

Docetaxel: use in non–small cell lung cancer and metastatic breast cancer and formulation update

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Objective. To summarize the systematic development of docetaxel as a new and effective treatment option for advanced non–small cell lung cancer (NSCLC) and breast cancer patients, and to discuss the physical and chemical stability, compatibility with drugs commonly used in cancer patients, and administration issues with the new docetaxel formulation.

Data Sources. A MEDLINE search was conducted using carboplatin, cisplatin, compatibility, docetaxel, doxorubicin, metastatic breast cancer (MBC), NSCLC, and stability as search terms. Reference lists, bibliographies of pertinent articles, and abstracts from the American Society of Clinical Oncology and the European Society for Medical Oncology annual meetings were also identified and reviewed. Information related to the new docetaxel formulation was obtained from the manufacturer. The clinical literature was reviewed and analyzed.

Data Synthesis. Docetaxel has recently emerged as an active agent in the treatment of advanced NSCLC and MBC. Results of phase II and III studies of single-agent docetaxel and docetaxel combinations, both as first- and second-line therapy, have

produced impressive response rates and improved survival times compared with current standards of care. Docetaxel has a unique toxicity profile that includes hypersensitivity reactions, skin toxicities, and fluid retention. Because docetaxel's toxicity profile differs from that of the platinum analogs and the anthracyclines, combinations with these agents for NSCLC and MBC are well tolerated.

Docetaxel was recently reformulated, allowing for improved stability, shelf-life, and storage requirements. Compatibility studies of docetaxel with 81 commonly used drugs in cancer patients were recently reported, showing that docetaxel is compatible with all but three drugs studied—amphotericin B, nalbuphine hydrochloride, and methylprednisolone sodium succinate—when administered as Y-site injections into existing intravenous lines. With the increasing use of this agent, the new docetaxel formulation and compatibility data should facilitate ease of administration.

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Key Words: Carboplatin; cisplatin; compatibility; docetaxel; doxorubicin; metastatic breast cancer; non – small cell lung cancer; stability.

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INTRODUCTION

New developments in the management of non – small cell lung cancer (NSCLC) and breast cancer are redefining the standards of treatment for these diseases. The taxanes, paclitaxel and docetaxel, are among the most used chemotherapy agents for these indications because of their broad spectrums of activity, impressive response rates (RRs), and low side effect profiles.

Docetaxel (Taxotere[®], Aventis Pharmaceuticals, Frankfurt, Germany or Parsippany, NJ, USA), a

semisynthetic taxoid derived from the needles of the yew tree, *Taxus baccata*, significantly improves RRs, median survival times (MSTs), and median time to disease progression (TTP) compared with best supportive care (BSC) in platinum-resistant NSCLC and standard salvage therapy (i.e., mitomycin–vinblastine) in anthracycline-resistant metastatic breast cancer (MBC).^{1–3} Therefore, docetaxel is indicated as second-line therapy in both locally advanced and metastatic NSCLC and breast cancer patients who have failed platinum-based chemotherapy or prior chemotherapy, respectively.

The side effect profile of docetaxel is distinct from that of other agents commonly used to treat NSCLC and MBC. Neutropenia is the dose-limiting toxicity (DLT) of docetaxel; grade 4 neutropenia occurs in up to 85% of patients receiving 100 mg/m² and 75% of patients receiving 60 mg/m². Severe fluid retention (6.5%) and hypersensitivity reactions (2.2%) characterized by hypotension and/or bronchospasm or a generalized rash with erythema occur infrequently, despite prophylactic corticosteroid therapy. Neurosensory effects such as paresthesias and dysesthesias were reported in approximately 5% of MBC patients receiving docetaxel; however, symptoms resolved completely within 9 weeks of therapy discontinuation. Unusual skin reactions including a pruritic rash, mainly on the hands and feet, but also on the arms, face, and thorax, have been observed and hypo- and hyperpigmentation of nail beds, occasionally accompanied by onycholysis and pain rarely occur.¹ Because these adverse effects are not generally observed with other agents commonly used to treat these diseases, i.e., the platinum compounds for NSCLC and the anthracyclines for MBC, docetaxel is well suited for combination therapy.

As a result of its substantial antitumor activity and unique side effect profile, docetaxel's clinical development has moved rapidly from single-agent trials to combination trials and from second-line therapy to first-line or adjuvant therapy. This article focuses on the systematic development of docetaxel as a new and effective treatment option for NSCLC and breast cancer patients.

DOCETAXEL IN NSCLC

Lung cancer is the most frequently occurring cancer worldwide and is the leading cause of cancer-related deaths in the United States.⁴ Results of a recent meta-analysis demonstrated a modest but statistically significant advantage ($P < 0.0001$) for patients treated with cisplatin-based regimens compared with supportive care alone.⁵ However, in NSCLC patients with refractory or platinum-resistant disease, few therapeutic options exist. Historically, chemotherapy has produced RRs of 10% or less.² Docetaxel is among the most active of several new agents that has been evaluated in patients with platinum-refractory NSCLC and as first-line treatment in both phase II and phase III trials.⁶

Docetaxel monotherapy

Phase II trials

Second-line therapy. Phase II trials show consistent activity with single-agent docetaxel as second-line therapy for NSCLC. Four phase II studies using 100 mg/m² in 151 assessable patients resulted in RRs of 16% to 27%, MSTs of 30 to 42 weeks, and 1-year survival rates of 25% to 44% (Table 1).^{7–10} A single study of 60 mg/m² yielded a RR, MST, and 1-year survival rate similar to those produced with 100 mg/m² (Table 1), indicating that a lower dose may be sufficient to yield the desired results.¹¹

First-line therapy. Results of numerous phase II trials evaluating single-agent docetaxel as first-line therapy for NSCLC show consistent RRs of 20% to 30%.⁶ Of 11 phase II trials, nine evaluated docetaxel at a dosage of 100 mg/m² every 3 weeks. Three hundred forty-nine patients were evaluated in these studies with observed RRs of 23% to 63%, MSTs of 27 to 48 weeks, and 1-year survival rates of 21% to 45% (Table 2).^{7,10,12–18} The other two trials evaluated lower dosages and observed similar RRs and survival times, indicating, again, that a lower dose may be sufficient to achieve the desired results (Table 2).^{19,20}

Table 1. Phase II Trials of Docetaxel Monotherapy in Pretreated NSCLC Patients

Author	Docetaxel dose, mg/m ²	No. of assessable patients	RR, %	MST, wk	1-Yr survival rate, %
Burris <i>et al</i> ⁷	100	11	27	NR	NR
Fossella <i>et al</i> ⁸	100	42	21	42	44
Gandara <i>et al</i> ⁹	100	80	16	30	25
Robinet <i>et al</i> ¹⁰	100	18	22	NR	NR
Nakamura <i>et al</i> ¹¹	60	29	21	41	27

MST = median survival time; NR = not reported; NSCLC = non-small cell lung cancer; RR = response rate. Modified and reprinted with permission from Fossella.⁶

Table 2. Phase II Trials of Single-Agent Docetaxel as First-Line Treatment of NSCLC

Author	Docetaxel dose, mg/m ²	No. of assessable patients	RR, %	MST, wk	1-Yr survival rate, %
Francis <i>et al</i> ¹²	100	29	38	27	21
Fossella <i>et al</i> ¹³	100	39	33	47	45
Cerny <i>et al</i> ¹⁴	100	35	23	48	NR
Burris <i>et al</i> ⁷	100	9	33	NR	NR
Gob <i>et al</i> ¹⁵	100	16	63	NR	NR
Robinet <i>et al</i> ¹⁰	100	54	31	NR	NR
Lira-Puerto <i>et al</i> ¹⁶	100	41	54	NR	NR
Latreille <i>et al</i> ¹⁷	100	35	25	44	NR
Mattson <i>et al</i> ¹⁸	100	91	26	36	36
Miller <i>et al</i> ¹⁹	75	20	25	39+	71
Kunitoh <i>et al</i> ²⁰	60	75	19	42	41

MST=median survival time; NR=not reported; NSCLC=non-small cell lung cancer; RR=response rate. Modified and reprinted with permission from Fossella.⁶

The results of these phase II trials clearly indicate that single-agent docetaxel in the first-line treatment of NSCLC demonstrate equally efficacious RRs and survival times compared with other commonly used chemotherapy agents in this disease.⁶

Phase III trials

Second-line therapy. An international trial by Shepherd *et al*²¹ compared single-agent docetaxel with BSC in platinum-pretreated NSCLC patients. BSC was determined by the treating physician and could include antibiotics, analgesics, transfusions, and palliative radiation therapy. This prospective trial randomized patients to either docetaxel 100 mg/m² (*n* = 104) or BSC (*n* = 100). Interim safety data revealed a significantly higher toxic death rate in the chemotherapy arm, thus the protocol was amended and the docetaxel dose was reduced to 75 mg/m² for the remainder of the study. Of 104 patients randomized to receive docetaxel, 49 received 100 mg/m² and 55 received 75 mg/m². The primary end point was prolongation of survival, with docetaxel achieving a greater MST (7 *vs* 4.6 months; *P* = 0.047) and 1-year survival rate (29% *vs* 19%, respectively) than BSC. When survival was compared separately for the differing doses of docetaxel, there was no difference between docetaxel 100 mg/m² and BSC. However, the MST and 1-year survival rate were significantly improved in patients treated with 75 mg/m² compared with BSC (7.5 *vs* 4.6 months, *P* = 0.01 and 37% *vs* 12%, *P* = 0.003). Although not a primary end point of the study, RR was evaluated in an intent-to-treat analysis and found to be disappointing at 5.8%. Overall TTP was longer for the docetaxel group compared with the BSC group (10.6 *vs* 6.7 weeks, *P* = 0.001). Furthermore, this effect was seen at both docetaxel dose levels (100 mg/m², *P* = 0.037; 75 mg/m², *P* = 0.004).

For patients receiving chemotherapy, neutropenia and febrile neutropenia were the most commonly

occurring hematologic toxicities observed. Eleven patients (22.4%) treated with docetaxel 100 mg/m² developed febrile neutropenia, three of whom died, whereas one patient treated with 75 mg/m² developed febrile neutropenia. The incidence of grades 3 and 4 nonhematologic toxicity was similar between the docetaxel and BSC groups, with the exception of diarrhea, which occurred more frequently in the docetaxel group. Although the RR in this trial was similar to that of other salvage regimens in NSCLC, this is the first trial to demonstrate a significant survival advantage. These results further suggest that at a dose of 75 mg/m², the benefits of therapy outweigh the risks.²¹

A randomized phase III trial (TAX320) by Fossella *et al*^{6,22} compared two dosages of docetaxel (100 mg/m² every 3 weeks or 75 mg/m² every 3 weeks) with a control of either vinorelbine (30 mg/m² weekly) or ifosfamide (2 gm/m²/d × 3 every 3 weeks) in 373 NSCLC patients previously treated with platinum-based therapy. Patients randomized to the control group received vinorelbine or ifosfamide (V/I) according to the choice of the treating physician and in the analysis were evaluated together. Patient characteristics among the groups were well matched. RRs were superior for both docetaxel groups (100 mg/m²: 10.8%, *P* = 0.001; 75 mg/m²: 6.7%, *P* = 0.036) compared with RRs for V/I (0.8%). Because patients were heavily pretreated, the low RRs are not surprising. TTP was longer in both docetaxel groups (*P* = 0.046) compared with V/I. MSTs were similar (range, 5.5–5.7 months) in all three groups; however, 1-year survival rates were more favorable in the docetaxel 75 mg/m² group (32%) compared with the docetaxel 100 mg/m² group (21%) and V/I group (19%) (*P* = 0.025). One third of patients in each group received subsequent chemotherapy following completion of the study, which may have had an impact on survival. Therefore, a survival analysis that censored for subsequent chemotherapy found that 1-year

survival was significantly higher in both docetaxel groups compared with V/I (32%, 32%, and 10%, respectively; $P < 0.01$).

The incidence of grade 4 neutropenia and febrile neutropenia was significantly more prevalent among patients receiving docetaxel compared with V/I ($P < 0.001$). Nonhematologic toxicities, including asthenia, fluid retention, and neurotoxicity, did not differ among the groups.^{6,22}

First-line therapy. Results of a phase III, multicenter trial of docetaxel plus BSC versus BSC alone as first-line treatment for patients with metastatic or unresectable localized NSCLC revealed improvement in survival times and quality of life for the docetaxel patients.²³ Of 207 randomized patients, 137 received docetaxel 100 mg/m² every 3 weeks in addition to the BSC defined by each institution. BSC could include antibiotics, analgesics, transfusions, palliative radiation, or other symptomatic therapy as medically indicated. Docetaxel was administered until progressive disease was documented, maximum benefit was obtained, or unacceptable side effects occurred. Overall survival (OS) time was the primary end point of the study; TTP, RR, and duration of response were the secondary end points. Patients treated with docetaxel exhibited significantly longer OS rates than patients treated with BSC alone ($P = 0.026$). Docetaxel plus BSC compared with BSC alone produced an MST of 6 months *vs* 5.7 months, a 1-year survival rate of 25% *vs* 16%, and a 2-year survival rate of 12% *vs* 0%, respectively. In addition, none of the BSC alone patients were alive after 20 months. In an intent-to-treat analysis, TTP was significantly longer ($P < 0.001$) in the docetaxel group compared with the BSC alone group (12.6 *vs* 8.9 weeks, respectively); the overall RR for docetaxel was 13.1% and durations of response ranged from 14 to 90 weeks, with a median duration of

37 weeks. Furthermore, patients treated with docetaxel used less opiate and nonopiate analgesics ($P < 0.01$), palliative radiation therapy ($P < 0.01$), and tumor-related medications other than for pain ($P < 0.01$). Docetaxel-treated patients did, however, use significantly more antibiotics ($P = 0.027$).

The results of these phase III trials comparing docetaxel with either BSC or standard salvage chemotherapy show that docetaxel has significant activity as both first-line treatment and in patients with platinum-refractory NSCLC. The hematologic toxicities, however, are significant, although the data suggest that fewer toxicities occur and survival is prolonged at a dose of 75 mg/m².

Docetaxel combination therapy

Docetaxel plus cisplatin

Docetaxel has been combined with several other agents traditionally used to treat NSCLC as first-line therapy, namely cisplatin and carboplatin. Results of several phase I studies confirm that the combination of docetaxel and cisplatin is active, with manageable toxicities.²⁴

Numerous phase II trials have now evaluated the combination of docetaxel and cisplatin in the first-line treatment of advanced NSCLC (Table 3).²⁵⁻³² Most trials evaluated patients receiving 75 mg/m² of both docetaxel and cisplatin, with RRs ranging from 21% to 52%, and MSTs ranging from 9 to 13 months. Cole *et al*²⁹ evaluated a lower dose of docetaxel (65 mg/m²) in combination with cisplatin 100 mg/m². Although the number of patients evaluated was small ($n = 10$), RRs and MSTs were similar to those observed with higher docetaxel dosages. The authors suggest that a lower dose of docetaxel has the potential for lower costs and reduced long-term toxicities without compromising efficacy (Table 3). Georgoulas *et al*³²

Table 3. Phase II Trials of Docetaxel Plus Cisplatin in the First-Line Treatment of NSCLC

Author	No. of assessable patients	Docetaxel/cisplatin, mg/m ²	RR, %	TTP, wk	MST, mo	1-Yr survival, %	Grade 3/4 neutropenia; FN, %
Belani <i>et al</i> ²⁵	47	75/75	21	NR	10	NR	NR; 8.5
Zalcberg <i>et al</i> ²⁶	36	75/75	39	19	9.6	33	87; 13
Kim <i>et al</i> ²⁷	18	75/75	50	NR	NR	NR	60*; 10*
Faderl <i>et al</i> ²⁸	47	75/75	40	NR	NR	NR	19; NR
Cole <i>et al</i> ²⁹						NR	
Dose level 1	10	65/100	50	NR	>9		50*; 30
Dose level 2	25	75/75	52	NR	>10		64*; 36
Le Chevalier <i>et al</i> ³⁰	42	75/100	33	18	8.4	35	67; 16
Georgoulas <i>et al</i> ³¹	53	100/80	45	34	13	48	43; 28
Georgoulas <i>et al</i> ³²	132	100/80	32	35	10	42	33; 16

*Grade 4 toxicity only.

FN=febrile neutropenia; MST=median survival time; NR=not reported; NSCLC=non-small cell lung cancer; RR=response rate.

evaluated a higher dose of docetaxel (100 mg/m²) and cisplatin (80 mg/m²) in 132 advanced NSCLC patients, showing a similar RR, TTP, MST, and 1-year survival rate to those reported in other docetaxel–cisplatin phase II trials (Table 3).

Docetaxel plus carboplatin

Carboplatin is considered by many practitioners to be therapeutically equivalent to cisplatin, while offering the benefit of reduced gastrointestinal, renal, and neurotoxic effects. While carboplatin is less nephrotoxic and emetogenic than cisplatin, and neurotoxicity and ototoxicity are virtually absent, myelosuppression, especially thrombocytopenia, is the dose-limiting toxicity.³³ Only one trial has compared cisplatin (120 mg/m²) and carboplatin (324 mg/m²), both combined with etoposide (300 mg/m²) in NSCLC patients. Two hundred twenty-two patients were assessable for response, with a trend favoring cisplatin (RR, 27% vs 16%), but no significant differences in survival rates were observed. Toxicities, especially renal and hematologic toxicities, were greater on the cisplatin arm.³³ Because of the comparable efficacy and lower toxicity of carboplatin, several phase I and II trials assessing a docetaxel and carboplatin combination have been reported.

Phase I trial. The Greek Lung Cancer Cooperative Group³⁴ recently conducted a phase I study of docetaxel combined with carboplatin in previously untreated advanced NSCLC patients. Docetaxel was administered at escalating doses, starting with 70 mg/m² and increasing incrementally by 10 mg/m²; carboplatin was then administered, also at escalating doses, starting with an area under the curve (AUC) of 5 and increasing to an AUC of 7. A total of 35 patients were enrolled, 23 of whom were assessable for response. A PR was achieved in 17%; whereas 39% and 43% had stable and progressive disease, respectively. Grade 4 neutropenia, febrile neutrope-

nia, and grades 3 and 4 diarrhea were the DLTs. Nonhematologic toxicities, including mucositis, fatigue, neurosensory toxicity, and fluid retention, were mild. Two maximally tolerated doses (MTDs) were defined: docetaxel 80 mg/m² plus carboplatin AUC 7 and docetaxel 100 mg/m² plus carboplatin AUC 6.

Phase II trials. A multicenter, phase II study by Belani *et al*³⁵ evaluated the combination of docetaxel (80 mg/m²) and carboplatin (AUC = 6) as first-line treatment in 33 stage IIIB and IV NSCLC patients. One CR and 11 PRs were observed among 28 assessable patients, yielding an overall RR of 43%. The median duration of response was 5.5 months, median TTP was 5.4 months, MST was 13.9 months, and the 1-year survival rate was 52%. Hematologic toxicities predominated in this study, with 79% of patients experiencing grade 4 neutropenia and 15% of patients experiencing febrile neutropenia. Nonhematologic toxicities were generally mild; however, two patients experienced grade 3 or 4 diarrhea and one patient each experienced grade 3 or 4 nausea, vomiting, stomatitis, hepatic toxicity, hypersensitivity, and cardiac ischemia.

Several other phase II trials have evaluated the combination of docetaxel and carboplatin in the first-line management of advanced NSCLC.^{36–39} Docetaxel doses ranged from 65 to 100 mg/m²; carboplatin was administered at AUCs of 5 to 7.5, with the combination being administered every 3 weeks. The RRs ranged from 30% to 75%; MSTs had not been reached by the time of the articles' publications. Neutropenia and febrile neutropenia were the most commonly observed hematologic toxicities, while grades 3 and 4 diarrhea was the most common nonhematologic toxicity (Table 4).

Given the results of the phase II studies discussed, single-agent docetaxel is clearly an active drug in the treatment of advanced NSCLC. In addition, phase II studies have confirmed the efficacy of docetaxel combined with both cisplatin and carboplatin. Recently, a phase III trial evaluating three treatment

Table 4. Phase II Trials of Docetaxel and Carboplatin in NSCLC

Author	No. of assessable patients	Carboplatin/docetaxel	RR, %	Grades 3/4 toxicity
Millward <i>et al</i> ³⁶	41	AUC 6/75 mg/m ²	37	Neutropenia, 46%; [†] FN, 27%; diarrhea, 10%
Arcenas <i>et al</i> ³⁷	10	AUC 6/65 mg/m ²	30	Neutropenia, 47%; FN, 7%; diarrhea, 27%
Schütte <i>et al</i> ³⁸	25	AUC 5/80 mg/m ²	36	Neutropenia, 57%
Griesinger <i>et al</i> ³⁹	Stratum 1 [‡] =8 Stratum 2 [‡] =8	AUC 7.5/100 mg/m ²	75 75	NR

[†]Grade 4 toxicity only.

[‡]Percentage of cycles rather than patients.

[‡]Stratum 1 = stage IIIB patients; stratum 2 = stage IV or functionally inoperable patients. AUC = area under the curve; FN = febrile neutropenia; NR = not reported; NSCLC = non-small cell lung cancer; RR = response rate.

regimens: (a) docetaxel 75 mg/m² plus cisplatin 75 mg/m² every 3 weeks; (b) docetaxel 75 mg/m² plus carboplatin AUC 6 every 3 weeks; and (c) vinorelbine 25 mg/m² plus cisplatin 75 mg/m² every 4 weeks has completed accrual.²⁴ The results of this trial are eagerly awaited and may further advocate the use of docetaxel therapy in the first-line management of patients with advanced NSCLC.

DOCETAXEL IN BREAST CANCER

Anthracycline-based chemotherapy regimens are considered the mainstay of therapy for the treatment of MBC; however, doxorubicin, the most commonly used anthracycline and one of the most active single agents in MBC treatment, is associated with numerous side effects that limit its use as a palliative agent. These side effects include myelosuppression, nausea and vomiting, mucositis, and cumulative dose-dependent and generally irreversible cardiotoxicity.⁴⁰ Furthermore, the increasing use of anthracyclines as both adjuvant and neoadjuvant therapy limits the ability to reuse these agents once patients experience a recurrence or develop advanced disease. Thus, recent attention has focused on the activity of newer agents, including docetaxel, in the treatment of MBC.M

Docetaxel monotherapy

Phase II trials

In 1996, the European Organization for Research and Treatment of Cancer⁴¹ reported the results of a multicenter phase II trial of docetaxel 75 mg/m² as

first-line treatment of MBC. Of 39 women receiving docetaxel, 31 were assessable for response. A total of 20 patients (64.5%) had received prior adjuvant or neoadjuvant chemotherapy; in 18 of these patients, therapy contained an anthracycline. An overall RR was achieved in 16 (51.6%) of the 31 assessable patients. No significant differences in response between patients who had or had not received prior therapy (57% and 46%, respectively) were observed. Median duration of response and TTP were 34 and 24 weeks, respectively. The 8-month study follow-up did not yield a MST.

All 39 patients were assessed for toxicity. Grade 4 neutropenia and febrile neutropenia occurred in 82% and 8% of patients, respectively. The most common nonhematologic side effect was fluid retention (72%), which was defined as peripheral edema, facial edema, effusions (pleural, pericardial, or ascitic), and/or weight gain. Fluid retention was considered severe in only 13% of patients. The median time to the onset of peripheral edema was four cycles, with six cycles being the median number of cycles received by each patient. Furthermore, the median time to resolution of the edema following discontinuation of therapy was 18 weeks. Other commonly reported nonhematologic side effects included asthenia (61.5%), nail disorders (54%), skin reactions (51%), and weight gain (51%), but these were considered mild to moderate in severity.⁴¹

Numerous other phase II trials have evaluated docetaxel monotherapy as both first- and second-line treatment of MBC (Table 5).⁴¹⁻⁴⁶ RRs ranged from 40% to 68% in 115 assessable patients receiving first-line treatment; second-line therapy yielded RRs of

Table 5. Phase II Trials of Single-Agent Docetaxel in MBC

Author	Line of therapy	No. of assessable patients	Docetaxel dose, mg/m ²	RR, %	Survival, mo		Toxicity
					Median	1-Yr	
Fumoleau <i>et al</i> ⁴²	First	37	100	68 [†]	NR	NR	Neutropenia, 97%; FN, 14%; fluid retention, 89%
Trudeau <i>et al</i> ⁴³	First	47	100 (n=32) 75 (n=15)	63 40	11.7	NR	Neutropenia, NR; FN, 21%; hypersensitivity, 60%
Dieras <i>et al</i> ⁴¹	First	31	75	52	NR	NR	Neutropenia, 82%; FN, 7.7%; fluid retention, 72%
ten Bokkel Huinink <i>et al</i> ⁴⁴	Second	31	100	53	NR	NR	Neutropenia, 89% [†] ; fluid retention, 59%
Ravdin <i>et al</i> ⁴⁵	Second	35	100	57	NR	NR	Neutropenia, 95%
Valero <i>et al</i> ⁴⁶	Second	34	100	53	9	NR	Neutropenia, 89%; FN, 51%; fluid retention, 43%

*RRs were 68% in patients with visceral metastases, 77% in patients with liver metastases, and 83% in patients with >2 organs involved.

†Percentage of cycles rather than patients.

FN=febrile neutropenia; MBC=metastatic breast cancer; NR=not reported; RR=response rate.

53% to 57%. Interestingly, at a dose of 75 mg/m², the RRs were 40% to 52%, but increased to a mean of 60% with docetaxel 100 mg/m². Toxicities were similar among all treatment groups.

Single-agent docetaxel: phase III trials

Second-line therapy. Two recently published studies compared single-agent docetaxel with “standard” salvage chemotherapy regimens in MBC patients whose disease recurred following anthracycline-based therapy.

The TAX 304 Study Group⁴⁷ compared single-agent docetaxel 100 mg/m² administered every 3 weeks ($n=203$) with the combination of mitomycin 12 mg/m² administered every 6 weeks and vinblastine 6 mg/m² given every 3 weeks ($n=189$). Patients in the docetaxel group received a 5-day course of corticosteroid premedication to prevent fluid retention. A total of 350 patients were assessable for response, 179 in the docetaxel group and 171 in the mitomycin–vinblastine (MV) group. Overall RR was higher in the docetaxel group compared with the MV group (33% *vs* 12%, $P<0.0001$) as was the CR rate (3.9% *vs* 1.2%), although statistically the difference in the CR rate was not significant. Analysis of several subgroups revealed that docetaxel produced a higher RR than did MV in patients with visceral involvement (30% *vs* 11%, $P<0.01$), liver involvement (33% *vs* 7%, $P<0.01$), and anthracycline resistance (30% *vs* 7%, $P<0.01$). Median TTF, TTP, and OS time were longer in the docetaxel group compared with the MV group (16 *vs* 10 weeks, $P=0.0003$; 19 *vs* 11 weeks, $P=0.0004$; and 11.4 *vs* 8.7 months, $P=0.0097$, respectively).

The docetaxel group produced more hematologic toxicities, particularly grades 3 and 4 neutropenia and febrile neutropenia (93% *vs* 62%, $P\leq 0.05$; 9% *vs* 0.5%, $P<0.05$, respectively) whereas MV produced more grades 3 and 4 thrombocytopenia (12% *vs* 4%, $P=0.004$). Overall, nonhematologic toxicities, including nausea (42% *vs* 33%), vomiting (23% *vs* 18%), and constipation (21% *vs* 8%), occurred more frequently in the MV group, whereas diarrhea (38% *vs* 8%), stomatitis (56% *vs* 18%), skin toxicity (32% *vs* 2%), nail disorders (41% *vs* 2%), and neurosensory toxicity (50% *vs* 20%) were more frequently associated with docetaxel. Each agent produced specific cumulative toxicities: severe pulmonary toxicity in the MV group (5%) and severe fluid retention in the docetaxel group (8%).⁴⁷

An open label, phase III trial in 283 advanced breast cancer patients failing anthracycline therapy was reported by Sjöström *et al.*⁴⁸ Patients were randomized to receive docetaxel ($n=143$) or sequential methotrexate and fluorouracil (MF; $n=139$). An

intent-to-treat analysis revealed that overall RR (42% *vs* 21%) and TTP (6.3 *vs* 3 months) were significantly improved in the docetaxel group compared with the MF group ($P<0.001$), although median OS was similar between the two groups (10.4 *vs* 11 months; $P=0.86$). Grades 3 and 4 neutropenia were more frequently observed in the docetaxel group (35% *vs* 13%; 42% *vs* 3%, respectively; $P<0.0005$); no significant differences were observed for other hematologic toxicities. More stomatitis, infection, fluid retention, peripheral neuropathy, skin toxicity, and nail changes were also observed in the docetaxel group ($P<0.001$); however, the majority of these adverse events were rated as mild or moderate in severity (grades 1 or 2). Mild to moderate conjunctivitis was the only adverse effect that occurred more frequently in the MF group ($P<0.01$).

These study results confirm the superiority of single-agent docetaxel over standard salvage chemotherapy with MV and MF in terms of RR, TTP, and OS; thus, docetaxel represents a distinct new treatment option for patients with MBC who experience disease progression following anthracycline-based therapy.

Docetaxel *vs* doxorubicin

As previously mentioned, doxorubicin has historically been considered the mainstay of MBC therapy, producing RRs of 25% to 33%.⁴⁰ Because single-agent docetaxel exhibits similar RRs, a comparison of these two agents was warranted.

In a phase III trial, the International TAX 303 Study Group⁴⁰ compared docetaxel 100 mg/m² with doxorubicin 75 mg/m² every 3 weeks for a maximum of seven cycles in MBC patients who had previously received alkylating-agent therapy. A total of 326 patients were randomized either to the docetaxel group ($n=161$) or the doxorubicin group ($n=165$). The baseline characteristics of the patients were not statistically significantly different. Of these randomized patients, 295 were assessable for response. The overall RR in the docetaxel group was significantly higher than that of the doxorubicin group (52% *vs* 37%, $P=0.012$). Additionally, the number of CRs was higher in the docetaxel group (7.4%) compared with the doxorubicin group (4.8%). Furthermore, TTP was longer in the docetaxel group, although this difference did not reach statistical significance (27 *vs* 23 weeks). Evaluation of all randomized patients revealed that the median OS time was similar between groups (docetaxel, 15 months; doxorubicin, 14 months).

The incidence of toxicity-related deaths was higher in the doxorubicin group compared with the docetaxel group (3% *vs* 1.2%). Of five deaths in the doxorubicin

group, one was infection related and four were cardiotoxicity related. Of two deaths in the docetaxel group, one was infection related and the other was due to disease progression. None of the docetaxel patients developed congestive heart failure (CHF), whereas six patients (3.7%) in the doxorubicin group developed clinical CHF. Interestingly, the patients who developed CHF did so following cumulative doses of doxorubicin below that considered to be high risk ($< 460 \text{ mg/m}^2$). Most hematologic adverse effects, specifically grade 4 neutropenia, were similar for both groups, but febrile neutropenia and infection were significantly higher in the doxorubicin group compared with the docetaxel group (16% *vs* 8%, $P = 0.02$). The doxorubicin group was more frequently associated with the nonhematologic toxicities of nausea, vomiting, and stomatitis, whereas common nonhematologic toxicities in the docetaxel group included diarrhea, skin toxicities, hypersensitivity reactions, nail disorders, and neurotoxicity. A higher treatment discontinuation rate (9.2%) in the doxorubicin group was due to cardiotoxicity, whereas 1.9% of docetaxel patients stopped treatment because of fluid retention.⁴⁰

This was the first randomized MBC trial in which a single agent produced significantly higher RRs than those of doxorubicin given at its highest tolerable dose without the aid of CSFs.⁴⁰ These results suggest that single-agent docetaxel is more effective than single-agent doxorubicin for the treatment of MBC.

Docetaxel plus doxorubicin. Because docetaxel and doxorubicin are two of the most active single agents in the treatment of MBC, have different side effect profiles, and docetaxel is active in anthracycline-resistant patients, the combination of these two agents was warranted.

Phase I trial. Misset *et al*⁴⁹ conducted a dose-finding study of docetaxel combined with doxorubicin in the first-line management of MBC, with the primary end points of MTD, DLT, and recommended doses of the combination. Forty-two untreated MBC patients received doxorubicin 40 to 60 mg/m^2 followed by docetaxel 50 to 85 mg/m^2 every 3 weeks without CSF support. To avoid hypersensitivity reactions, skin toxicity, and fluid retention, all patients were given a 3-day course of corticosteroid premedication beginning the day before chemotherapy initiation.

The doxorubicin–docetaxel combination was active at all dose levels, with an overall RR of 71%, which included two CRs (4.7%) and 28 PRs (66.6%). Patients treated at dose levels 3 through 6 (docetaxel 60–85 mg/m^2 and doxorubicin 50–60 mg/m^2) experienced the highest RR—81%. Other response indicators included

TTP (46 weeks) and a 2-year survival rate (66%). MST had not been reached at the time of publication.⁴⁹

After six courses of therapy, all patients were assessable for toxicity. Neutropenia was the DLT of the combination, occurring in all patients; 93% experienced grade 4 episodes. Febrile neutropenia requiring intravenous antibiotics and/or hospitalization was observed in 38% of patients. Both neutropenia and febrile neutropenia were brief. Other noted nonhematologic toxicities included GI toxicity, nail disorders, neurosensory toxicity, skin toxicity, and fluid retention, all of which were frequent but mild. Interestingly, no patients developed CHF, despite doxorubicin's reputation as a cardiotoxin. The recommended doses for phase II/III studies were doxorubicin 50 mg/m^2 plus docetaxel 75 mg/m^2 or docetaxel 60 mg/m^2 and doxorubicin 60 mg/m^2 .⁴⁹

Docetaxel plus doxorubicin: Phase III trial. The International TAX 306 Study Group⁵⁰ compared doxorubicin (50 mg/m^2) plus docetaxel (75 mg/m^2) (AT) with standard doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2) (AC), each administered every 3 weeks without CSFs. Of 429 enrolled patients, 423 were assessable for response. The overall RR was significantly higher for patients receiving AT compared with AC (60% *vs* 47%, $P = 0.008$), as was the CR rate (11% *vs* 8%). Subgroup analyses in patients with involvement of the viscera, liver, or three or more organs revealed higher RRs in those treated with AT compared with those treated with AC (58% *vs* 43%; 60% *vs* 48%; 61% *vs* 39%, respectively). Survival times were not available at the time of publication.

Discontinuation rates due to toxicity were equal between groups (AT 15% and AC 14%), but grades 3 and 4 adverse events, including neutropenia (82% *vs* 69%), febrile neutropenia (6% *vs* 2%), infection (1% *vs* $< 1\%$), and diarrhea (2% *vs* 1%), were all higher in the AT group. Although neutropenia was higher with AT, treatment discontinuation was not necessary. Cardiotoxicity was uncommon in both treatment groups with the incidence of CHF being 2% and 4% in the AT and AC groups, respectively. Additionally, the percentage of patients that developed a $\geq 30\%$ decrease in left ventricular ejection fraction was 2% in the AT group compared with 5% in the AC group. The lack of significant differences in cardiotoxicity observed between the AT and AC groups in this study is important because a well-documented drug interaction between paclitaxel and doxorubicin that results in significantly increased clinical cardiotoxicity has been reported.^{51,52} No drug interaction between docetaxel and doxorubicin has been observed *in vitro*

or *in vivo*. This important trial was the first to establish a doxorubicin–docetaxel combination as more effective than a standard anthracycline-containing regimen in the treatment of MBC.^{50,53}

Docetaxel as adjuvant therapy in breast cancer

Historically, the development of new chemotherapy regimens in MBC has been a tedious process involving a succession of trials, from phase I, II, and III single-agent studies in second-line metastatic disease therapy to first-line therapy studies to, finally, studies of the agent in combination with other agents. Consequently, evaluation of new agents for adjuvant therapy occurs only after this process has been completed, which is somewhat paradoxical because only in the adjuvant setting has a significant effect of chemotherapy on the natural history of breast cancer been demonstrated.⁵³

The National Surgical Adjuvant Breast and Bowel Project (NSABP)⁵⁴ was the first group to initiate a phase III adjuvant chemotherapy trial evaluating whether adding docetaxel sequentially to AC in the neoadjuvant setting prolongs DFS or OS. The control group is receiving AC for four courses plus tamoxifen followed by surgery; the two experimental groups are receiving AC for four courses plus tamoxifen followed by docetaxel either before or after surgery. This trial was initiated in 1995 and is anticipated to last for 5 years. In 1997, preliminary data were published regarding the first 283 patients, of a projected 1606 patients, with no unexpected toxicities having occurred. Final results of the trial, due in 2000, are anxiously awaited to determine if docetaxel with neoadjuvant AC prolongs survival times in patients with operable breast cancer.

Similarly, two additional trials are comparing docetaxel–doxorubicin–based therapy with non-taxane–doxorubicin–based therapy. The Breast Cancer International Research Group (BCIRG) randomized node-positive breast cancer patients to either TAC (docetaxel, doxorubicin, cyclophosphamide) \times 6 cycles or FAC (5-fluorouracil, doxorubicin, cyclophosphamide) \times 6 cycles; while the North American Intergroup is comparing AC \times 4 with AT \times 4 both in patients with high-risk, node-negative disease and in those with one to three positive nodes.⁵³ The results of these trials are anxiously awaited, as the prospect of docetaxel–doxorubicin–based therapy in the adjuvant setting appears promising.

There are two strategies for the incorporation of docetaxel into current adjuvant chemotherapy regimens, the administration of the drugs either in sequence or in combination. To determine which method is superior, Di Leo *et al*⁵⁵ evaluated the feasibility of docetaxel-based sequential and combina-

tion regimens in node-positive breast cancer patients. Three groups were compared: (a) doxorubicin 75 mg/m² every 3 weeks for three courses followed by docetaxel 100 mg/m² every 3 weeks for three courses followed by cyclophosphamide, methotrexate, and fluorouracil (CMF) every 4 weeks for three courses (A→T→CMF); (b) sequential accelerated A→T→CMF, where doxorubicin and docetaxel were administered at the same doses, but every 2 weeks; and (c) combination therapy consisting of doxorubicin 50 mg/m² plus docetaxel 75 mg/m² every 3 weeks for four courses followed by CMF for four courses. Patients receiving accelerated sequential A→T→CMF experienced a 23% withdrawal rate, primarily due to skin toxicity. Therefore, the accelerated sequential A→T→CMF cannot be recommended, but the combination regimen and nonaccelerated sequential regimens are feasible and currently under evaluation in phase III trials.

Docetaxel plus trastuzumab in HER2-positive patients

The oncogene HER2/*neu* (human epidermal growth factor receptor 2) is important in the regulation of normal cell growth. Overexpression causes the receptor to remain in an active state, resulting in increased tumor growth.⁵⁶ HER2 is overexpressed in 20% to 30% of breast cancer patients and is associated with a faster tumor growth rate, increased metastases rates, and decreased disease-free and overall survival times.⁵⁶ Therefore, HER2 status is considered to be an important prognostic factor in patients with breast cancer. Trastuzumab (Herceptin[®], Genentech, S. South Francisco, CA, USA), as a single agent, is indicated for the treatment of patients with MBC whose tumors overexpress the HER-2 protein and who have received one or more chemotherapy regimens for their metastatic disease. Trastuzumab in combination with paclitaxel is indicated for the treatment of patients with MBC whose tumors overexpress the HER-2 protein and who have not received chemotherapy for their metastatic disease.⁵⁷ Preliminary data in mice suggest trastuzumab plus docetaxel provide a synergistic combination.⁵⁸ More recently, preliminary data on 16 breast cancer patients who received docetaxel 75 mg/m² every 3 weeks plus trastuzumab 2 mg/kg weekly (4 mg/kg loading dose) until disease progression were reported. It is too early to measure RR, but two PRs have been observed. No grades 3 or 4 nonhematologic toxicities or febrile neutropenia has occurred. The trial will conclude after accrual of 30 patients.^{56,59}

The BCIRG has proposed two phase III adjuvant breast cancer trials using docetaxel–trastuzumab com-

binations. The BCIRG 005 trial will randomized HER2/*neu*-negative and -status unknown patients to receive (a) AC every 3 weeks for four cycles followed by docetaxel (100 mg/m^2) every 3 weeks for four cycles or (b) a combination of docetaxel 75 mg/m^2 , doxorubicin 50 mg/m^2 , and cyclophosphamide 500 mg/m^2 every 3 weeks for six cycles. The BCIRG 006 trial will randomize HER2/*neu*-positive patients to one of three treatment groups: (a) AC every 3 weeks for four cycles followed by docetaxel (100 mg/m^2) every 3 weeks for 4 cycles and weekly trastuzumab (4 mg, followed by 2 mg/kg per week) for 1 year; (b) docetaxel (75 mg/m^2) plus cisplatin (75 mg/m^2) or carboplatin ($\text{AUC} = 6$) every 3 weeks for six cycles plus weekly trastuzumab for 1 year; or (c) AC every 3 weeks for four cycles followed by docetaxel (100 mg/m^2) every 3 weeks for four cycles.⁶⁰

Docetaxel represents a new and exciting treatment option for both NSCLC and MBC patients. Ongoing research will further define docetaxel's role in combination regimens and in the adjuvant treatment of these diseases.

DOCETAXEL: PHARMACEUTICAL ISSUES

Physical and chemical properties

Recently, a new, more physically and chemically stable formulation of docetaxel was developed for use in Europe and the United States (US). The new formulation consists of a clear, viscous, yellow to yellow-brown solution containing docetaxel 40 mg/mL and polysorbate 80 1040 mg/mL . Docetaxel is supplied in 20- and 80-mg single-dose vials as a sterile, pyrogen-free, nonaqueous solution and requires dilution before use with the single-dose 13% ethanol-in-water diluent provided with each vial. The manufacturer recommends that docetaxel be stored between 2°C and 25°C ($36\text{--}77^\circ\text{F}$) before mixing and retained in the original packaging for protection from bright light. This recommendation differs slightly from that for the previous formulation, which required storage between 2°C and 8°C ($36\text{--}46^\circ\text{F}$). This newer formulation also offers a longer shelf life of 18 months for the 20-mg vial and 24 months for the 80-mg vial—the older formulation offered shelf lives of only 12 months and 15 months for each of these strengths, respectively. Most importantly, the newer formulation confers greater stability of the final dilution for infusion. The previous formulation required immediate administration upon mixing the final dilution for infusion. Although the manufacturer continues to recommend that the final docetaxel infusion solution be used as soon as possible following dilution, it may be stored for up to 4 hours, provided it is stored between 2°C and 25°C . The new formulation of docetaxel requires a

final concentration between 0.3 and 0.74 mg/mL compared with the previous formulation, which allowed for a concentration up to 0.9 mg/mL .⁶⁰

Administration procedures

The manufacturer-recommended administration procedures for docetaxel differ for the US and Europe. According to the US prescribing information, diluted docetaxel should be stored in bottles or plastic bags made of polypropylene or polyolefin and administered through polyethylene-lined infusion sets in order to minimize patient exposure to the plasticizer diethylhexyl phthalate (DEHP), a substance which may be leached from polyvinyl chloride (PVC) infusion bags or sets. In Europe, however, PVC bags and administration sets are commonly used.

In 1997, Mazzo *et al*⁶¹ evaluated the extent to which DEHP was leached from PVC infusion sets by docetaxel and paclitaxel solutions. During 1-hour simulated infusions, the brand of PVC infusion bag, final diluent, and docetaxel concentration had no effect on the DEHP concentration leached at the end of the infusion. Conversely, following a 3-hour simulated infusion, paclitaxel leached two to eight times more DEHP as did docetaxel.⁶¹ Results of another study by Thiesen and Krämer⁶², demonstrated that prolonged physical stability and decreased DEHP load favored the use of non-PVC containers versus PVC containers for docetaxel infusion solutions when more than 8 hours of storage intervals were required. Diluted docetaxel solutions may be stored in PVC containers for short periods; however, these solutions should be inspected carefully for precipitants prior to administration.⁶²

Compatibility of docetaxel

Pharmaceutical compatibility issues are important in treating oncology patients, who typically receive a myriad of drugs. Because docetaxel has become a widely used chemotherapeutic agent, Trissel *et al*⁶³ evaluated the physical compatibility of docetaxel (prior formulation), during simulated, simultaneous Y-site injections, with selected anti-infective and supportive care agents commonly used in oncology patients, including antiemetics, steroids, and analgesics. Of 81 agents tested, only 3—amphotericin B, nalbuphine hydrochloride, and methylprednisolone sodium succinate—were found to be incompatible.⁶³ The purpose of this study was to evaluate the physical compatibility of docetaxel with drugs that may be administered concurrently using a Y-site injection. These study results, however, do not establish the physical or chemical compatibility of these drug combinations when mixed together in the same container.

CONCLUSIONS

Data confirm docetaxel's activity in the treatment of both advanced NSCLC and MBC. When docetaxel is combined with either cisplatin or carboplatin in NSCLC, efficacy is apparent, although studies to date have not clearly defined the recommended dosages of each agent when used in combination. Furthermore, TTP and survival times are significantly prolonged with the use of docetaxel compared with BSC, which further reinforces docetaxel's status as one of the most favorable drugs in the treatment of advanced NSCLC.

As first-line MBC therapy, the combination of docetaxel and doxorubicin has proved superior to standard anthracycline-containing combination regimens; additionally, in a phase III trial, the taxane combination produced a higher RR than did the established doxorubicin-cyclophosphamide combination. Survival data from this phase III study are awaited, but the docetaxel-doxorubicin combination offers great promise and may have a substantial impact on the natural history of breast cancer.⁵³ Several phase III trials are evaluating the use of docetaxel-based therapy as adjuvant treatment in patients with operable breast cancer. The results of these studies, especially those comparing AC with sequential versus concurrent docetaxel with or without trastuzumab and docetaxel-trastuzumab-platinum analog combinations, are eagerly awaited.

Docetaxel is clearly a multifaceted agent that may well challenge the use of currently accepted treatment methods for both NSCLC and MBC.

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