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First-line treatment of metastatic breast cancer

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Although metastatic breast cancer is an incurable disease, chemotherapy has had an impact on survival since the use of anthracycline drugs has become widespread. The optimal time for chemotherapeutic intervention for disseminated disease is in the first-line setting, but optimal treatments vary amongst patients, and the treatment must be chosen after consideration of the characteristics of the patient and the disease. Amongst the new drugs which have been used in the treatment of metastatic breast cancer, vinorelbine and the taxoids, docetaxel (Taxotere®) and paclitaxel (Taxol®), challenge monotherapy with anthracycline drugs, and even combination therapies, with regard to the response rate obtainable. In five multicentre phase II trials, the response rate to docetaxel, 75 or 100 mg/m², given intravenously over 1 hour every 3 weeks, varied from 38 to 68%, with a median survival of 16.4 months across all studies. Good performance status and treatment with the higher dose improved response rates, though these effects were not statistically significant. Docetaxel has proved to be a highly active monotherapy for metastatic breast cancer in the first-line setting.

Keywords: Metastatic breast cancer, docetaxel (Taxotere®), first-line treatment.

Introduction

Since metastatic breast cancer remains an incurable disease, the aims of chemotherapy for metastatic disease are palliation of symptoms, improved quality of life, and disease regression. These aims may correlate with response to treatment [1–4] but it is always important to balance the efficacy of the treatment against its toxicity.

Chemotherapy is not the treatment of first choice for all patients who have relapsed after adjuvant therapy, or have been initially diagnosed with metastatic disease. Candidates for chemotherapy include patients with:

- oestrogen and/or progesterone receptor-negative tumours;
- disease refractory to hormonal therapies;
- a short disease-free interval after adjuvant therapy;
- rapidly progressive disease;
- a visceral crisis.

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It is difficult to prove that there has been prolongation of survival with the use of chemotherapy in metastatic breast cancer. The MD Anderson Cancer Center used retrospective historical controls to look at survival of patients in the 1950s, 1960s and 1970s [4,5]. The median survival for the 1950s and 1960s, before the widespread use of chemotherapy for metastatic disease was approximately 18 months, but during the 1970s when more aggressive chemotherapy became commonplace, largely because of the development of anthracycline drugs, the average survival increased to 24 months. These data indicate that improvements in chemotherapy, particularly the use of anthracyclines, may have had some impact on the overall survival of breast cancer patients.

Amongst those patients who are candidates for chemotherapy, there are prognostic factors which are associated with responsiveness to chemotherapy and good response duration or survival [6–8], including:

- good performance status;
- limited number of disease sites (one or two);
- prior response to hormone therapy;
- the presence of lymph node metastases.

Conversely, there are also prognostic factors which are associated with a decreased probability of response to chemotherapy, which include:

- prior chemotherapy;
- three or more sites of disease;
- liver metastases;
- receptor-negative tumour.

Doxorubicin therapy has the highest response rate amongst the standard therapies for metastatic breast cancer, with response rates from 43–54%. The other commonly used therapies have lower response rates, with a 36% response rate for cyclophosphamide, 28% for 5-fluorouracil, 26% for methotrexate, and 25% for melphalan [6]. The optimal place in which to test new agents for chemotherapy is in first-line treatment for metastatic disease, and several new agents, other than docetaxel (Taxotere®), have been introduced into this setting in the past decade (Table 1).

Vinorelbine and the taxoids challenge doxorubicin with regard to the response rate achieved. The response rate for paclitaxel given in Table 1 is derived

Table 1. Single-agent chemotherapy in the first-line setting: agents introduced in recent years

Drug	Overall response rate (%)	References
Paclitaxel	30–62	[9–15]
Vinorelbine	37–60	[4,16–18]
Edatrexate	34–41	[19,20]
Gemcitabine	18–40	[21–23]

from results obtained with the various doses (135–250 mg/m²) and schedules (3–96-h i.v. infusion) which have been used in different studies. The lower response rates are generally from those studies which have used lower doses (135 mg/m²) and shorter infusion durations (3-h), whereas higher response rates derive from studies using higher doses (225–250 mg/m²) given over longer periods (24–96-h).

Combination chemotherapies are often used in the first-line setting, and results for the two most commmonly used combinations are shown in Table 2 [6].

Docetaxel has been studied as first-line monotherapy in metastatic breast cancer in five multicentre studies involving 209 women in North America and Europe, the results of which will be summarized in this review.

Methods

The entry criteria for all of these phase II studies were standardized and all the women recruited had progressive metastatic disease more than 1 year after the end of adjuvant therapy, and bidimensionally measurable lesions. All responses were reviewed by an independent panel. As well as the 209 women recruited into trials of first-line chemotherapy, eight patients were included from a phase II study which involved mainly second-line therapy. The patient characteristics for these studies are shown in Table 3. Adjuvant chemotherapy had been used in about 50% of these patients, and the majority of these regimens had contained an anthracycline. About 40% of patients had three or more organs involved in metastatic disease, and 75% had visceral involvement. The dose used was 75 mg/m² in 46 evaluable patients, and 100 mg/m² in 142 evaluable patients.

Docetaxel was infused at a dose of 100 or 75 mg/m² as a 1-h infusion in an outpatient setting, and cycles were repeated every 3 weeks. The lower dose of 75 mg/m² was the starting dose used in one study [24], and was used in one cohort of patients in a second study [25].

Table 2. Combination chemotherapy in the first-line setting

Regimen	Trials *(n)*	Evaluable patients *(n)*	Overall response rate (%)	Time to progression (months)	Survival (months)
CMF	7	434	30–62	6–8	16–20
CAF	8	709	43–82	9–12	18–26

CMF, regimens including cyclophosphamide, methotrexate and 5-fluorouracil; CAF, regimens including cyclophosphamide, doxorubicin and 5-fluorouracil.

Table 3. Patient characteristics: first-line treatment with docetaxel

Initial dose	100 mg/m² *n* = 54 (%)	75 mg/m² *n* = 55 (%)
Age <50 years	40	46
Performance status 0–1	84	84
Adjuvant chemotherapy		
No	49	51
Yes	51	49
Anthracyclines	38	40
Organs involved		
≤ 2	57	62
≥ 3	43	38
Metastatic sites		
Visceral	75	78
Lung	36	33
Liver	44	51
Non-visceral	25	22
Bone	45	49

Results

The overall response rate with docetaxel, 100 mg/m², given over 1-h was 61% and varied from 68% in two first-line European Organization for Research and Treatment of Cancer (EORTC) studies, to only 38% in the group of eight patients from a predominantly second-line EORTC study. The overall response rate for patients given 75 mg/m² as the initial dose was 48%. These results are shown in Table 4. Responses were not significantly affected by age, by high organ involvement, or by visceral involvement, as shown in Table 5. Patients with good performance status did somewhat better than patients with poor performance status, especially at the lower dose, and patients given the higher dose had a higher response rate than those given the lower dose, but this was not statistically significant. Response was not affected by prior adjuvant chemotherapy received. The median duration of response was 8.3 months (range 2–22.8+), median time to disease progression was 4.9 months (range

Table 4. Response: first-line treatment with docetaxel

Initial dose	Institution (evaluable patients)	CR *(n)*	PR *(n)*	CR + PR (%, 95% CI)
75 mg/m²	NCI–C (15) [25]	1	5	40 (16–68)
	EORTC (31) [24,26]	4	12	52 (33–70)
100 mg/m²	EORTC (8) [27]	1	2	38 (8–75)
	MSKCC (34) [28]	2	17	56 (38–73)
	NCI-C (32) [25]	2	16	56 (44–79)
	EORTC (31) [29]	5	16	68 (49–83)
	EORTC (37) [30]	2	23	68 (50–82)

NCI-C, National Cancer Institute of Canada; MSKCC, Memorial Sloan-Kettering Cancer Center; EORTC, European Organization for Research and Treatment of Cancer; CR, complete response; PR, partial response; CI, confidence interval.

Table 5. Response by subgroup: first-line treatment with docetaxel in evaluable patients

Initial planned dose	75 mg/m² (*n* = 46) Reponse rate (%)	100 mg/m² (*n* = 142) Response rate (%)
Age		
18–49 years	52	66
≥ 50 years	44	57
Organs involved		
≤ 2	59	60
≥ 3	29	63
Visceral disease	49	58
Target lesions		
Liver	45	60
Lung	58	26
Soft tissue	44	64
WHO performance status		
0	50	66
1	53	62
2	33	56

WHO, World Health Organization

0.2–22.8+), and median survival was 16.4 months (range 0.2–24.1+).

Conclusions

The response rates for docetaxel, at the recommended dose of 100 mg/m², challenge the responses seen with standard therapies, and illustrate the impressive activity of docetaxel in patients with multiple organs involved in metastatic disease, and in patients with visceral disease. These results support the contention that docetaxel is a highly active first-line monotherapy for patients with metastatic breast cancer, regardless of prior adjuvant chemotherapy received, whether cyclophosphamide, methotrexate, fluorouracil-based or anthracycline-based.

References

1. Tannock I, Boyd N, De Boer G, *et al.* A randomized trial of two dose levels of cyclophosphamide, methotrexate, and fluorouracil chemotherapy for patients with metastatic breast cancer. *J Clin Oncol* 1988; **6**: 1377–1387.
2. Coates A, Gebski V, Bishop JF, *et al.* Improving the quality of life during chemotherapy for advanced breast cancer. *N Engl J Med* 1987; **317**: 1490–1495.
3. Coates A, Gebski V, Signorini D, *et al.* Prognostic value of quality of life scores during chemotherapy for advanced breast cancer. *J Clin Oncol* 1992; **10**: 1833–1838.
4. Hayes DF, Henderson IC, Shapiro CL. Treatment of metastatic breast cancer: present and future prospects. *Semin Oncol* 1995; **22**: 5–19.
5. Ross MB, Buzdar AU, Smith TL, *et al.* Improved survival of patients with metastatic breast cancer receiving combination chemotherapy: comparison of consecutive series of patients in 1950's, 1960's, and 1970's. *Cancer* 1985; **55**: 341–346.
6. Henderson IC. Chemotherapy for metastatic disease. In: Harris JR, Hellman S, Henderson IC, *et al.*, eds. *Breast diseases (2nd edn)*. Philadelphia, PA: Lippincott; 1991: 604–665.
7. Dunphy FR, Spitzer G, Rossiter Fornoff JE *et al.* Factors predicting long-term survival for metastatic breast cancer patients treated with high-dose chemotherapy and bone marrow support. *Cancer* 1994; **73**: 2157–2167.
8. Falkson G, Gelman R, Falkson CI *et al.* Factors predicting for response, time to treatment failure, and survival in women with metastatic breast cancer treated with DAVTH: a prospective eastern cooperative oncology group study. *J Clin Oncol* 1991; **9**: 2153–2161.
9. Holmes FA, Walters RS, Theriault RL *et al.* Phase II trial of Taxol, an active drug in the treatment of metastatic breast cancer. *J Natl Cancer Inst* 1991; **83**: 1797–1805.
10. Wilson WH, Berg SI, Bryant G, *et al.* Paclitaxel in doxorubicin-refractory or mitoxantrone-refractory breast cancer: a phase I/II trial of 96-hour infusion. *J Clin Oncol* 1994; **12**: 1621–1629.
11. Abrams JS, Vena DA, Baltz J, *et al.* Paclitaxel activity in heavily pretreated breast cancer: a National Cancer Institute Treatment Referral Center trial. *J Clin Oncol* 1995; **13**: 2056–2065.
12. Gianni L, Munzone E, Capri G, *et al.* Paclitaxel in metastatic breast cancer: a trial of two doses by 3-hour infusion in patients with recurrence after prior therapy with anthracyclines. *J Natl Cancer Inst* 1995; **87**: 1169–1175.
13. Seidman A, Hudis C, Tiersten A, *et al.* Phase II trial of paclitaxel by three hour infusion as initial and as salvage chemotherapy for metastatic breast cancer. *J Clin Oncol* 1995; **13**: 2575–2581.
14. Seidman A, Reichman BS, Crown JPA, *et al.* Paclitaxel as second and subsequent therapy for metastatic breast cancer: activity independent of prior anthracycline response. *J Clin Oncol* 1995b; **13**: 1152–1159.
15. Vermorken JB, ten Bokkel-Huinink WW, Mandjes IAM, *et al.* High-dose paclitaxel with granulocyte colony-stimulat-

ing factor in patients with advanced breast cancer refractory to anthracycline therapy: a European Cancer Center trial. *Semin Oncol* 1995; **22** (suppl 8): 16–22.
16. Canobbio L, Boccardo F, Pastorino G, *et al.* Phase II study of Navelbine in advanced breast cancer. *Semin Oncol* 1989; **16**: 33–36.
17. Fumoleau P, Delgado FM, Delozier T, *et al.* Phase II trial of weekly intravenous vinorelbine in first-line advanced breast cancer chemotherapy. *J Clin Oncol* 1993; **11**: 1245–1252.
18. Romera A, Rabinovich MG, Vallejo CT, *et al.* Vinorelbine as a first-line chemotherapy for metastatic breast cancer. *J Clin Oncol* 1994; **12**: 336–341.
19. Vandenberg TA, Pritchard KI, Eisenhauer EA, *et al.* Phase II study of weekly edatrexate as first-line chemotherapy for metastatic breast cancer: a National Cancer Institute of Canada Clinical Trials Group study. *J Clin Oncol* 1993; **11**: 1241–1244.
20. Schornagel JH, van der Vegt S, de Graff A, *et al.* Phase II study of edatrexate in chemotherapy-naive patients with metastatic breast cancer. *Ann Oncol* 1992; **3**: 549–552.
21. Possinger K, Kaufmann M, Helsing M, *et al.* Advanced breast cancer: a phase II trial with gemcitabine (GEM) [abstract 369]. *Eur J Cancer* 1995; **31A** (suppl 5): S80.
22. Carmichael J, Possinger K, Philip P, *et al.* Advanced breast cancer: a phase II trial with gemcitabine. *J Clin Oncol* 1995; **13**: 2731–2736.
23. Blackstein M, Vogel CL, Ambinder R, *et al.* Phase II study of gemcitabine in patients with metastatic breast cancer [abstract 135]. Proceedings of *Asco* 1996;**15.**
24. Dieras V, Fumoleau P, Chevallier B, *et al.* A phase II trial of Taxotere® (docetaxel) 75 mg/m^2 every 3 weeks, as first line chemotherapy in advanced breast cancer. A second EORTC Clinical Screening Group Study [abstract 199]. *Ann Oncol* 1994; **5** (suppl 8): 40.
25. Trudeau ME, Eisenhauer EA, Higgins BP, *et al.* Docetaxel in patients with metastatic breast cancer: a phase II study of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1996; **14**: 422–428.
26. Fumoleau P, Chevallier B, Dieras V, *et al.* Evaluation of two doses of Taxotere (docetaxel) as first line in advanced breast cancer: EORTC Clinical Screening Group report [abstract A622]. *Breast Cancer Res Treat* 1994; **32**: 34. (abstrac
27. ten Bokkel-Huinink WW, Prove AM, Piccart M, *et al.* A phase II trial with docetaxel (Taxotere) in second line treatment with chemotherapy for advanced breast cancer. A study of the EORTC Early Clinical Trials Group. *Ann Oncol* 1994; **5**: 527–532.
28. Seidman AD, Hudis C, Crown JP, *et al.* Phase II evaluation of Taxotere (RP 56976, NSC 628503) as initial chemotherapy for metastatic breast cancer [abstract]. *Proc Am Soc Clin Oncol* 1993; **12**: A52.
29. Chevallier B, Fumoleau P, Kerbrat P, *et al.* Docetaxel is a major cytotoxic drug for the treatment of advanced breast cancer: a phase II trial of the Clinical Screening Co-operative Group of the European Organization for Research and Treatment for Cancer. *J Clin Oncol* 1995; **13**: 314–322.
30. Krakowsky I, Rios M, Fumoleau P, *et al.* Phase II first line chemotherapy (CT) study with docetaxel (Taxotere*) and prophylactic premedication of fluid retention (FR) in patients (pts) with metastatic (mts) or locally advanced breast cancer (ABC). EORTC Clinical Screening Group (CSG) [abstract 87]. *Proc Am Soc Clin Oncol* 1995; **14**: 97.