractory*. Patients who relapsed more than 2 months after treatment cessation were characterized as *anthracycline resistant*.

Anthracycline-resistant patients were further divided into two subgroups: those who relapsed between 2 and 6 months after the cessation of anthracycline therapy (*early-resistance* patients) and those who relapsed 6 months or more after cessation (*late-resistance* patients).

The study was conducted in accordance with the Declaration of Helsinki and approved by the ethics committees of the participating centers. Informed consent was obtained from all patients before study entry.

Study design

This was a multicenter, open, nonrandomized phase II clinical trial. Docetaxel (100 mg/m^2) was administered intravenously over 1 h every 3 weeks. If the ANC was less than 1500/mm^3 on day 21, the docetaxel dose was reduced by 25% in the next cycle. Unless early disease progression (defined as progression in the first 6 weeks) was observed, three courses of treatment were given before the first response evaluation. The second evaluation was performed after the sixth treatment cycle. Patients with a partial response at that time were given a total of nine courses.

Antiemetic therapy was permitted at the discretion of the investigators, and all patients received consistent corticosteroid premedication. Primary prophylaxis with colony-stimulating factors was not allowed; however, secondary prophylaxis was given when febrile neutropenia (ANC < 500/mm^3 and fever with temperature $\geq$38.5 °C) developed between chemotherapeutic cycles or when an ANC of less than 1500/mm^3 persisted beyond 28 days.

Grade 2 or lower were treated symptomatically, and docetaxel could be readministered. In the event of grade 3 or higher HSR or grade 3 or higher skin reactions or neurosensory toxicity, docetaxel was discontinued. Fluid retention was treated with diuretics and/or corticosteroids at the discretion of the investigator.

Study assessments

Patients who received a minimum of two cycles of docetaxel and patients with early progression were evaluable for response. Response to chemotherapy was assessed using the WHO criteria. Duration of CR was measured from their first documentation, and duration of PR was measured from the beginning of treatment until the start of progression. Adverse events were classified according to the National Cancer Institute (NCI) Common Toxicity Criteria. Response to chemotherapy and assessment of toxicity was performed by mutual cross-evaluation of patients' data by the heads of the three medical departments involved in the study. No extramural review of the responses was performed.

Statistical analysis

All comparisons between patient groups were performed using the chi-squared test. Response duration and survival curves were calculated using the Kaplan-Meier method. Response duration and survival curves between anthracycline-refractory and anthracycline-resistant patients were compared using log-rank analysis.

Results

Patient disposition and characteristics

Forty-nine patients with a median age of 60 years (range, 30–70 years) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 entered the study, of whom 45 were evaluable for response. Patient's clinical characteristics are given in Table 1. One patient was lost to follow-up after the first cycle of docetaxel, two discontinued docetaxel after the first cycle because of severe HSR, and one patient died of neutropenic sepsis soon after the first cycle. All 49 patients were evaluable for safety over 295 treatment courses.

Response to docetaxel

Thirty of 45 evaluable patients (66.7%) had a PR and one patient (2.2%) had a CR, giving an ORR of 68.9%. According to an intent-to-treat analysis, the observed PR and CR rates were 61% and 2%, respectively, for an ORR of 63% (Table 2). There was no significant difference in ORR between anthracycline-refractory and anthracycline-resistant patients or between early- and late-resistance patients. Among the 31 responders to docetaxel, 30 (96.8%) experienced the onset of response by the end of the third course of treatment.

Analysis of responses to docetaxel according to the site of involvement demonstrated an ORR of 68% for lung/pleural metastases, 56% for osseous metastases, 87% for lymph node/skin metastases, 77% for liver metastases, and 80% for local relapses. No CR were observed in patients with lung/pleural or skeletal metastases, but more than 40% of patients with lymph node/skin metastases, 27% of those with local relapses, and 15% of those with liver metastases had a complete remission at these sites.

Table 1 Prior chemotherapy and tumor characteristics

Variable	Patients	
	(*n*)	(%)
Performance status (ECOG)		
Level 0	22	45
Level 1	24	49
Level 2	3	6
Prior chemotherapy	49	100
Adjuvant only	6	12.2
For metastatic disease	43	87.8
Anthracycline-based chemotherapy	41	83.7
Anthracycline-refractory disease	16	32.7
Anthracycline-resistant disease	25	51
Early-resistance disease	10	20.4
Late-resistance disease	15	30.6
Site of metastases		
Bone	30	61.2
Lung ± pleural effusion	24	49
Lymph nodes/skin	27	55
Liver	16	32.7

ECOG, Eastern cooperative Oncology Group

Table 2 Response to docetaxel according to previous chemotherapy

Type of prior chemotherapy	Evaluable patients (*n*)	Total patients (*n*)	Evaluable patients (on an intent-to-treat basis) (%)				
			PR	CR	OR	NC	PD
Adjuvant only	6	6	50 (50)	0 (0)	3 (50)	0 (0)	3 (50)
For metastatic disease	39	43	69 (63)	2.6 (2.3)	72 (65)	1 (2.3)	27 (23)
Anthracyline-refractory disease*	15	16	60 (56)	0 (0)	60 (56)	6.6 (6.3)	33 (31)
Anthracycline-resistant disease*	23	25	78 (72)	4.3 (4)	82.6 (76)	4.3 (4)	13 (12)
Early resistance**	8	10	63 (50)	0 (0)	62.5 (50)	12 (10)	25 (20)
Late resistance**	15	15	87 (87)	7 (7)	93.4 (93)	0 (0)	7 (7)
Total	45	49	66.7 (61)	2.2 (2)	68.9 (63)	2.2 (2)	29 (27)

PR, partial response; CR, complete response; OR, overall response; NC, no change; PD, progressive disease
* Not significant; ** $0.05 < P < 0.1$

Table 3 Response duration and survival after docetaxel treatment

Type of prior chemotherapy	Evaluable patients (*n*)	Responders (*n*)	Response duration (months)	Survival (months)	Responders surviving >12 months (%)
Adjuvant only	6	3	8, 12, 17	10, 23+, 31+	66.7
For metastatic disease	39	28	8 (4–23+)	11.5 (4–31+)	50.0
Anthracycline-refractory disease	15	9	7 (5–12)	9 (7–15+)	33.3
Anthracycline-resistant disease	23	19	10 (5–23+)	14 (7–31+)	57.8
Early resistance	8	5	8 (5–13)	14 (8–31+)	60.0
Late resistance	15	14	11 (5–23+)	12 (7–31+)	57.1

With the exception of adjuvant-only patients, where individual patient values are given, response duration and survival data are presented as the median (range)

A dose–intensity analysis demonstrated that the median relative dose intensity (RDI) was 0.89, with a range from 0.72 to 1. A total of 82% of patients received more than 80% of the predicted dose. There seems to be no correlation between RDI and type of response, since 75% of patients with stable and progressive disease had received 90% or more of the predicted dose.

Duration of response and survival

Response duration and survival after docetaxel treatment are shown in Table 3. No significant difference in patients surviving more than 12 months was found between "adjuvant only" patients (66%) and those treated for metastatic disease (50%). There was also no signifi-

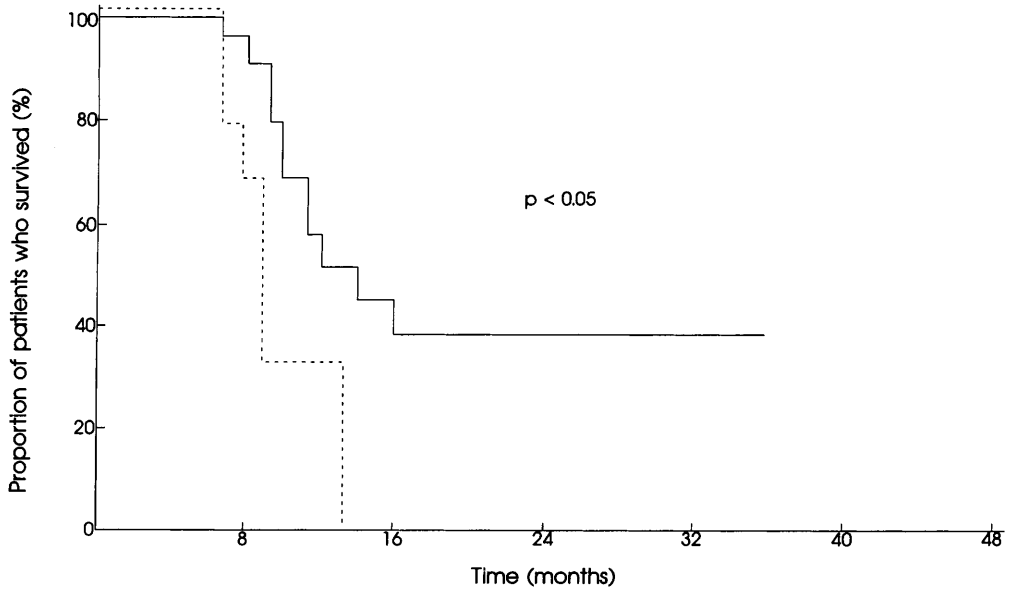

Fig. 1 Actuarial survival of patients previously treated with anthracyclines. *Solid line*, anthracycline resistant ($n = 19$); *dotted line*, anthracycline refractory ($n = 9$)

Table 4 Incidence of toxicity (NCI Common Toxicity Criteria)

Event	Patients					Courses				
	Total (*n*)	Grades 1 + 2		Grades 3 + 4		Total (*n*)	Grades 1 + 2		Grades 3 + 4	
		(*n*)	(%)	(*n*)	(%)		(*n*)	(%)	(*n*)	(%)
Hematological toxicity										
Anemia	23	20	40.8	3	6.1	109	106	35.9	3	1.0
Neutropenia	39	25	51.0	14	28.6	70	33	11.2	37	12.5
Febrile neutropenia	20	7	14.3	13	26.5	29	11	3.7	18	6.1
Thrombocytopenia	2	1	2.0	1	2.0	6	5	1.7	1	0.4
Nonhematological non-taxoid-specific										
Reversible alopecia	42	42	85.7	–	–	–	–	–	–	–
Nausea	9	9	18.4	–	–	18	18	6.1	–	–
Vomiting	4	4	8.2	–	–	4	4	1.4	–	–
Stomatitis	10	7	14.3	3	6.1	15	12	4.1	3	1.0
Diarrhea	16	15	30.6	1	2.0	19	18	6.1	1	0.3
Neurosensory reactions	16	14	28.6	2	4.1	–	–	–	–	–
Cardiac	4	3	75	1	25	7	6	86	1	14
Nonhematological taxoid-specific										
Hypersensitivity reactions	8	6	12.2	2	4.1	8	6	2.0	2	0.7
Cutaneous reactions	15	13	26.5	2	4.1	39	37	12.5	2	0.7
Fluid retention	17	15	30.6	2	4.1	35	33	11.2	2	0.7
Nail dystrophy	6	NA	NA	NA	NA	–	NA	NA	NA	NA

NA, not applicable

cant difference in 12-month survival rates between anthracycline-resistant and anthracycline-refractory patients (58% and 33%, respectively) or early- and late anthracycline-resistant patients (60% and 57%, respectively).

Duration of response was not significantly different between anthracycline-refractory and anthracycline-resistant patients, but the corresponding survival curves differed significantly ($P < 0.05$) in favor of the anthracycline-resistant group (Fig. 1).

Adverse events

The incidence and types of adverse events are given in Table 4. One documented infection and one septic death were recorded. Apart from this last patient, no patients discontinued treatment because of neutropenia, although one third of the patients received secondary prophylaxis with granulocyte colony-stimulating factor. Cardiac events constituted four episodes of extreme sinus tachycardia and one each of supraventricular tachycardia, ventricular extrasystole, and severe cardiac hypotension.

Two patients (4.1%) discontinued treatment because of HSR. Cutaneous reactions ranged from mild scattered maculopapular eruptions, primarily in the extremities, to sizeable infiltrative plaques and bullous eruptions. Two patients required symptomatic treatment of fluid retention. The median number of courses leading to moderate fluid retention was five (range, three to eight), and the median dose was 500 mg/m^2 (range, 300–800 mg/m^2).

Discussion

Historically, the effectiveness of second-line chemotherapy in metastatic breast cancer has been modest [3, 8, 25], with ORR of 6%–29% reported for various agents [2, 8, 23, 25]. Patients with anthracycline-resistant breast cancer have a particularly poor prognosis [7, 11]. For example, vinorelbine and paclitaxel have produced ORR of only 16% [3, 12] and 6%–33% [10, 22], respectively, in this patient group. Only one study has reported a higher ORR (48%) in a second-line setting, and 27% of these patients had disease that progressed while on mitoxantrone rather than on anthracycline therapy [24]. The ORR of 69% reported in our study therefore shows that docetaxel is a highly effective antineoplastic agent in previously treated advanced breast cancer. For evaluable patients pretreated with anthracycline-based chemotherapy, an ORR of 74% was observed. An ORR of 60% was achieved in anthracycline-refractory patients, which is similar to the ORR of 53% [20] and 57% [15] previously reported in equivalent patient groups.

In a recent review, an ORR of 50% was reported for 162 patients with metastatic breast cancer treated with second-line docetaxel, 134 of whom were anthracycline resistant [21]. In similarly defined anthracycline-resistant groups, ORR of 6% and 18% were reported with paclitaxel [22, 18].

Several definitions of anthracycline resistance have been used in published studies [5, 10, 14, 24], making comparisons difficult. In our study, patients who had received anthracyclines previously were subdivided into

anthracycline-refractory, early-resistance, and late-resistance subgroups (see ''patients and methods'' section). Each subgroup was analyzed separately for its response to docetaxel. Anthracycline-refractory patients had a lower ORR than anthracycline-resistant patients, but a higher ORR than early-resistance patients. Late-resistance patients had a higher ORR than both anthracycline-refractory and early-resistance patients. These findings suggest that anthracycline-resistant patients constitute a heterogeneous group in terms of sensitivity to second-line chemotherapy. The actuarial survival of responders to docetaxel was also significantly higher in the anthracycline-resistant group than in the anthracycline-refractory group. Over 50% of responders in the anthracycline-resistant group were alive after 12 months compared with 33% of responders in the anthracycline-refractory group, although the small size of the subgroups compared does not allow firm conclusions to be drawn.

Docetaxel was shown to have major activity at all sites of disease, including skeletal and visceral metastases. A high proportion of evaluable patients with liver metastases responded to docetaxel treatment, including two CR. In previous studies using the same docetaxel schedule as second-line treatment, an ORR of 61% and a CR of 11% were reported in 18 patients with liver involvement [19], and ORR of 44% and 33% were observed in liver metastases in strictly defined anthracycline-resistant or anthracenedione-resistant patients, respectively [15, 20]. Thus docetaxel appears to be particularly active against liver metastases derived from breast cancer. Although no CR was documented in skeletal metastases, only a small number of evaluable patients had progressive bone disease while receiving docetaxel. Furthermore, most patients with skeletal symptoms had a greatly improved quality of life.

The profile of docetaxel-induced hematological and nonhematological, non-taxoid-specific adverse events was similar to that reported elsewhere [4, 15, 19, 20]. However, our study showed that gradual reduction of corticosteroid premedication, rather than abrupt discontinuation on the fifth day, alleviated arthralgia and myalgia. The most serious manifestation of taxoid-specific toxicity is HSR [17], although its incidence and severity are decreased significantly with corticosteroid prophylaxis [20]. Despite systematic corticosteroid premedication, HSR were observed in 16% of patients in our study, and one third of patients experienced fluid retention, which was cumulative and dose related, as reported previously [1, 15, 20].

In conclusion, docetaxel is effective when used as a second-line single-agent chemotherapy in advanced breast cancer. The ORR in anthracycline-resistant and anthracycline-refractory patients was unprecedentedly high. Given the lack of full cross-resistance with anthracyclines, it may be possible to combine the two treatments to offer an improved chemotherapeutic regimen for patients with advanced breast cancer.

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