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Treatment of patients resistant to anthracycline therapy

PM Ravdin

University of Texas Health Science Center, 78284–7884 San Antonio, Texas, USA.

The results of three multicentre phase II trials in which docetaxel (Taxotere®) was used in previously treated patients with metastatic breast cancer resistant to anthracyclines or anthracenediones are summarized here. Docetaxel was given to a total of 134 patients who had evidence of disease progression while receiving anthracyclines or anthracenediones for metastatic disease or had relapsed during adjuvant therapy which included these agents. The overall response rate (ORR) across the three studies was 41% in an intent-to-treat analysis. The median duration of response varied from 24 to 28 weeks between studies and the median survival varied from 9 to 12 months. The response rate was well maintained in evaluable patients with visceral metastases (ORR 43%), or multiple (>2) sites of disease (ORR 48%). These response rates are the highest ever reported for a single agent in patients with anthracycline-resistant disease. The recommended dose and schedule for docetaxel (100 mg/m² intravenously over 1-h every 3 weeks), which was used in all three studies, was found to be well tolerated, with neutropenia as the most common toxicity (grade 4 in 90% of patients) and febrile neutropenia requiring hospitalisation occurring in only 4% of cycles of therapy.

Keywords: Metastatic breast cancer, docetaxel (Taxotere®), anthracyclines, anthracenediones.

Introduction

This review will report data from three trials in which docetaxel (Taxotere®) has been shown to have the highest response rates ever reported for a single agent in patients with metastatic breast cancer which is resistant to anthracyclines.

It is well established that one in four women who are diagnosed with breast cancer will eventually die of breast cancer. Metastatic breast cancer is the leading cause of death in women aged 40–55 [1] and accounts for 19% of cancer deaths in women in the United States. Anthracyclines are widely recognized as agents central to the treatment of cancer, particularly breast cancer. Inclusion of an anthracycline in first-line treatment for metastatic breast cancer has been shown to improve the response rate, time to disease progression and survival duration when compared with treatment regimens that did not include an anthracycline [2]. A compilation of phase II trials using doxorubicin showed that this agent has a 43% response rate in the first-line setting [3]. However, in the second-line setting, doxorubicin has a response rate of only 29% [4]. The response rates to second- and third-line therapy with single agents are generally under 30% and of short duration, with a median survival of less than 6 months, and combination therapy has not proved superior in these settings [3].

The falling response rates in successive regimens of therapy reflect the development of drug resistance, and most patients treated with anthracyclines will have disease which is intrinsically resistant to these agents, or will develop resistance during the course of their disease. Docetaxel has been shown to have impressive activity in patients with anthracycline-resistant disease. The three major phase II trials of docetaxel therapy in this population of patients will be reviewed here.

Correspondence to PM Ravdin

Methods

Three multicentre phase II trials have been conducted to evaluate the safety and efficacy of docetaxel in breast cancer patients with anthracycline-resistant disease. Two studies were conducted in the United States: one by MD Anderson [5] referred to here as study 1, and the other by the University of Texas, San Antonio, [6] referred to here as study 2. The multicentre European trial referred to here as study 3 has been reported by Guastalla *et al.* [7]. There were 134 patients recruited from these trials from 20 participating centres.

Patients

All patients had World Health Organization (WHO) performance status <2 (or Karnofsky performance status >60%) and adequate haematologic, renal and hepatic function. All patients had bidimensionally measurable disease. Table 1 shows some characteristics of patients at study entry.

Table 1. Baseline patient characteristics

Patients	Study 1 [5]	Study 2 [6]	Study 3 [7]	Total
No. of patients	41	42	51	134
No. of centres	3	4	13	20
< 50 years	19	17	32	68
≥ 50 years	22	25	19	66
Visceral involvement	33	28	34	95
Liver	20	15	22	57
Lung	13	14	17	44
No. of organs involved				
1	6	11	11	28
2	13	13	19	45
≥ 2	22	18	21	61
Prior chemotherapy				
Adjuvant only	4	2	6	12
Advanced only	22	14	20	56
Adjuvant and advanced	15	26	25	66
Primary resistance				
To anthracycline	35	25	49	109
To anthracenedione	5	15	0	20

All patients were required to have had evidence of prior resistance to anthracyclines or anthracenediones. The definition of resistance was rigorous and clinically relevant. In these trials resistance was defined as either:

- evidence of progression while receiving anthracyclines or anthracenediones;
- relapse during adjuvant therapy with such a regimen.

The European trial used the most rigorous definition of anthracycline resistance, recruiting only those patients, who in addition to meeting the standard for anthracycline resistance, had not shown evidence of any initial favourable response to anthracyclines, including partial remission. On review of clinical records after the trial all but five patients were found to meet these strict definitions.

Treatment

The therapy used in all these trials was docetaxel, 100 mg/m^2 infused over 1-h every 3 weeks. Colony-stimulating factors and antiemetics were not routinely used. Patients received several different regimens as premedication to lessen the risk of hypersensitivity reactions and to lessen the impact of fluid retention, although the first patients in study 1 and 2 did not receive premedication. Table 2 shows the premedication regimens used.

Efficacy assessment

The objective response rate was assessed according to WHO criteria (complete response, partial response, stable disease and progressive disease). The duration of response was dated from the start of treatment until the documentation of progression, and the duration of survival from the start of therapy until the date of death. An outside panel reviewed and verified the objective responses in study 1 and study 2.

Table 2. Premedication regimens

	Study		
	1[5]	2 [6]	3 [7]
No prophylaxis	9	10	0
Diphenhydramine 50 mg i.v. 30 min prior to docetaxel	12	12	0
Diphenhydramine 50 mg i.v. 30 min prior to docetaxel + dexamethasone 8 mg orally twice daily beginning 1 day prior to docetaxel	20	20	0
Oral methylprednisolone 32 mg, cetrizine 10 mg and ketotifen 1 mg 12 and 3-h prior to docetaxel	0	0	51

Results

The objective response rates, analysed on an intent-to-treat basis are summarized in Table 3. The overall response rate in the 134 patients in these three trials was 41%. The response rates in the two studies conducted in the United States were nearly 50%. The European trial which used the strictest definition of anthracycline resistance found a slightly lower response rate. Median response duration was >20 weeks in all studies, and median survival in the three trials ranged from 9 to 12 months.

Table 4 shows the response rates in the evaluable patients. Response rates were well maintained in patients with visceral disease, and in patients with multiple sites of disease. Multivariate analyses suggest that the efficacy of docetaxel was not compromized in the patients who received premedication with glucocorticoids.

The safety profile of docetaxel is reviewed elsewhere in this volume. In general, the drug was well tolerated, with febrile neutropenia being the most common toxicity requiring hospitalization in 4% of the cycles. Ninety per cent of patients did experience grade 4 neutropenia.

Discussion

These studies demonstrate that docetaxel has impressive activity against metastatic breast cancer which is

Table 3. Treatment efficacy based on an intent-to-treat analysis

Parameter	Study 1 [5]	Study 2 [6]	Study 3 [7]	Overall
PR (%)	46	43	29	39
CR (%)	0	7	0	2
Overall response (%) (CR + PR)	46	50	29	41
Median response duration (weeks)	27	28	24	—
Median survival (months)	9	12	10	—

PR, partial response; CR, complete response.

Table 4. Treatment efficacy in evaluable patients

	Overall response rate (% PR + CR)			
Patients	Study 1 [5]	Study 2 [6]	Study 3 [7]	Overall
All patients	55	57	32	47
Organs				
Visceral	61 (16/26)	44 (10/23)	26 (7/27)	43
Lung	86 (6/7)	50 (4/8)	22 (2/9)	50
Liver	46 (6/13)	33 (4/12)	14 (2/14)	31
Non-visceral	29 (2/7)	83 (10/12)	46 (5/11)	57
Sites				
1	80 (4/5)	67 (6/9)	17 (1/6)	55
2	40 (4/10)	70 (7/10)	25 (4/16)	42
>2	56 (10/18)	44 (7/16)	44 (4/16)	48

PR, partial response; CR, complete response.

resistant to anthracyclines or anthracenediones. The overall response rate in these three multicentre trials was 41%, which is lower than the overall response rate for first-line treatment, using the same dose and treatment schedule, reported by Dr Trudeau in this volume (61%), but is higher than the responses reported for paclitaxel (Taxol®) (29%, with 28% for anthracycline-resistant disease) [8], and vinorelbine (16%) [9] at their recommended doses and schedules of 175 mg/m^2 over 3 h every 3 weeks, and 30 mg/m^2 weekly, respectively.

Paclitaxel and docetaxel are related drugs with a similar mechanism of action but some differences in their pharmacokinetics, and preclinical and clinical activity profiles [10]. Unlike docetaxel, which does not show significant schedule-dependency in preclinical tests [11], paclitaxel is schedule-dependent. This schedule-dependency has contributed to the continuing failure to define the optimal dose and schedule for paclitaxel treatment in various disease indications. An examination of the available data for the response of anthracycline-resistant metastatic breast cancer to paclitaxel reveals that shorter infusion durations are associated with lower response rates. However, it must be added that variation in the response rates obtained in the various paclitaxel studies could also be attributed to variations in the definition of anthracycline resistance which were used. The study with the highest response rate [12] also has the least stringent definition of anthracycline resistance, and the longest duration of infusion (96 h). It is the consistency of the dose and schedule used, and the responses obtained, which makes the docetaxel results impressive.

Phase III trials will be necessary to establish whether docetaxel therapy has substantial advantages over other single-agent therapies which show activity in anthracycline-resistant disease. One such trial is a phase III comparison of docetaxel and paclitaxel which is ongoing in the United States. This trial will use measures of efficacy, safety and quality of life as important endpoints. On the basis of current phase II evidence, docetaxel appears to be as good as, and possibly better than, any other single agent for the treatment of anthracycline-resistant breast cancer.

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