REVIEW

Docetaxel in the treatment of non-small cell lung carcinoma: an update and analysis

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Abstract: Docetaxel, a semisynthetic taxane, was the first agent to show efficacy in the second-line treatment of non-small cell lung cancer (NSCLC), and has since become a mainstay of NSCLC therapy. We review its mode of action, pharmacology, toxicity and efficacy and describe both its established role in the treatment of NSCLC and future directions in research. Docetaxel works primarily by promoting microtubule assembly and polymerization, and through this hyperstabilization, causes cell cycle arrest and death. The primary toxicity of docetaxel is neutropenia, which can be mitigated by weekly administration in selected patients. Less common toxicities are peripheral edema, which can be reduced by appropriate premedication and interstitial pneumonitis. Hypersensitivity reactions are less frequent than with paclitaxel. Docetaxel has shown a survival and quality of life advantage as a single agent first- and second-line versus placebo, as well as first-line in a platinum-based doublet therapy compared to a single agent. Increasingly docetaxel has also been used effectively in adjuvant regimens in earlier stages of the disease. Future areas of research include combinations with novel targeted therapies, and a greater understanding of biomarkers that might help predict efficacy and personalize therapy.

Keywords: Docetaxel, taxanes, non-small cell lung carcinoma, review, metastatic, adjuvant

Introduction

Lung cancer continues to be the most common cause of cancer-related morbidity, leading to an estimated 159,840 deaths in the United States in 2009 alone.[1] Among incident lung cancer cases in the US, about 85% are non-small cell lung cancer (NSCLC). Unfortunately, only approximately 30% of NSCLC is detected at an early, resectable stage, and nearly half of patients present with metastatic disease.[2] Even a substantial portion of the patients that are diagnosed at the earlier stages progress and will require systemic therapy.

The mainstay of therapy for over 15 years in stage IV or inoperable stage III cancer has been a platinum doublet (ie, either cisplatin or carboplatin in combination with a second chemotherapeutic agent), initiated at the time of diagnosis as first-line therapy. Until the introduction of the semisynthetic taxane docetaxel (Taxotere®; sanofi-aventis, Paris, France), no treatment had been shown in randomized clinical trials to improve survival or quality of life in the second-line treatment of advanced or metastatic NSCLC. Since its approval for this indication, docetaxel has also been approved for use in the first-line setting, either alone or in combination with a platinum agent and has been investigated for earlier stages of disease and in a variety of combinations with novel agents as well. Although other chemotherapy agents with utility in this clinical niche

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have since been introduced, docetaxel remains a mainstay of the NSCLC therapy.

This paper will discuss the pharmacology of docetaxel and its toxicity profile. The clinical efficacy of docetaxel will then be reviewed in various clinical scenarios with an emphasis on phase III and notable phase II studies. We will briefly review the significance of patient-related outcome data associated with docetaxel, and will then conclude with a discussion of selected trials currently underway.

Pharmacology

Docetaxel is a member of the taxane family that includes paclitaxel. Whereas paclitaxel is the active ingredient of the bark of the Pacific Yew tree, *Taxus brevifolia*, docetaxel is a semi-synthetic combination formed by the esterification of a noncytotoxic precursor extracted from the needles of the European yew, *Taxus baccata*.[3] An early advantage of the drug was the more widespread availability (and ability for regeneration) of this different yew species,[4] but over time some relative clinical advantages of docetaxel over paclitaxel have emerged.

Like paclitaxel, docetaxel promotes microtubule assembly and polymerization. By stabilizing the growing microtubule, the drug disrupts the equilibrium between tubulin formation and breakdown, ultimately leading to the impairment of mitosis and then cell cycle arrest.[4] Docetaxel is twice as potent as paclitaxel in its ability to inhibit depolymerization, and cross resistance between taxanes is incomplete, with the second-line activity of docetaxel documented in patients previously treated with paclitaxel.[5] For example, in the pivotal TAX 320 study of second-line docetaxel versus vinorelbine or ifosfamide after a platinum doublet, a subgroup analysis was performed of patients who had previously been treated with paclitaxel. Among patients on the docetaxel arm, there was no difference in efficacy or survival between the patients who had previously progressed on paclitaxel and those who had never previously been exposed to a taxane.[6]

The taxanes may also work by other mechanisms. They may directly influence apoptosis pathways, and the higher potency docetaxel exhibits in phosphorylating bcl-2, compared to paclitaxel, may explain its stronger proapoptotic activity.[7] Docetaxel also has some antiangiogenic effect that has been demonstrated both *in vitro* and *in vivo* to a greater extent than paclitaxel.[7] Though less well understood, aside from their antimitotic properties, taxanes also appear to induce proinflammatory genes and proteins, including tumor necrosis factor-α, various interleukins and enzymes such as nitric oxide synthase and cycloocygenase-2, and

though it is unclear what role this may play in its tumor cytotoxic effect,[8] there is a suggestion this upregulation may play a role in the hypersensitivity reactions experienced by patients.[7]

Toxicity

The primary dose-limiting toxicity in early studies of docetaxel was neutropenia, and even at the therapeutic doses given in current practice, neutropenia persists as a frequent toxicity effect.[3] A systematic review of studies enrolling a total of 1609 patients reported a pooled estimate of febrile neutropenia incidence of about 6%.[9] Another meta-analysis reported that weekly dosing led to a reduction of grade 3 and 4 neutropenia (18% versus 5%, $P < 0.0001$) and febrile neutropenia (6% versus <1%, $P < 0.0001$).[10] Low grade anemia is noted in a large majority of patients treated with docetaxel, but less than 10% have grade 3 or above anemia. This is not significantly different in weekly dosing.

Though a weekly schedule confers less neutropenia, it is associated with significantly elevated rates of epiphora, or excessive tearing. While more frequently noted in trials of docetaxel in breast cancer patients than in NSCLC, this toxicity can occasionally be dose-limiting. Prompt symptom control is critical with ocular moisturizers or even short course ophthalmologic steroids.[11]

Another toxicity more commonly seen with docetaxel than with paclitaxel is peripheral edema, typically starting with the lower extremities. Use of a dexamethasone premedication regimen of 8 mg by mouth, twice daily, the day before, the day of, and the day after treatment with docetaxel can significantly reduce the incidence of edema.

Though hypersensitivity reactions are less common in patients receiving docetaxel compared with paclitaxel, they have been observed, and may be related to the Polysorbate 80 in which the drug is dissolved.[12] It is thought that the above dexamethasone protocol may also help prevent hypersensitivity reactions.

Less common grade 3 and grade 4 toxicities include interstitial pneumonitis, which is related to both type I and type IV hypersensitivity reactions, and which may be increased in the setting of concomitant treatments such as gemcitabine.[13] Asthenia can be seen in as many as 18% of patients, although this is more common in the elderly. Common grades 1 and 2 toxicities associated with docetaxel include fatigue, nausea and vomiting, stomatitis and alopecia, but these do not typically worsen to grade 3. Nail dystrophy is also a common toxicity, which can lead to superinfection.[14] Neurotoxicity has

been noted infrequently, including paresthesias and dysesthesisas, though typically in grade 1 or 2.

Metabolism and drug–drug interactions

Docetaxel is metabolized extensively by the cytochrome P450 CYP system, with CYP3A representing the major route of inactivation. Other chemotherapeutics used in NSCLC do not appear to impair the clearance of docetaxel. Though the potential interactions between antiepileptic drugs and docetaxel have not been formally studied, they may reduce the effectiveness of docetaxel through increased clearance given they are powerful inducers of CYP3A4. Conversely, ketoconazole, a strong inhibitor of CYP3A, results in decreased docetaxel clearance.[15]

Docetaxel is primarily excreted through feces and bile, and must be dose reduced in the setting of hepatic impairment. However, the product insert directs the drug not be given when bilirubin is above the upper limit of normal, or when transaminases are above 1.5 times the upper limit of normal when alkaline phosphatase is more than 2.5 times the upper limit of normal. Docetaxel has minimal renal excretion and thus renal impairment does not preclude use of docetaxel.[16]

Efficacy

Docetaxel was first approved by the US Food and Drug Administration (FDA) in 1996 for use in metastatic breast cancer, but shortly thereafter garnered indications for first and second-line use in NSCLC. Below we review all the phase III trials involving docetaxel in the treatment of lung cancer, with selected references to pertinent phase II trials. Tables 1 and 2 summarize the efficacy data from the phase III trials, in advanced and metastatic disease, in the first and second line, respectively. Also we briefly describe efforts to study the use of docetaxel in earlier stages of the disease to complement chemoradiation and surgical modalities of treatment.

First-line use of docetaxel in advanced and metastatic NSCLC

The American Society of Clinical Oncology (ASCO) and most other oncology organizations endorse combination therapy for first-line use in most advanced stage NSCLC patients.[17] Typically these regimens consist of platinum chemotherapy doublets, and docetaxel is a frequently utilized component in these doublets as discussed below. However, for the elderly and those with a poor performance status combination regimens are rarely well tolerated and in such

patients single chemotherapeutics, including docetaxel, can be considered.[17]

Docetaxel as single agent

A seminal phase III study in advanced stage NSCLC reported by Roszkowski and colleagues in 2000 showed the superiority of docetaxel over best supportive care (BSC), increasing survival from 5.7 to 6.0 months, and 1-year survival from 16% to 25% ($P = 0.04$). Response and quality of life (QoL) were also superior in the docetaxel arm.[18] Notably, the study used a dose of 100 mg/m^2, which is now disfavored when compared to 75 mg/m^2 which gives a more favorable toxicity profile without any sacrifice of clinical efficacy, as demonstrated by the TAX 317 and 320 studies described below in the section on second-line treatment section.

WJTOG 9904, another phase III study, compared docetaxel at 60 mg/m^2 with vinorelbine in an elderly population over the age of 70 in Japan, and demonstrated a statistically significant improvement in response (22.7% versus 9.9%, $P = 0.019$), and a trend towards improved survival in patients treated with docetaxel (14.3 versus 9.9 months, hazard ratio 0.78, $P = 0.065$). This finding was of particular relevance given the concern for poor tolerability of combination regimens in the elderly demographic.[19]

Docetaxel in combination with a platinum agent

Several phase III studies have evaluated use of docetaxel as a component of a platinum doublet with either cisplatin or carboplatin. Georgoulias and colleagues compared a cisplatin/docetaxel doublet to docetaxel alone, using a dose of 100 mg/m^2 in both, and finding with the doublet an improved response rate (36.5% versus 21.1%, $P = 0.004$), though only a trend toward improved survival (10.5 versus 8.0 months, $P = 0.020$).[20]

Several studies have compared docetaxel-containing doublets to other doublets, with most making use of what has become the standard dose of docetaxel in doublet regimens, 75 mg/m^2. The large TAX 326 trial compared either cisplatin or carboplatin plus docetaxel with cisplatin plus vinorelbine as a control. This study showed improved response and survival with the cisplatin plus docetaxel regimen as compared to the cisplatin plus vinorelbine arm (31.6% versus 24.5%, $P = 0.029$ and 11.3 versus 10.1 months, $P = 0.044$). However, there was no significant difference between the control arm and the carboplatin plus docetaxel arm, indicating better efficacy with use of cisplatin.[21] These findings were confirmed in a subgroup analysis of patients over the age of 65.[22]

Table 1 Phase III trials of docetaxel used first-line in advanced or metastatic NSCLC

Trial and reference	Regimen	N	RR (%)	MST (months)	1 year OS (%)
Roszkowski[18]	– Doce 100 d1 q3w	207	13.1*	6.0*	25*
	– Best supportive care		0	5.7	16
WJTOG 9904	In elderly >70				
Kudoh[19]	– Doce 60 d1 q3w	182	22.7*	14.3	58.6
	– Vin 25 d1 + 8 q3w		9.9	9.9	36.7
Georgoulias[20]	– Doce 100 d1 + cis 80 d2 q3w	319	36.5*	10.5	44
	– Doce 100 d1 q3w		21.2	8.0	43
TAX 326	– Doce 75 + cis 75 d1 q3w	1218	31.6*	11.3*	46*
Fossella[21]	– Doce 75 + carbo AUC 6 d1 q3w		23.9	9.4	38
	– Vin 25 d1/8/15/22 + cis 100 d1 q4w		24.5	10.1	41
TAX 326 elderly only	In elderly >65				
	– Doce 75 + cis 75 d1 q3w	401	NR	12.6*	52*
Belani[22]	– Doce 75 + carbo AUC 6 d1 q3w			9	38
	– Vin 25 d1/8/15/22 + cis 100 d1 q4w			9.9	41
Kubota[23]	– Doce 60 + cis 80 d1 q3 or 4w	311	37.1*	11.3*	47.7*
	– Cis 80 d1 + vindesine d1/8/15 q4w		21.2	9.6	24.4
GLOB 3	– Doce 75 + cis 75 d1 q3w	390	27.2	9.8	40.9
Tan[24]	– Cis 80 d1 + vin IV 30 d1 + vin PO 80 d8 q3w (first cycle IV 25 and oral 60)		27.4	9.9	39.4
Booton[25]	– Doce 75 + carbo AUC 6 d1 q3w	433	67	9.5	39
	– Choice of Mito 6 + ifos 3 + cis 50 d1 q3w Mito 6 + vinblastine 6 + cis 50 d1 q3w		65	8.7	35
Schiller[26]	– Cis 75 + doce 75 q3w	1155	17	7.4	31
	– Cis 75 d2 + paclitaxel 135 d1 q3w		21	7.8	31
	– Cis 75 d1 + gem 1000 d1/8/15 q3w		22	8.1	36
	– Carbo AUC 6 + paclitaxel 225 q3w		17	8.1	34
Kubota[31]	– Vin 25 d1 + gem 1000 d1/8 q3w × 3, then doce 60 d1 q3w × 3	401	25*	13.6	57.1
	– Carbo AUC 6 + pac 225 d1 q3w × 6		37	14.1	56.5
Georgoulias[32]	– Doce 100 d8 + gem 1000 d1/8 q3w	413	30	9.0	34.3
	– Cis 80 d8 + vin 30 d1/8 q3w		39.2	9.7	40.8
Pujol[33]	– Doce 85 d8 + gem 1000 d1/8 q3w	311	31	11.1	46
	– Cis 100 d1 + vin 30 d1/8/15/22 q4w		35.9	9.6	42
Georgoulias[34]	– Doce 100 d1 q3w	312	11.6*	8.3*	35.5
	– Doce 75 d8 + gem 1100 d1/8 q3w		26.8	9.4	41.4
Hainsworth[35]	In elderly >65				
	– Doce 35 d1/8/15 q4w	350	17	5.1	24
	– Doce 30 + gem 800 d1/8/15 q4w		25	5.5	26
Cobo[36]	– Doce 75 + cis 75 d1 q3w	444	37.6*	9.8	39.0
	– Selection based on ERCC1 level		47.2	9.9	40.4
	– Low: doce 75 + cis 75 d1 q3w		53.2	10.4	44.0
	– High: doce 40 + gem 1000 d1/8 q3w		47.2	9.5	33.0
BMS-099	– Doce 75 or paclitaxel 225 + carbo AUC 6 d1 q3w + cetuximab 400, then 250 q1w	676	25.7*	NR	NR
Lynch[39]	– Doce 75 or paclitaxel 225 + carbo AUC 6 d1 q3w		17.2		

Notes: *denotes statistically significant result. All doses in milligrams per meter squared (mg/m²) except as noted.
Abbreviations: N, number of subjects; RR, response rate; MST, median survival time; OS, overall survival; Doce, docetaxel; q3w, every 3 weeks; Vin, vinblastine; Cis, cisplatin; Carbo, carboplatin; AUC, area under the curve; NR, not reported; PO, oral; IV, intravenous; Ifos, ifosfamide; Mito, mitomycin; Gem, gemcitabine.

Table 2 Phase III trials of docetaxel used second-line in advanced or metastatic NSCLC

Trial and reference	Regimen	N	RR	MST	I year OS
TAX 317 Shepherd[41]	– Doce 75 q3w	204	7	7.5*	37*
	– Doce 100 q3w		7	5.9	19
	– Best supportive care		0	4.6	19
TAX 320 Fossella[6]	– Doce 100 d1 q3w	373	10.8*	5.5	21
	– Doce 75 d1 q3w		6.7*	5.7	32*
	– Vin or ifos		0.8	5.6	19
Ramlau[43]	– Doce 75 d1 q3w	829	4	31w	29
	– Oral topotecan 2.3 d1–5 q3w		5	28w	25
STELLAR1 Paz-Ares[45]	– Doce 75 d1 q3w	849	12	6.9	29
	– Paclitaxel poliglumex 210 (for PS 0 or 1) or 175 (for PS 2) d1 q3w		8	6.9	25
Hanna[46]	– Doce 75 d1 q3ws	571	8.8	7.9	29.7
	– Pem 500 d1 q3w		9.1	8.3	29.7
Camps[47]	– Doce 75 d1 q3w	259	9.3	6.6	27.0
	– Doce 35 d1/8/15/22 q6w		4.8	5.4	22.0
DISTAL01 Gridelli[48]	– Doce 75 d1 q3w	220	2.7	29w	21
	– Doce 33.3 d1/8/15/22/29/36 q8w		5.5	25w	31
Schuette[49]	– Doce 75 d1 q3w	215	12.6	6.3	26.9
	– Doce 35 d1/8/15 q4w		10.5	9.2	39.5
INTEREST Kim[50]	– Doce 75 d1 q3w	1433	7.6	8.0	34
	– Gefitinib 250 mg PO daily		9.1	7.6	32
V-15–32 Maruyama[51]	– Doce 60 d1 q3w	490	12.8*	14.0	54
	– Gefitinib 250 mg PO daily		22.5	11.5	48
JCOG014 Takeda[53]	– Doce 60 d1/8 q3w	130	6.8	10.1	43.1
	– Doce 60 + gem 800 d1/8 q3w *terminated early for ILD		7.0	10.3	46.0
DISTAL-2 Gebbia[54]	– Doce 33.3 d1/8/15 q4w	84	6.4	40.0	0.38
	– Doce 30 d1/8/15 + gem 800 d1/8 q4w		16.7	32.6	0.17
	– Doce 30 d1/8/15 + cape 625 BID d5-18 q4w		5.3	39.7	0.39
ZODIAC Herbst[58]	– Doce 75 d1 + vandetanib 100 mg PO daily q3w	1391	17*	NR, but hazard ratio of death: 0.91 favoring vandetanib, NS	
	– Doce 75 d1 + placebo PO daily q3w		10		
Fidias[59]	Carbo AUC 5 d1 and gem 1000 d1/8 q3wks × 4, then if no PD, randomize to	566			
	– Doce 75 q3w × 6 immediately	153	11.7	12.3	51.1
	– Doce 75 q3w × 6 upon progression	156	11.2	9.7	43.5

Notes: *denotes statistically significant result. All doses in milligrams per meter squared (mg/m²) except as noted.
Abbreviations: N, number of subjects; RR, response rate; MST, median survival time; OS, overall survival; Doce, docetaxel; q3w, every 3 weeks; Vin, vinblastine. Ifos, ifosfamide; PS, performance status; ILD, interstitial lung disease; Gem, gemcitabine; Cape, capecitabine; BID, twice daily; AUC, area under the curve; NR, not reported; NS, nonsignificant; PD, progressive disease.

Kubota and colleagues also demonstrated improved response and survival with cisplatin/docetaxel when compared to a combination of cisplatin and vindesine.[23]

However, two other phase III studies have shown that docetaxel-containing doublets are comparable, although not superior, to other choices. The GLOB-3 study reported by Tan and colleagues showed no significant difference between cisplatin/docetaxel and a combination of cisplatin with both oral and IV vinorelbine.[24] Finally, another phase III reported by Booton and colleagues compared docetaxel and carboplatin with a triple drug regimen of cisplatin, mitomycin and either ifosfamide or vinblastine, and showed there to be no difference in survival between the arms.[25]

In a large Eastern Cooperative Oncology Group (ECOG) study designed to compare the efficacy of the various "third-generation" chemotherapeutic agents, 1207 patients were randomized to the control arm of cisplatin/paclitaxel or to one of three experimental arms: cisplatin/docetaxel; cisplatin/gemcitabine; and carboplatin/paclitaxel. Schiller and colleagues reported that none of these combinations was superior with respect to survival or response. As a reference point, the cisplatin/docetaxel arm had a median survival time of 7.4 months, compared to 7.9 months median for all enrolled patients.[26] Overall the results have been mixed with the cisplatin/docetaxel first-line trials, with several showing superiority of this regimen as compared to cisplatin/vinca

alkaloid, with others showing equivalence of the combination to other platinum doublets.

Aside from the TAX 326 elderly subgroup analysis, some groups have investigated use of platinum doublets specifically in the elderly. Yoshimura and colleagues considered three-weekly carboplatin/docetaxel doses in a phase II trial and showed a 47% overall response rate, with median progression-free survival (PFS) 4.4 months and survival 9.9 months.[27] Although weekly docetaxel dosing has been explored more often in the second-line setting as noted below, Han and colleagues did consider a first-line weekly cisplatin/docetaxel doublet in an elderly population over the age of 70. Less than 10% of patients had grade 3 neutropenia; with only diarrhea (11%), neuropathy (11%) and stomatitis (11%) noted at grade 3 intensity in over 10% of patients. Median survival was 10.9 months, with a median time to progression 5.0 months, suggesting this may be a viable alternative to three-weekly dosing in the elderly.[28] Similar results were seen in a phase II study by Ohe and colleagues, with a 12% incidence of grade 3 neutropenia and a median survival of 15.8 months.[29] Based on these results, the Japanese Cooperative Oncology Group (JCOG) initiated a phase III study for elderly patients comparing docetaxel and cisplatin to docetaxel alone; this study is ongoing.

To investigate an alternative dosing doublet strategy, Miller and colleagues performed a randomized phase II trial of dose-dense docetaxel and cisplatin (75 mg/m^2 on day 1 of each 14 day cycle) with or without the putative chemoprotective agent BNP7787. To accomplish this dose-dense strategy, they mandated darbepoetin and pegfilgrastim on day 2 of each cycle. With 160 patients enrolled, they found a response rate of 55% versus 51% and median survival of 10.7 versus 14.1 months, with an incidence of only 4% febrile neutropenia; although neurotoxicity of grade 2 or greater was 31% and was not improved with the use of BNP7787.[30] Thus the dose-dense regimen has not been pursued. Another alternative strategy, to use docetaxel sequentially after a nonplatinum doublet, was also evaluated. Kubota and colleagues compared carboplatin and paclitaxel to a strategy of three cycles of vinorelbine/gemcitabine followed by three cycles of docetaxel. Response was significantly better in the carboplatin arm, although there was no difference in survival, and this sequential dosing approach is not under further investigation.[31]

Docetaxel in combination with gemcitabine

Given the toxicity associated with platinum doublet therapy, there has been interest in evaluating whether a combination of gemcitabine and docetaxel may be comparably effective. Two phase III studies by Georgoulias and colleagues[32] and Pujol and colleagues[33] compared docetaxel/gemcitabine with cisplatin/vinorelbine, and yet neither showed a statistically significant difference in response or survival, although a P value of 0.053 in the Georgoulias study suggested a trend in response rate favoring the cisplatin/vinorelbine combination, 39.2% versus 30.0%.[32] However both studies showed significantly less neutropenia in the docetaxel arm, even despite the standardized use of growth factor in one of the protocols.[32] On the other hand, the incidence of significant grade 3 or 4 pneumonitis was prominent in the Pujol protocol, with eight patients (5.2%) noted to have pneumonitis attributed to the docetaxel/gemcitabine regimen.[33]

Two other phase III studies have assessed whether docetaxel with gemcitabine is superior to docetaxel alone. Georgoulias and colleagues showed significantly improved response and survival with the combination (26.8% versus 11.1%, $P < 0.001$ and 9.4 versus 8.3 months, $P = 0.037$),[34] while Hainsworth and colleagues showed a nonsignificant trend in the same direction among elderly patients over the age of 65.[35] While both studies showed slightly more neutropenia in the combination arms, neither showed a significant increase in febrile neutropenia.

Docetaxel in a biomarker-driven regimen choice

Research into the development of prognostic and predictive biomarkers in lung cancer has flourished, and accordingly, there has been interest in prospectively analyzing whether a treatment regimen based on biomarkers can yield superior efficacy. One biomarker of interest is endonuclease excision repair cross-complementing 1 (ERCC1), a DNA repair enzyme involved in the nucleotide excision repair process. High levels of ERCC1 mRNA are predictive of increased resistance to platinum therapy and prognostic for worse survival overall, regardless of treatment. In an innovative phase III study design, the Spanish Lung Cancer Group sought to assess whether personalization of therapy based on ERCC1 would be more effective than a standard choice. The control arm consisted of cisplatin and docetaxel, while patients randomized to the experimental arm received treatment depending on their ERCC1 level; if low, they would receive cisplatin/docetaxel, and if high, they would receive gemcitabine/docetaxel. Response was significantly improved in the arm with the directed therapy, 47% versus 38%, $P = 0.02$), though survival was not significantly improved with a median survival of 9.8 versus 9.9 months, $P = 0.59$.[36]

Expanding further on the idea of the personalization of chemotherapy and given the finding that BRCA1 expression is predictive of a better response to docetaxel and worse response to platinum therapy, the Spanish Lung Cancer Group completed a phase II study that sorted patients based on EGFR and BRCA1 expression. Carriers of an EGFR mutation (either exon 19 deletion or the L858R mutation) received erlotinib, while patients with wild-type EFGR were assessed for BRCA1 mRNA expression levels. Patients with low BRCA1 received gemcitabine/cisplatin, patients with medium BRCA1 received docetaxel/cisplatin, and patients with high BRCA1 received docetaxel alone. While median survival exceeded 28 months in the EGFR mutants, it was: 11 months in the low BRCA1 group; 9 months in the intermediate group; and 11 months in the high group. The investigators also measured RAP80, which modulates the effect of BRCA1, finding that low RAP80 coupled with low BRCA1 would confer a median survival of 26 months.[37] A phase III study is underway randomizing patients between a standard regimen of cisplatin/docetaxel and a regimen dictated by BRCA1 mRNA levels.

Docetaxel in combination with targeted agents

Particularly as an "efficacy plateau" appears to have been reached in traditional chemotherapy combinations in NSCLC,[38] there has been greater interest in combining chemotherapy drugs like docetaxel with the newest generation of targeted therapies, with the goal of improving efficacy with manageable toxicity. In an important phase II study, Belani and colleagues added cetuximab, a chimeric epidermal growth factor receptor (EGFR) inhibitor, to a carboplatin/docetaxel doublet, and patients were allowed to continue cetuximab for up to a year as a single agent if there was no progression. Unlike the study noted below, patients were not required to show over-expression of the EGFR. Therapy was well-tolerated, with neutropenia at only 30% showing greater than 10% incidence of grade 3 or higher toxicity, and the patients who received single-agent cetuximab found it to be well-tolerated. The overall response rate (ORR) was 15.2% with medial survival of 10.3 months, suggesting some modest benefit, however; further work on clarifying appropriate patient selection is warranted.[38]

Another phase III study, BMS-099, evaluated carboplatin with docetaxel or paclitaxel at the option of the investigator, randomized to cetuximab or not. The study did not meet its primary endpoint of improvement in centrally reviewed PFS (4.40 versus 4.24 months, $P = 0.2358$) even though an investigator-determined PFS did favor the cetuximab arm

at 4.30 versus 3.78 months ($P = 0.0015$). Interestingly, the response rate, as judged by central review, favored cetuximab as well (25.7% versus 17.2%, $P = 0.0066$), but was not significantly different by investigator review, 26.9% versus 22.8%, P value not reported in the abstract). Furthermore, no overall survival benefit was seen with the addition of cetuximab (9.7 versus 8.4 months, $P = 0.170$).[39]

A recent randomized phase II study by Lilenbaum and colleagues evaluated two targeted treatments combined with a docetaxel backbone in patients with ECOG performance status (PS) 2, cetuximab and bortezomib, a proteosome inhibitor. Unfortunately, with a PFS of 3.4 and 1.9 months and median survivals of 5.0 and 3.9 months repectively, the trial did not meet its own prespecified PFS endpoint to justify moving to a phase III trial.[40]

Second-line use of docetaxel in advanced or metastatic NSCLC

After the failure of a traditional platinum doublet in advanced or metastatic disease, there was no treatment choice with proven efficacy until the introduction of docetaxel. Work has continued apace to clarify the best way to use docetaxel in a patient population that is often typified by declining performance status, with an even greater emphasis on toxicity and quality of life endpoints in addition to survival.

Docetaxel as single agent

The TAX 317 study established docetaxel as superior to best supportive care with respect to survival,[41] and also showed that quality of life was improved with active therapy.[42] The study randomized patients to docetaxel, evenly divided between doses of 75 mg/m^2 or 100 mg/m^2 on a 3-weekly regimen, versus best supportive care in the control arm. Only the 75 mg/m^2 dose was found to improve survival, with a median survival of 7.5 months compared to 4.6 months on best supportive care ($P = 0.010$), though with a median survival on the higher dose arm of 5.9 months. This was thought to reflect some contribution from toxicity, with 85.7% of patients on the 100 mg/m^2 arm experiencing grade 3 or 4 neutropenia compared with 67.3% on the 75 mg/m^2 arm. Notably, 11 patients (22.4%) on the 100 mg/m^2 arm developed febrile neutropenia, 3 of whom died, as compared with just one case (1.8%) of nonfatal febrile neutropenia in the 75 mg/m^2 arm.[41] The quality of life improvement was demonstrated by a statistically significant difference in a pain scale in patients treated with docetaxel ($P = 0.006$), with trends toward less fatigue ($P = 0.06$) and weight loss ($P = 0.07$). Additionally significantly less tumor-related medication was used in the docetaxel patients ($P = 0.02$).[42]

The first phase III trial to show the superiority of docetaxel over another agent was TAX 320, in which docetaxel (at 75 mg/m² and 100 mg/m²) was compared to the investigator's choice of vinorelbine or ifosfamide. Both doses of docetaxel showed greater response, although as in TAX 317, only docetaxel at 75 mg/m² showed a statistically significant improvement in 1-year survival, from 19% in the control arm to 32% ($P = 0.025$), with survival in the 100 mg/m² group of only 21%. There was again a large difference between grade 4 neutropenia incidence in the two arms, with 77% of patients treated at 100 mg/m² versus 54% treated at 75 mg/m² developing this toxicity.[6] Another study by Ramlau and colleagues compared docetaxel to the oral form of topotecan, and found no difference, with respect to response or survival, although there was an improved quality of life in patients treated with docetaxel.[43]

Based on the impressive results in the TAX 317 and TAX 320 trials, docetaxel was approved by the US FDA as a single agent for the second line treatment of NSCLC in 1999, the first drug to receive this indication.[44] It is still considered a reference second-line regimen.

Docetaxel has also served as the control arm in phase III studies of newer experimental agents. The STELLAR 2 trial compared docetaxel to paclitaxel poliglumex (PPX), a conjugate that links paclitaxel to a polymeric backbone designed to increase permeation and retention of drug intratumorally. However there was no difference in response or survival, and while PPX was associated with less neutropenia and febrile neutropenia, there was a higher incidence of hypersensitivity reaction and neuropathy with PPX, the latter apparently associated with cumulative doses.[45]

Finally, Hanna and colleagues compared docetaxel to pemetrexed in 571 patients, and found no significant difference in response or survival, although there was significantly more neutropenia in the docetaxel arm, suggesting pemetrexed to be the more tolerated agent.[46] Based on these results, pemetrexed is the only other chemotherapeutic besides docetaxel approved by the US FDA as a second line therapy for NSCLC.

Docetaxel as single agent dosed weekly

The assessment as to what extent the weekly dosing of docetaxel could reduce toxicity, particularly of febrile neutropenia, and whether efficacy was retained, three phase III studies have compared 3-weekly to weekly dosing. None of the three studies showed significant changes in response or survival, although two trended toward favoring the 3-weekly dosing[47,48] while one showed a trend in favor of weekly dosing.[49] All three, however, showed decreased grade 3 and 4 neutropenia with the weekly schedule. Results from these three studies and two additional randomized phase II studies were compiled in a meta-analysis, which analyzed data from 865 patients in total and found overall a non-significant difference in median survival (27.4 weeks in the 3-week dosing versus 26.1 weeks in the weekly dosing, $P = 0.245$), however, as expected, a reduction of grade 3 and 4 neutropenia (18% versus 5%) and febrile neutropenia (6% versus <1%) with weekly dosing (both $P < 0.001$).[10] Collectively these results suggest that weekly dosing is an acceptable alternative, particularly in a patient at greater baseline risk for neutropenia, although one must weigh the burden of time and expense of more frequent visits, and the chance of slightly less efficacy when deciding on the dosing regimen for a patient.

Docetaxel as single agent versus targeted therapies

Two large randomized trials have compared the oral EGFR inhibitor gefitinib to docetaxel. INTEREST, the larger of the two with 1433 patients on 4 continents, was designed to evaluate the noninferiority of gefitinib in the entire study population and superiority among those with a high EGFR copy number. The study met its criteria for noninferiority, achieving a similar response and survival but with considerably less neutropenia for gefitinib treated patients when compared to those receiving docetaxel. However, the subgroup of patients with high a EGFR copy number did not show any improved response or survival with gefitinib.[50] A Japanese trial, V-15–32, also randomized patients to docetaxel or gefitinib with an endpoint of noninferiority. The endpoint was not met, and there was no statistically significant difference in survival.[51] Notably, a combined phase I/II trial was designed to study the combination of docetaxel and gefitinib in an elderly population over the age of 70, however, after 11 of the 26 enrolled patients experienced grade 3–5 nonhematologic toxicity in the first cycle, the study was discontinued.[52]

Docetaxel in combination with chemotherapy

Docetaxel has been evaluated in combination with gemcitabine for second-line use in two phase III studies. JCOG0104 compared docetaxel given days on 1 and 8 in a 3-weekly cycle both with and without gemcitabine. The study was halted early for excessive incidence of interstitial lung disease in the combination arm, with a 17% incidence (and three deaths) compared to an incidence of only 2%

in the docetaxel arm. At the time of discontinuation there was no difference between the arms in response rate or survival.[53] In the DISTAL-2 study weekly docetaxel was compared alone versus docetaxel in combination with either gemcitabine or capecitabine; once again, there was no difference among the arms in response or survival.[54] A phase II trial by Schneider and colleagues evaluated the addition of celecoxib to docetaxel in second-line therapy, and yet with a 58% incidence of grade 3 neutropenia, and 21% neutropenic fever the study was halted early with a median survival of only 6.9 months.[55] Thus the concept of chemotherapy doublets as second-line therapy has largely been abandoned.

Docetaxel in combination with targeted therapies
Combinations of docetaxel with drugs targeting EGFR and other pathways have shown more promise. Kim and colleagues evaluated docetaxel in combination with cetuximab in a phase II trial. Patients had to show an overexpression of EGFR and to have progressed or relapsed within 3 months of the original chemotherapy. Leucopenia and rash were noted in 27% and 22% of patients respectively at a grade 3 severity. Response rate was 20% with a median time to progression of 104 days and survival of 7.5 months, suggesting to the authors that further phase III testing was warranted.[56]

Combining EGFR and vascular endothelial growth factor (VEGF) inhibition in a single oral tyrosine kinase inhibitor, vandetanib, has been one focus of study. Heymach and colleagues reported a randomized phase II trial adding vandetanib or placebo to docetaxel. Though there was no survival benefit noted, the study met its endpoint of prolonged PFS, ie, 18.7 weeks at dose of 100 mg versus 17.0 weeks at a dose of 300 mg versus 12 weeks for docetaxel alone ($P = 0.037$ comparing 100 mg dose to placebo).[57] Preliminary findings from the phase III ZODIAC study have now been reported that also show a statistically significant difference in PFS when vandetanib as compared to placebo was added to docetaxel, 17.3 versus 14.0 weeks (hazard ratio 0.79, $P < 0.001$), though survival was not significantly different with a hazard ratio of 0.91, ($P = 0.196$; median survival not reported). These results represent the first time an oral targeted therapy has increased efficacy when added to standard chemotherapy in NSCLC.[58] However, the lack of a survival benefit may limit further development of this combination.

Docetaxel immediately after first-line treatment versus waiting for progression
Given the consistent findings of efficacy in second-line treatment, Fidias and colleagues investigated whether it would be advantageous to give docetaxel as consolidation immediately after a full course of a first-line platinum doublet (in this case, carboplatin and gemcitabine) rather than to wait for progression before starting docetaxel. A total of 309 of 566 enrolled patients completed four cycles of the doublet without developing progressive disease and were randomized. There was a trend toward better survival in the early treatment arm, 12.3 versus 9.7 months ($P = 0.0853$). Notably, only 98 out of 156 patients in the delayed arm were able to receive at least one cycle of docetaxel, suggesting that treatment intensity is higher if docetaxel can be given earlier, presumably when patients are more fit.[59] In a secondary analysis of those patients on the delayed arm who did go on to receive docetaxel, the survival was equivalent to patients on the immediate docetaxel arm.

Use of docetaxel in earlier-stage disease
Given the proven activity of docetaxel in advanced and metastatic NSCLC, multiple approaches with the agent in earlier stages of disease have been investigated.

Docetaxel for chemoradiation or as consolidation after chemoradiation in unresectable stage III disease
Preclinical data suggest that docetaxel is an effective radiosensitizer in addition to its antitumor properties, and so its use in inoperable locally or regionally advanced NSCLC as part of a regimen that includes radiation therapy has been an important area of study.[60] However, consensus regarding the best approach for unresectable stage III disease with respect to the order of treatment and the choice of agents remains elusive. A phase II Southwest Oncology Group (SWOG) study in unresectable stage IIIB disease showed an impressive 26-month median survival time with a regimen of chemoradiation (with cisplatin and etoposide) followed by docetaxel consolidation.[61] This regimen has subsequently been adopted as the SWOG reference standard, and thus serves as a platform for ongoing trials in this patient population. For example, the SWOG S0023 study was a phase III trial of cisplatin/etoposide with radiation, then docetaxel consolidation as a standard, followed by a randomization to gefitinib or placebo. This study was halted early for not meeting a midpoint efficacy criterion, and the final results actually reported a 35 versus 23 month advantage for the placebo arm with respect to survival ($P = 0.013$).[62]

In the phase III setting, US Oncology and the Hoosier Oncology Group randomized patients to docetaxel 75 mg/m² every 3 weeks or observation after definitive chemoradiation

with cisplatin and etoposide, as in the SWOG reference standard regimen. Unfortunately, the study was terminated early for not exceeding pre-determined futility criteria, and on final review of the data mean survival time MST was 21.2 months in the patients receiving docetaxel versus 23.3 months in the control arm ($P = 0.883$), with 5.5% deaths classified as premature on account of docetaxel.[63]

Docetaxel has also been studied as part of a combined chemoradiation regimen in locally advanced disease. In the OLCSG 0007 trial, Kiura and colleagues randomized patients to either docetaxel/cisplatin or mitomycin, cisplatin and vindesine, both regimens given concurrently with radiation. The 2-year survival target, the primary endpoint of the study, was significantly better in the docetaxel and cisplatin arm, 60.3% versus 48.1% ($P = 0.0183$), with trends toward an improved response rate and 5-year survival. Hematologic toxicities were also significantly less in the arm with docetaxel.[64]

Other groups have used regimens employing docetaxel as part of chemoradiation therapy as either induction or consolidation. Scagliotti and colleagues performed a randomized phase II trial using induction chemotherapy with cisplatin/docetaxel, and then randomized patients to radiation alone or with concurrent weekly docetaxel at 20 mg/m². ORR was 58% in the chemoradiation arm compared to 48% in the radiation arm, with a survival of 14.9 versus 14.0 months suggesting a trend towards improvement, however, this result was not significant, with having overlapping confidence intervals.[65] Jain and colleagues recently published a phase II trial using weekly carboplatin/docetaxel with radiation, followed by consolidation with carboplatin/docetaxel in stage IIIA or IIIB patients. The regimen was fairly well-tolerated with leucopenia and esophagitis the primary toxicities, although the 1- and 2-year survival rates were 45% and 20% respectively, which did not appear to improve significantly on historical experience.[66] Thus, while considerable controversy surrounds the appropriate regimen for the treatment of stage III NSCLC, many active options contain docetaxel.

Docetaxel as neoadjuvant therapy in resectable stage III disease

An international phase III trial was performed by Mattson and colleagues to evaluate docetaxel (100 mg/m²) every 3 weeks for at least three cycles, before local surgery or radiation, with a curative intent in radically resectable stage III patients versus no neoadjuvant therapy. There was no statistically significant difference between the arms despite a 28% response rate in the docetaxel arm; although there was a trend toward improved survival (14.8 versus 12.6 months).[67,68]

Although docetaxel alone in the neoadjuvant setting was not shown to be particularly efficacious there has been some promising data in phase II trials evaluating docetaxel in combination with cisplatin or carboplatin in this setting.[69] However, these findings have yet to be replicated in a large randomized study.

Docetaxel as neoadjuvant or adjuvant therapy in stage IB through III disease

A recent randomized phase II study by Kunitoh and colleagues investigated the use of docetaxel with or without cisplatin as neoadjuvant therapy before surgery in clinical stage IB and II patients. The response rate and compete resection rates were higher in the arm with docetaxel/platinum (45% versus 15% and 95% versus 87% respectively), and the 1-year survival, the primary endpoint, was good at 78% and 62% respectively, suggesting that further study is warranted in this clinical setting.[70]

Other investigators have considered adjuvant docetaxel in phase II studies. Kawamura and colleagues evaluated a docetaxel/gemcitabine doublet for adjuvant use in stage IIA–IIIA NSCLC. Three of the first 21 patients experienced interstitial lung disease ILD, so the gemcitabine was decreased in dose from 1000 to 800 mg/m² for the duration of the study. Twenty-nine of 35 patients completed at least three cycles of therapy. The 4-year survival rate was 65.8%, with 42.9% recurrence-free survival.[71] In another phase II study, Stinchcombe and colleagues administered carboplatin and docetaxel in an adjuvant setting to patients with curatively resected NSCLC. Among the 72 patients: 40% were stage I; 36% were stage II; 22% were stage IIIA; and 1% were stage IIIB. This was designed as a feasibility study and 79% of patients were able to receive four cycles of treatment with acceptable toxicity. However, the efficacy results have yet to be reported.[72] Azzoli and colleagues, meanwhile, evaluated the feasibility of a cisplatin/docetaxel doublet in stage I–III disease, finding that 5 of 16 patients were unable to complete three cycles of weekly docetaxel with cisplatin, as compared to 6 of 11 unable to complete 3-weekly dosing of both medications.[73]

Quality of life and other patient-reported outcomes

Along with other areas of oncology, the field of lung cancer research has come to recognize the importance of assessing patient-reported outcomes, and this is reflected in their inclusion in many of the trials detailed above. Particularly in advanced NSCLC; when treatment with curative intent is

not feasible and one regimen may confer only a small incremental survival benefit compared to another regimen, it is important to consider how the toxicities of the regimens affect the quality of life of patients. Such differences can influence regulatory approval decisions about a drug, and just as importantly, can impact an individual treatment decision made in the clinic. Aside from assessing toxicity directly with common terminology criteria for adverse events (CTCAE) criteria, there are at least three validated measures in lung cancer to help assess how toxicity, as well as other factors, impact a patient's quality of life. These include the lung cancer symptom scale (LCSS), the EORTC lung cancer module, and the functional assessment of cancer therapy – lung (FACT-L).[74]

An example of how patient-reported outcomes can complement traditional endpoints of response and survival is seen in the pivotal trial published by Roszkowski and colleagues comparing docetaxel with best supportive care and that described above.[18] Though the survival difference was statistically significant, the increment was only 0.3 months (6.0 versus 5.7 months) which may not be considered clinically relevant by all patients or practitioners. However, when informed by quality of life data collected prospectively, alongside survival data that showed an improvement in patient-reported pain, the difference between the two approaches becomes more meaningful.[75]

Future directions

Large phase III trials are now underway that use docetaxel as a standard therapeutic backbone for all patients, who are then additionally randomized to a novel drug versus placebo. Some novel drug examples include:

- ASA 404, a small molecule vascular disrupting agent;
- BIBF 1120, a novel inhibitor of VEGF, platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR), targeting angiogenesis;
- Cetuximab, an EGFR inhibitor;
- Enoxaparin, a low-molecular-weight heparin;
- Tavocept, a chemoprotective agent that may reduce the incidence of neurotoxicity in taxane and platinum agents, while allowing greater dose intensity;

Many novel agents are also being assessed in a phase II setting in combination with docetaxel, including sunitinib, sorafenib, bortezimib, AZD6244 (a MEK inhibitor), PR104 (a hypoxia-induced alkylating agent), nimotuzumab (an EGFR inhibitor), apricoxib (a COX-2 inhibitor), and MGCD265 (a multitargeted tyrosine kinase inhibitor, including c-MET), among others.

Aside from novel agents, adaptive use of docetaxel based on predictive biomarkers is being considered. The Spanish Lung Cancer Group is using BRCA1 to select treatments in the experimental arm, while a phase III SWOG study uses RRM1 and ERCC1, with docetaxel given to patients with high RRM1, indicative of resistance to gemcitabine.

Docetaxel-based platinum doublets are also used in ongoing studies enrolling patients in earlier stages of the disease. For example, in the adjuvant trial ECOG E1505 exploring the addition of bevacizumab to adjuvant chemotherapy for patients with resected stage IB through IIIA disease, cisplatin/docetaxel is one of the four backbone regimens. In CALGB 20506, designed to assess the utility of a genomic prognostic model to identify stage I patients who would benefit from adjuvant chemotherapy, cisplatin/docetaxel is one of the three options for patients randomized to treatment rather than observation.

Conclusions

The advent of docetaxel as the first effective drug for use in advanced and metastatic NSCLC after progression on a platinum doublet was an important milestone, offering renewed hope in a morbid disease state. Unfortunately there has been somewhat of a plateau in efficacy with chemotherapeutic agents; however, as the molecular biology of NSCLC has been further elucidated over the past decade there is hope that targeted therapies may yield improved results, with tolerable toxicity profiles, in appropriately chosen patients. Even as new compounds and novel regimens are developed, docetaxel will continue to play an important role in the treatment of NSCLC, both as a backbone for new regimens, and as the current standard of care in the both the first-line setting as part of a platinum doublet, and as a single agent for second-line therapy. Important work continues to evaluate how to identify *a priori* which patients will most benefit from docetaxel, based on clinical characteristics and biomarkers.

Disclosures

The authors report no conflicts of interest relevant to this research.

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