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Prospects with Docetaxel in the Treatment of Patients with Breast Cancer

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Docetaxel (Taxotere®) has been shown to be one of the most active cytotoxic agents in patients with breast cancer, achieving response rates of 41% when used as second-line treatment for metastatic breast cancer (34% in anthracycline-refractory patients) and 50–72% when used as first-line therapy. In both situations meaningful response durations of 7–8 months have been obtained. Based on these results, docetaxel is a promising candidate for new therapeutic strategies in patients with breast cancer. Studies comparing docetaxel with paclitaxel or anthracyclines in first-line therapy are ongoing. These studies should allow for an unequivocal definition of activity of docetaxel, yet not alter—as such—therapeutic strategies. A number of regimens are currently being explored combining docetaxel with anthracyclines, vinorelbine, 5-fluorouracil, cyclophosphamide and cisplatin. The preliminary conclusions are as follows: the main side-effect is non-cumulative neutropenia of short duration, and response rates are > 75%. Further, no cumulative cardiotoxicity has been observed with doxorubicin. The duration of response and length of the progression-free survival cannot yet be defined. Another option for combination chemotherapy is sequential combinations, the value of which has been demonstrated in advanced breast cancer as well as in the adjuvant setting. The short duration and non-cumulative character of docetaxel-induced neutropenia are good rationales for the use of dose-densified docetaxel-containing regimens. A dose of 100 mg/m²/14 days can be used as single-agent therapy. A phase I trial combining cyclophosphamide at doses increased from 750 to 1200 mg/m² and docetaxel at doses increased from 66 to 100 mg/m² every 2 weeks, is ongoing; at the first dose-levels, the combination appears feasible although cumulative asthenia has been observed. Further, responses have been observed at all dose levels. The value of single-agent chemotherapy added to tamoxifen has been emphasised for stage I–II breast cancer in postmenopausal patients. A randomised phase III study comparing tamoxifen (20 mg/day for 5 years) and epirubicin (50 mg/m² days 1 and 8/28 days for 6 cycles) with the same regimen with epirubicin for 3 months followed by docetaxel (100 mg/m²/21 days×3) was initiated at the end of 1996. Thus, docetaxel is currently under study in most therapeutic situations to better define its impact on the prognosis and curability of patients with breast cancer. © **1997 Published by Elsevier Science Ltd.**

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INTRODUCTION

DOCETAXEL HAS rapidly been established as one of the most active cytotoxic agents in the treatment of patients with advanced breast cancer. This finding is based upon the high response rates recorded in patients with advanced breast cancer, whether after failure of first-line therapy—specifically anthracycline-containing first-line therapy—or in patients who have not received prior cytotoxic therapy for metastatic progression (Table 1), as well as the long duration of response to this treatment.

These results have been achieved with a dose of 100 mg/m² docetaxel every 3 weeks [1]. The safety profile is well defined, with grade III–IV neutropenia occurring in > 90% of the patients, alopecia reported by almost all patients, and fluid retention syndrome—although reduced in incidence and severity by premedication with corticosteroids—still responsible for treatment discontinuation in 5% of patients. Indeed, the incidence of main side-effects are similar for docetaxel

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Table 1. Response rate with cytotoxics in first- or second-line treatment of advanced breast cancer [4]

Agent (ICD)	Dose (mg/m²)	Response rate (%) First line	Second line
Doxorubicin	50	38–52	15–29
Epirubicin	50–90	32–48	15–25
Mitoxantrone	10–14	28–40	15–25
Pirarubicine	45	30–50	>20
Paclitaxel	175	30–45	200–35
Docetaxel	100	50–65	40–55
Vinorelbine	30/7 days	38–54	>20
Cyclophosphamide	400–600	34	22
Fluorouracil	600	34	15
Methotrexate	60	34	NA
Ifosfamide	4–6000	30–40	NA
Altrétamine	150/jx7–14 days	27	2
Melphalan	2–6/dx5–30	23	4
Amétycine	10–12	20–25	8–20
Elliptinium	80/dx3	20–30	15–25
Vincristine	1.4/7d	21	NA
Chlorambucil	2–6/dx5–30	20	NA

D, days; NA, not available. RR, response rate.

and doxorubicin, thus establishing an improved therapeutic index for docetaxel.

The remarkable activity of docetaxel has been confirmed by randomised trials comparing (i) docetaxel (100 mg/m² every 3 weeks) with doxorubicin (75 mg/m² every 3 weeks) as first-line treatment of metastatic breast cancer [1]; and (ii) docetaxel given according to the same schedule as for mitomycin C and vinblastine as second-line treatment of metastatic breast cancer. Such data would raise the following questions:

(i) Which drugs will prove feasible in combination with docetaxel?
(ii) How efficacious would these combinations be?
(iii) When should treatment with docetaxel or docetaxel-containing regimens be started in patients with metastatic breast cancer?
(iv) Should patients with non-metastatic breast cancer be treated with docetaxel-containing regimens?

One of the aims is to improve the therapeutic results achieved so far in the treatment of patients with advanced breast cancer, but also to determine whether docetaxel should be considered as adjuvant or neo-adjuvant therapy for non-metastatic breast cancer.

DOCETAXEL IN THE TREATMENT OF ADVANCED BREAST CANCER

Until now, treatment of advanced breast cancer could be divided into (i) treatment with curative intent: although the cure rates achieved in patients with advanced breast cancer remain low, they are consistently in the range of 3–5%. This finding has led investigators to study intensive chemotherapy regimens—double or multiple intensive sequential cycles of chemotherapy supported by haemopoietic stem cells. The results show greatly improved response rates but only a marginal improvement in the length of the progression-free survival [2, 3]. (ii) Treatment with palliative intent: the use of adequate regimens and sequential combinations of hormonal and cytotoxic therapies can lead to a significant disease-free survival and median overall survival of 2–3 years [4].

In both curative and palliative treatments the most active therapies are those using combination chemotherapy incorporating anthracyclines or related agents. However, the use of anthracyclines is now expanding in the adjuvant setting based on the established superiority of these regimens in both pre- and post-menopausal women with localised breast cancer [5, 6]; the use of anthracyclines in patients who relapse is thus decreasing because of the reduced antitumor activity and the risk of cumulative cardiotoxicity with these agents. Furthermore, despite their proven superiority over non-anthracycline-containing regimens, these approaches have had only a minimal impact on the length of the progression-free and overall survival. Docetaxel thus appears to be a promising candidate for first-line combination regimens.

Docetaxel-containing combination regimens conventional dose-intensity

A variety of docetaxel-containing regimens have been studied in phase I trials. The results are extensively covered in this issue and are summarised in Table 2. Some preliminary conclusions are outlined below.

(i) The combinations studied allow for minimal reductions in the active dose of each agent.
(ii) Febrile neutropenia has been the dose-limiting toxicity for each combination.
(iii) No unexpected side-effects have been encountered. In particular, no increase in cardiotoxicity has been reported with doxorubicin or in neurotoxicity with vinorelbine.
(iv) The every 3 weeks schedule was tolerated with each combination.
(v) High response rates (> 70%) have been reported with each combination.

Thus, docetaxel should be studied as part of both anthracycline-containing regimens and alternative regimens for first-line therapy of advanced breast cancer. Ongoing studies have already demonstrated the feasibility of a large number of combinations; the docetaxel-based non-anthracycline-containing regimens might well prove one of the best treatment options for patients who relapse following anthracycline-based adjuvant therapy, while docetaxel/anthracycline

Table 2. Recommended dose of docetaxel in combination therapy

Docetaxel (mg/m²)	Second agent/dose (mg/m²)	Schedule (weeks)	DLT	Response rate %
75	Doxorubicin/50	every 3	Febrile neutropenia	>70
75	Fluorouracil CIV*5d/350	every 3	Febrile neutropenia	>65
85	Cyclophosphamide/600	every 3	Febrile neutropenia	>70
85	Vinorelbine/20 d1&5	every 3	Febrile neutropenia	>70

DLT, dose-limiting toxicity; CIV, continuous infusion. Data taken from Rhône-Poulenc Rorer clinical trials (unpublished).

regimens should be considered for patients who have not received anthracyclines as part of their adjuvant therapy.

The marked activity of docetaxel in patients with anthracycline-refractory breast cancer suggests that sequential regimens (anthracyclines followed by docetaxel) should be studied. Questions that need to be answered include what is the incidence of fluid retention syndrome, should docetaxel be used as part of a maintenance regimen, and how long do patients respond to the treatment?

Dose-densified regimens with docetaxel

Dose-densified regimens could prove promising in patients undergoing treatment with 'curative intent'. Few data are, however, available so far.

Dose-densified cyclophosphamide/docetaxel regimen

We are currently conducting a phase I trial where both cyclophosphamide and docetaxel are given every 2 weeks: the starting dose of docetaxel is 66 mg/m^2 and that of cyclophosphamide is 600 mg/m^2. The second level (cyclophosphamide 800 mg/m^2) has been studied in 12 patients: the incidence of grade IV neutropenia was 100%, while the incidence of febrile neutropenia (no haemopoietic growth factor was used at this stage) was 24%. No unexpected toxicity, apart from asthenia, was observed. Patients were able to complete the planned six cycles in 3 months without needing a dose reduction.

Dose-densified doxorubicin/docetaxel combination

Both doxorubicin and docetaxel are given every 2 weeks with granulocyte colony-stimulating factor support as part of the induction phase of a European multicentric protocol addressing first-line treatment of metastatic breast cancer. This study will also investigate the benefit of a double intensification with blood stem-cell support. Preliminary data have confirmed the feasibility of this regimen, the effective priming of peripheral blood stem-cells achieved with this regimen and the absence of unexpected toxicity. Based on these data the phase III study should start in the first quarter of 1997.

Thus, docetaxel is already integrated in therapeutic approaches with curative intent; however, the ultimate activity of these treatment regimens will be assessable only within 2–3 years.

Docetaxel as part of adjuvant/neo-adjuvant therapy of patients with breast cancer

The inclusion of docetaxel as part of adjuvant therapy for stage I–III breast cancer is already being considered by a number of collaborative groups. Based on the established superiority of the tamoxifen/epirubicin combination over tamoxifen monotherapy [6], The International Collaborative Cancer Group will start a study in 1997 comparing the previous combination to tamoxifen and the sequential epirubicin/docetaxel regimen in post-menopausal patients with node-positive breast cancer.

Using a factorial design, two sequential combinations (doxorubicin followed by cyclophosphamide/methotrexate/5-fluorouracil [CMF] versus doxorubicin followed by docetaxel then by CMF) will be assessed in an intergroup study, along with the increase in relative dose-intensity in patients with high risk node-positive breast cancer. The third trial will compare six cycles of dose-intensive FEC ($FE_{100}C$)—a reference regimen to docetaxel*3 followed by $FE_{100}C$*3.

Other regimens can also be considered. In any case such adjuvant trials will require a large number of patients (800–1400) studied for a substantial period of time (median follow-up of 3–5 years) to establish the role of docetaxel in the adjuvant treatment of breast cancer.

CONCLUSIONS

Docetaxel has rapidly been shown to be one of the most active agents in the treatment of patients with breast cancer, a finding that leads to several interesting possibilities.

First-line treatment of advanced breast cancer

The increasing use of anthracyclines as part of adjuvant therapy prompts oncologists to define alternative regimens for patients who relapse following such adjuvant therapy. The interesting activity of some regimens has already been reported [7]. Nevertheless there is a need for more-active combinations: the available data suggest that docetaxel could contribute to the definition of such regimens.

Treatment of patients with metastatic breast cancer and no prior exposure to anthracyclines

While anthracycline-based regimens remain the gold-standard for patients with metastatic breast cancer and no prior exposure to anthracyclines, the activity of such treatments is deceiving because they have failed to significantly alter the evolution of the disease. Docetaxel/anthracycline combinations—whether sequential or simultaneous—offer a new window of opportunity for such patients. Furthermore, the feasibility and activity of dose-densified regimens may alter the course of the disease.

Treatment of stage I–III breast cancer

Over the past 10 years the most significant advances have been seen in the treatment of stage I–III breast cancer. Increasing the dose intensity of anthracycline-based regimens is now a valid treatment option [7, 8]. These advances may have reached their limits, however, at least when conventional dose-intensity is used. The availability of an active agent with a different mechanism of action and limited cross-resistance with anthracyclines opens new possibilities, and will be addressed in phase III studies planned with docetaxel as part of the adjuvant therapy.

Second-line treatment of advanced breast cancer

Docetaxel has been validated as an effective treatment for advanced breast cancer. While docetaxel improves the prognosis of such patients, either as a single agent or as part of a combination regimen, we believe that the ultimate impact on the disease will remain limited; efforts should therefore be made to improve the efficacy of treatment strategies for patients with less-advanced breast cancer.

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