Docetaxel in non-small cell lung cancer

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Docetaxel is a semisynthetic taxane, targeting the β subunit of tubulin, with a broad spectrum anticancer activity, not only in non-small cell lung cancer (NSCLC), but also in breast and prostate cancer. Docetaxel in combination with cisplatin is now a standard strategy in the first-line treatment of advanced NSCLC (with >30% objective response rate and a median survival of 10–12 months) and has been approved for use in this setting. As a single agent, docetaxel has also been approved in the second-line setting. Ongoing trials are investigating a method for the association of docetaxel with thoracic radiotherapy, and how to integrate docetaxel in multimodality treatment of earlier stage NSCLC (before surgery or after concurrent thoracic radiotherapy and platinum-based doublets). The toxicity profile of docetaxel and the facility of its administration in an out-patient setting are supporting arguments for its use.

Lung cancer is the leading cause of cancer-related death for both women and men. Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancers. Every year, approximately 130,000 new cases of NSCLC are diagnosed in the USA and almost 200,000 in Europe. The 5-year survival for localized, locally advanced and metastatic disease is approximately 40, 20 and 1%, respectively. **Table 1** outlines the tumor node metastasis (TNM) staging system and the actual treatment options [1]. In advanced NSCLC, cisplatin-based chemotherapy increases survival by 1 year and improves the quality of life (QoL) [2,3], even if the aim of treatment is merely palliative. In elderly patients, even monochemotherapy increases survival and QoL [4]. In locally advanced NSCLC, cisplatin-based chemotherapy associated with thoracic radiotherapy (concurrent or sequential combination) is effective in increasing cure rates. In localized NSCLC, recent studies have clearly demonstrated the benefit of adjuvant chemotherapy [5,6], which makes polychemotherapy a widely used treatment in almost every case of NSCLC at each and every stage. However, the most important prognosis factors in NSCLC are still performance status and stage.

Keywords: chemotherapy, docetaxel, non-small cell lung cancer, taxanes

Mechanism of action of taxanes

Paclitaxel and docetaxel are taxanes, a class of anticancer agents that bind to and stabilize microtubules, causing cell cycle arrest and apoptosis. Docetaxel (Taxotere®) is a semisynthetic taxane derived from the precursor 10-deacteyl baccatin III, extracted from the needles of the European yew tree *Taxus baccata*. Paclitaxel (Taxol®) is derived from the bark of the North American yew tree. Taxanes selectively bind to the β-subunit of polymerized tubulin at sites distinct from those of the vinca alkaloids and colchicines [7–10]. Vinca alkaloids work to destabilize microtubule networks while, in contrast, the taxanes promote tubulin polymerization. Structurally, docetaxel differs from paclitaxel at both the 3′ position on the side chain and the 10′ position on the baccatin ring (**Figure 1**). Docetaxel targets the same site on microtubules as paclitaxel, but with an almost twofold higher binding affinity [9]. Due to this difference, patients previously treated with paclitaxel may benefit clinically from treatment with docetaxel, while the reverse is rarely observed. Treatment with docetaxel generally results in M-phase arrest, often leading to apoptosis. One of the advantages of taxanes over other chemotherapy drugs is their activity in tumors lacking functional p53 [7,11]. The antitumor activity of platinum salts, alkylating agents, anthracyclines and topoisomerase inhibitors is correlated with wild-type p53. As the loss of functional p53 is common in NSCLC, the activity of docetaxel in tumors with dysfunctional p53 may, in part, explain the spectrum of clinical response in tumors such as NSCLC. The novel mechanism of action of docetaxel has led to considerable interest in its combined effect with other antineoplastic agents. Consequently, combinations such as docetaxel and cisplatin, docetaxel and vinorelbine, and docetaxel and gemcitabine, have been shown to exert an additive cytotoxic effect on NSCLC lines [10].

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Table 1. Staging and treatment options.

Stage	Tumor node metastasis	Description	Recommended treatment
0	Carcinoma *in situ*	Noninvasive tumor	Local treatment (laser, brachytherapy)
IA	T1N0M0	Tumor <3 cm, localized to lung	Surgery (option radiotherapy)
IB	T2N0M0	Tumor >3 cm, involvement of main bronchus, or invasion of visceral pleura	Surgery + chemotherapy (option chemoradiotherapy)
IIA	T1N1M0	Tumor <3 cm, involvement of ipsilateral peribronchial or hilar lymph nodes	Surgery + chemotherapy (option chemoradiotherapy)
IIB	T2N1M0, T3N1M0	Tumor >3 cm or involvement of main bronchus or visceral pleura, with involvement of ipsilateral peribronchial or hilar lymph nodes. Tumor of any size invading chest wall, diaphragm, mediastinal pleura	Surgery + chemotherapy (option chemoradiotherapy)
IIIA	T1–3 N2M0, T3N1M0	Tumor of any size invading chest wall, diaphragm, mediastinal pleura, with involvement of ipsilateral peribronchial or hilar lymph nodes Involvement of ipsilateral mediastinal/subcarinal lymph nodes	Chemotherapy + surgery, surgery + chemotherapy, chemoradiotherapy
IIIB	T any N3 M0, T4N any M0	Tumor of any size invading the mediastinum, heart, great vessels, trachea, carina, esophagus, vertebral body Involvement of controlateral mediastinal or supraclavicular lymph nodes	Chemoradiotherapy Surgery in selected cases
IV	T any N any M1	Distant metastasis	Chemotherapy, palliative radiotherapy

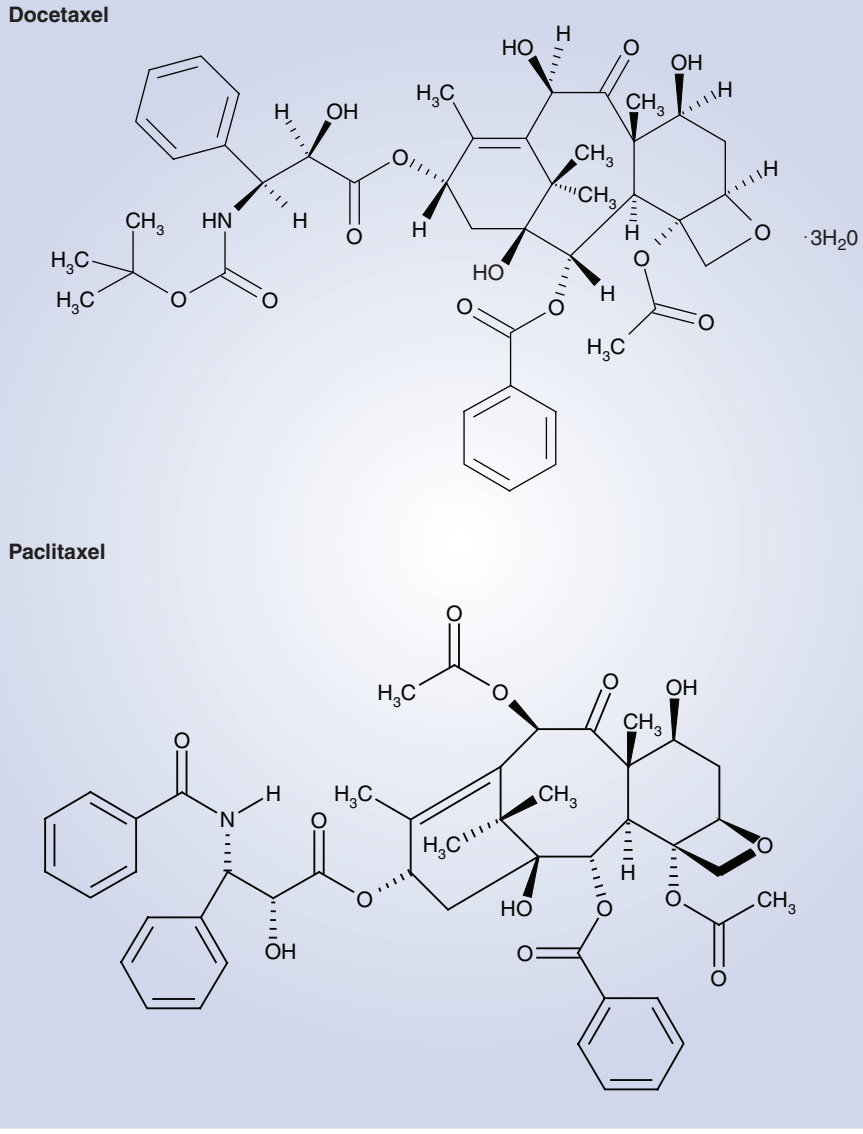
Mechanisms of tumor resistance

Two main mechanisms are responsible for cellular resistance to docetaxel. The first is alteration in the tubulin subunits, thereby resulting in decreased tubulin polymerization and increased expression of the antiapoptotic protein Bcl-2 [12]. The second mechanism is expression of the multidrug resistance gene *MDR-1*. The *MDR-1* gene produces a 170-kDa membrane-associated P glycoprotein (P-gp) that functions as a drug efflux pump [13].

Pharmacology & pharmacokinetics

The pharmacokinetics of docetaxel can be described by a linear three-compartment model at doses greater than 70 mg/m^2. A total of 93–94% of docetaxel binds to plasma proteins, predominantly α_1-acid glycoprotein (AAG) and lipoproteins, in a concentration-independent manner [8,10,14]. The hematologic toxicity profile of docetaxel appears to be markedly influenced by AAG levels [8]. Low baseline levels of AAG are a significant predictor of grade 4 neutropenia. Docetaxel is metabolized primarily by cytochrome P450 3A4 and 3A5 enzymes in the liver, being finally eliminated by excretion via the biliary tract into the faeces, with approximately 4% eliminated unchanged in the urine. Docetaxel systemic clearance significantly declines with worsening hepatic dysfunction. Therefore, adjustments are required when administering docetaxel in patients with hepatic dysfunction. Pharmacokinetics studies show that decreased plasma clearance is a strongly independent predictor of grade 4 neutropenia and cumulative dose – the best predictor of fluid retention. Clinical trials have revealed that

Figure 1. Docetaxel and paclitaxel.



cycle-to-cycle variability in docetaxel clearance is low and some interpatient variability can be explained by covariates (hepatic functions, albumin, AAG); however, no relevant clinical interactions of docetaxel with other drugs (either other antineoplastic drugs, steroids or antiemetics) were studied [8]

Taxanes are hydrophobic and therefore highly insoluble in saline, requiring vehicles for intravenous administration (paclitaxel: cremophor EL and docetaxel: Tween 80), which results in a number of side effects often thought to be related to these vehicles, such as anaphylaxis with paclitaxel.

The oral bioavailability of docetaxel is less than 1%. Poor intestinal absorption seems to occur due to the P-gp efflux transport system. Agents that modulate P-gp (such as cyclosporin A) have been shown to increase intestinal absorption of oral docetaxel.

Although there is a wide variability in paclitaxel infusion duration, clinical trials of docetaxel uniformly utilized a 1-h infusion. Moreover, no formal dose-intensification studies of docetaxel were conducted in NSCLC. Phase II trials of single-agent docetaxel 60–100 mg/m^2 every 3 weeks suggest that the escalation of dose does not increase the

Table 2. Common toxicities associated with docetaxel.

Type	Toxicity
Allergic	Anaphylactoid reactions, hypersensitivity reactions
Dermatological	Maculopapular rash, erythema, nail changes, alopecia, peripheral edema
Hematological	Neutropenia (dose-limiting), thrombocytopenia, anemia
Gastrointestinal	Nausea, vomiting, diarrhea, anorexia
Pulmonary	Pleural effusions, bronchospasm
Hepatic	Increase of hepatic enzymes
Neurological	Paresthesias, peripheral neuropathy, ototoxicity
General	Headache, lethargy, epiphora

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response rate or have an impact on the survival rate, but that it does increase toxicities, especially neutropenia and fluid retention. In combination with cisplatin, the increasing dose did not demonstrate improved results. One exception to this could be the dose dense with the weekly administration by decreasing the delay between administration.

Toxicities

Common toxicities are listed in **Table 2**. Toxicities are dose- and schedule-dependent. Administered every 3 weeks, docetaxel is more associated with neutropenia, whereas weekly administration more commonly presents with asthenia and nail changes.

Hematological toxicities

Neutropenia is the main dose-limiting adverse event in patients with NSCLC (**Table 3**). With a dose of 100 mg/m^2, grade 3 and 4 neutropenia occurs in 89% of patients (with 29% of febrile neutropenia and 3% of deaths occurring during neutropenic infection in Phase II studies). However, with 75 mg/m^2, grade 3 and 4 neutropenia is presented in only 28% of chemonaive patients and approximately 60% of pretreated patients. Toxicities such as anemia and thrombocytopenia are infrequently reported.

Fluid retention

Steroids are systematically administered to reduce fluid accumulation syndrome (peripheral edema, pleural effusion). A review of Phase II trials in NSCLC reported that the onset of fluid retention occurred after a median cumulative dose of 408 mg/m^2 [10]. Two-thirds of patients experienced fluid retention but was severe in only 8% of cases. In some cases, oral diuretics are needed. Docetaxel-induced fluid retention is probably caused by abnormal capillary permeability and excessive protein leakage into the interstitial space, and perhaps insufficient lymphatic drainage.

Neurological toxicities

Peripheral neuropathy is less frequent with paclitaxel, being generally mild-to-moderate and reaching grade 3/4 in less than 10% of patients. Peripheral neuropathy seems more frequent in patients pretreated with cisplatin alone or in a combination. Peripheral neuropathy requires dose reductions or discontinuation.

Cutaneous toxicities

Dermatological events (e.g., erythema, dermatitis, rash) were observed in 60% of patients but grade 3/4 toxicities were rare (6%). Nail changes were observed in 19% of patients especially in the weekly schedule. Some cases of radiation recall severe mucositis [15] and dermatitis [16] have been described with drugs similar to docetaxel.

Table 3. Incidence of grade 3 and 4 hematological events in Phase III trials of docetaxel in second-line therapy.

Events (%)	Docetaxel 100 mg/m^2		Docetaxel 75 mg/m^2		
Number of patients	49	121	55	121	276
Anemia	17	16	6	11	4.3
Neutropenia	88	89	67	66	40.2
Febrile neutropenia	22	12	2	8	12.7
Infection	14	15	6	12	NR
Thrombocytopenia	2	3	0	4	0.4
Toxic death	10	5	2	3	0.5
Ref.	[41]	[42]	[41]	[43]	[44]

NR: Not reported.

Box 1. Pharmacological treatment with docetaxel.

Standard dose:

- Every 3 weeks: Docetaxel 75 mg/m^2 intravenously, over 30–60 min every 21 days
- Weekly: Docetaxel 35–40 mg/m^2 x 3 weeks every 28 days or x 6 weeks every 8 weeks
- With cisplatin: Docetaxel 75 mg/m^2 + cisplatin 75 mg/m^2 every 21 days
- With carboplatin: Docetaxel 75 mg/m^2 + carboplatin AUC 6 every 21 days

Contraindications:

- Absolute neutrophil count less than1.5 giga/l
- Caution in patients with hepatic dysfunction characterised by total bilirubin over the upper limit of normal (ULN), alkaline phosphatase greater than five-times the ULN, serum aspartate aminotransferase greater than five-times the ULN
- A 25% dose reduction is recommended or withholding the drugs until recovery of normal values

Main drug interactions:

- None reported

Recommended steroid dose:

- Dexamethasone 8 mg *per oral* twice-daily for 3 days starting 1 day before chemotherapy

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Hypersensitivity

Symptoms of hypersensitivity reactions (flush, rash, pruritus, dyspnea, hypotension, bronchospasm) usually occur within minutes of commencing docetaxel infusion and stop within minutes of ceasing infusion. The frequency is approximately 30%, but grade 3 and 4 events are less than 10 and 1%, respectively. Furthermore, hypersensitivity pneumonitis has also been described, with docetaxel requiring pretreatment with steroids in order to decrease the incidence of reaction [17]. Treatment with docetaxel needs to be discontinued in case of grade 3/4 hypersensitivity reactions despite steroids.

Various toxicities

Epiphora (excessive lacrymation) is seen in some patients, especially in weekly administration [10], and is found to be linked with a dose of more than 300 mg/m^2. In case of epiphora, treatment may need to be withheld. Docetaxel is only modestly emetogenic and does not require post-treatment with antiemetics.

Docetaxel: first-line treatment in advanced NSCLC

Preclinical studies

Initial studies have shown that docetaxel has a significantly inhibitory activity against cell lines N417 (small cell lung carcinoma), KB (epidermoid carcinoma), SW 15–73 (NSCLC cell line), and demonstrated superiority over paclitaxel, as well as cisplatin. *In vivo* evidence from murine tumor models has indicated that the tumor activity is independent of the tumor suppressor gene and has a radiosensitizing action on certain cell lines. Docetaxel has shown greater activity against freshly explanted human tumors in mice than paclitaxel, and at the maximum tolerated doses, docetaxel is also more effective [7,9].

Phase I trial

Five schedules were investigated to determine the dose range, safety and toxicity of docetaxel (**Table 4**) [10]. The dose-limiting toxicity was neutropenia, which was dose- and not schedule-dependent. Neutropenia appeared on days 5–12, resolved in a few days, and did not delay administration of docetaxel every 21 days. Thrombocytopenia and anemia were not significant. Grade 3 oral mucositis was associated with prolonged infusion (over 6–24 h), repeated dosing or a day 1/8 schedule. Other minor toxic effects included hypersensitivity and cutaneous reactions; neurotoxicity was not commonly observed.

Phase II trial

Docetaxel has demonstrated its efficacy in NSCLC in the first-line treatment setting as a single agent in Phase II trials (dose range 75–100 mg/m^2 every 3 weeks) with response rates ranging 19–63% and a median survival of approximately 9 months (range 7–14 months), along with a 1-year survival rate of 39% (range 21–74%) (**Box 1**). The dose-limiting toxicity is neutropenia. The association of docetaxel (75 mg/m^2) with cisplatin (75 mg/m^2 day 1) every 3 weeks, or carboplatin, has demonstrated its efficacy, and all doublets based on platinum have established themselves as standard therapy for good performance status NSCLC [18–21]. Docetaxel had been also widely studied in nonplatinum doublets.

Docetaxel/gemcitabine association is well tolerated and is the most common nonplatinum combination studied in the first- and second-line setting. Myelosuppression is the dose-limiting step and appears to be schedule-dependent. Dose reductions are often necessary in heavily pretreated patients. Dose ranges for docetaxel are 75–100 mg/m^2 day 8, and for gemcitabine 800–1000 mg/m^2 days 1 and 8 [22], every 3 weeks. A Phase I/II trial had established the dose with docetaxel as 85 mg/m^2 day 8 and with

Table 4. Phase I trial of docetaxel.

Schedule every 3 weeks	Recommended Phase II dose	Dose-limiting toxicity
1 h x 5 days	14 mg/m^2/day x 5	Neutropenia, mucositis
1-h infusion	100 mg/m^2	Neutropenia, mucositis
6-h infusion	80 mg/m^2	Neutropenia, mucositis
1–2-h infusion	100 mg/m^2	Neutropenia
1 h, day 1 and 8	50 mg/m^2 day 1 and 8	Neutropenia
24-h infusion	70 mg/m^2	Neutropenia, fever, mucositis

gemcitabine at 1000 mg/m^2 days 1 and 8 [23]. This regimen has been studied in three Phase III trials compared with platinum doublets.

Docetaxel/vinorelbine association has a significant toxicity and especially high hematological toxicity, despite the use of prophylactic granulocyte colony-stimulating facor (G-CSF). A total of 46 chemonaive NSCLC patients were treated with vinorelbine (25 mg/m^2 day 1) and docetaxel (100 mg/m^2 day 2) for 3 weeks with G-CSF [24]. Overall response rate was 36.6%, with a median survival of 5 months and 1-year survival of 24%. A total of 20 patients were hospitalized, of which 11 presented with neutropenic fever and four deaths occurred, two by sepsis and two from cardiopulmonary insufficiency. Another trial with docetaxel (75 mg/m^2 day 1) followed by vinorelbine (20 mg/m^2 days 1 and 5) every 3 weeks, displayed the same toxicities, with 41% febrile neutropenia and 6% toxic deaths)[25].

Docetaxel/irinotecan schedules practised for this combination involved weekly irinotecan (50–70 mg/m^2 days 1, 8 and 15) for all 4 weeks and docetaxel (50 mg/m^2 day 2 or 25 mg/m^2 days 1 and 8) [26,27]. Limiting toxicities included neutropenia and diarrhea.

Docetaxel-based triplets have also been studied in combination with a platinum and a third agent, such as ifosfamide, vinorelbine or gemcitabine [28,29]. Similar to other triplet combinations, results are not better than doublets, rather more toxic hematological side effects are observed [30]. Doublet combinations with platinum remain the standard therapy.

Phase III trial

Docetaxel has been widely studied in Phase III trials for the best supportive care (BSC) in one trial [31], and various regimens in nine other trials [32–40] (**Table 5**). Comparison of docetaxel 100 mg/m^2 every 3 weeks with BSC in 207 chemotherapy-naive patients with unresectable Stage IIIB or IV NSCLC showed a survival benefit for docetaxel as; 1-year survival 25 versus 16% (p = 0.026), 2-year survival 12 versus 0% [31]. This study also prospectively assessed the QoL and the survey showed significant differences between groups for pain, dyspnea, emotional function and nausea and vomiting, to be presented on treatment with docetaxel. Patients in the docetaxel group received less palliative radiotherapy and analgesics than those in the BSC group. Adverse toxic effects in the treatment group were much similar to the previous studies, with asthenia (28%), neutropenia (28%) and fluid retention (23%) being the most reported grade 3/4 toxic effects associated with docetaxel. 4% of patients had febrile neutropenia whereas 7% had nonfebrile neutropenia.

Eastern Cooperative Oncology Group (ECOG) 1594 compared docetaxel and cisplatin with three other combinations (paclitaxel/cisplatin, paclitaxel/carboplatin and cisplatin/gemcitabine) as first-line therapy in patients with Stage IIIB and IV NSCLC; however, the survival did not differ between the four groups [32]. In the docetaxel/cisplatin group (each 75 mg/m^2 day 1 for 3 weeks), the overall response was 17%, median survival was 7.4 months and 1-year survival 31%. Neutropenia did not differ between the groups, but fever was most frequent in the docetaxel group.

Georgoulias and colleagues randomly allocated 441 chemotherapy-naive patients with Stage IIIB and IV NSCLC to receive docetaxel (100 mg/m^2 day 1) and cisplatin (80 mg/m^2 day 1) every 3 weeks, to 1100 mg/m^2 gemcitabine on days 1 and 8 and docetaxel 100 mg/m^2 day 8, every 3 weeks [34]. The overall response and survival were the same in the two groups; however, the toxic effects in the docetaxel/gemcitabine group were more noticeable in terms of neutropenia and diarrhea.

A large, randomized trial of docetaxel in first-line therapy for NSCLC (TAX 326) randomly allocated 1218 chemotherapy-naive patients with Stage IIIB or IV NSCLC to docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2, day 1, every 3 weeks; docetaxel 75 mg/m^2 and carboplatin area under the curve 6 mg/ml/min, day 1 every 3 weeks; or

Table 5. Phase III trials in first-line non-small cell lung cancer.

Trials	Overall response (%)	Time-to-progression (months)	Median survival (months)	Overall survival (95%)		Ref.
				1 year (%)	2 year (%)	
D vs	13	3.2*	6.0*	25*	12*	[31]
BSC	NA	2.3	5.7	16	0	
CDDP + D vs	17	3.7	7.4	31 (26–36)	11 (7–14)	[32]
CDDP + GMZ vs	22	4.2*	8.1	36 (31–42)	13 (7–15)	
CDDP + PCT vs	21	3.4	7.8	31 (26–36)	10 (5–12)	
CaP + PCT	17	3.1	8.2	34 (29–40)	11 (7–14)	
CDDP + D vs	35	8.0	10.0	42	8	[33]
D + GMZ	33	9.0	9.5	39	8	
CDDP + D vs	32*	5.5	11.3*	46 (42–51)*	21 (16–25)*	[34]
CaP + D vs	24	5.0	9.4	38 (33–43)	18 (13–22)	
CDDP + VRB	25	5.8	10.1	41 (36–46)	14 (10–18)	
CDDP + D vs	37*	4.0	7.0	44	19	[35]
D vs	22	2.5	8.0	43	19	
CDDP + D vs	37*	NR	11.3	47.7	24.4	[36]
CDDP + VD	21	NR	9.6	41.1	12.2	
CaP + D vs	33	NR	NR	32	12	[37]
MIC and MVP	33			37	9	
D + GMZ vs	31	4.2	11.1	46	NR	[38]
CDDP + VRB	35.9	4.0	9.6	42	NR	
D + GMZ vs	30	4.0	9.0	34.4	14.1	[39]
CDDP + VRB	39.2	5.2	9.7	40.8	11.3	
D vs	22.7	13.9*	5.5*	59.2*	NR	[40]
VRB	9.9	9.9	3.1	36.7	NR	

BSC: Best supportive care; CaP: Carboplatin; CDDP: Cisplatin; D: Docetaxel; GMZ: Gemcitabine; MIC: Mitomycin, ifosfamide and cisplatin; MVP: Mitomycin, vinblastine and cisplatin; NR: Not reported; PCT: Paclitaxel; VD: Vindesine; VRB: Vinorelbine;
**Significant difference ($p < 0.05$).*

cisplatin 100 mg/m^2 day 1 and vinorelbine 25 mg/m^2 on days 1, 8, 15 and 22, every 4 weeks [34]. The overall response and survival were higher in the docetaxel/cisplatin group than in the carboplatin/docetaxel and cisplatin/vinorelbine groups. The docetaxel-based group had a better QoL than the vinorelbine arm. Grade 3 and 4 toxicities were similar in the three groups, except for nausea and vomiting being higher in the vinorelbine/cisplatin group. This study also supports the fact that cisplatin is more effective in NSCLC than carboplatin, as demonstrated in a recent meta-analysis [41].

A recently published trial randomized the same chemotherapy regimen on cisplatin (100 mg/m^2 day 1) and vinorelbine (30 mg/m^2, each week) every 4 weeks, versus gemcitabine (1000 mg/m^2 days 1 and 8) plus docetaxel (85 mg/m^2 day 8, every 3 weeks) in 311 patients with locally advanced and Stage IV NSCLC [38]. There was no difference in all studied parameters: progression-free survival, overall survival, response rate and 1-year survival. Myelosuppression, emesis and febrile neutropenia were more frequent in the cisplatin/vinorelbine group, whereas pulmonary events and fluid retention were more pronounced in the associatied docetaxel–gemcitabine group. There was no difference in the QoL analysis between the two arms. Pujol and colleagues described the association of docetaxel and gemcitabine to be a possible alternative to platinum-based chemotherapy in the first-line setting, especially in the case of contraindication of platinum salts or poor performance status. Similar results were found by Georgoulias and colleagues in a similar Phase III trial: docetaxel (100 mg/m^2 day 8) and gemcitabine (1000 mg/m^2 days 1 and 8) versus vinorelbine

(30 mg/m^2 days 1 and 8) and cisplatin (80 mg/m^2 day 8), every 3 weeks, with systematic G-CSF in both arms [39].

A Phase III study of particular interest was recently reported at the 11th World Conference on Lung Cancer by a Japanese group [40]. A total of 182 patients aged over 70 years, with a good performans status, were randomized to vinorelbine (25 mg/m^2 on days 1 and 8) or docetaxel (60 mg/m^2 day 1) every 3 weeks. Response rate, progression-free survival, overall survival and survival at 1 year were statistically better in the docetaxel arm than in the vinorelbine arm. Toxicities were globally identical except for grade 3 and 4 neutropenia, and were statistically more frequent in the docetaxel arm.

Docetaxel: second-line treatment in advanced NSCLC

Two trials have shown the benefit of docetaxel as a second-line agent in patients with NSCLC who received platinum-based chemotherapy in the first-line setting (**Table 6**). The first trial (TAX 317) compared docetaxel (75 or 100 mg/m^2) with BSC [42]. The dose of docetaxel was reduced from 100 to 75 mg/m^2, due to a high incidence of febrile neutropenia and death by sepsis. Median time-to-progression, overall survival and response rate favored the docetaxel group. The second study (TAX 320) assigned 373 patients with Stage IIIB or IV NSCLC, who had disease progression during or after one or more platinum-based chemotherapy regimens to one of the three following treatments: docetaxel (100 or 75 mg/m^2 every 3 weeks), weekly vinorelbine 30 mg/m^2 or ifosfamide 2 g/m^2 for 3 days every 3 weeks [43]. Approximately 90% of patients had Stage IV disease at the time of enrolment. Overall response was 11% with docetaxel 100 mg/m^2 and 7% with docetaxel 75 mg/m^2, both of which were greater than the 1% response noted in the vinorelbine or ifosfamide groups. Intention-to-treat analysis showed a modest but significant improvement in time to progression in favor of docetaxel, depicting a 1-year overall survival with docetaxel 75 mg/m^2. Prospective QoL analysis suggested that docetaxel was more effective than the control treatment. Grade 4 neutropenia and febrile neutropenia were more frequent with docetaxel. A further Phase III study confirmed the efficacy and toxicity profile of docetaxel 75 mg/m^2 every 3 weeks [44]. In this study, docetaxel was compared with pemetrexed, a new antifolate drug, in more than 550 patients in the second-line setting. As expected from previous studies, a response rate of approximately 9% and a median survival of 8 months were noted with docetaxel. Nevertheless, pemetrexed appeared to have less toxic effects, specially grade 3/4 neutropenia (5.3 vs 40.2%) and febrile neutropenia (1.9 vs 12.7%), but there was no difference in anemia, thrombocytopenia or extrahematological toxicities.

Docetaxel: treatment in earlier stage of NSCLC

Only one neoadjuvant Phase III trial was published with single-agent docetaxel given before definitive local therapy (either surgery or radical radiotherapy). Mattson and colleagues randomly assigned 274 newly diagnosed patients to either neoadjuvant docetaxel before surgery or definitive radiotherapy, or to local therapy alone [45]. The

Table 6. Randomized Phase III trial in second-line NSCLC.

Trials	Overall response (%)	Time-to-progression (months)	Overall survival (%)	Overall survival (%)		Ref.
				1 year	2 year	
D vs	65*	2.7	7.0*	29*	NR	[42]
BSC	0	1.7	4.6	19	NR	
D 75 mg/m^2 vs	7*	2.1	5.7	32*	NR	[43]
D 100 mg/m^2 vs	11*	2.1	5.5	21	NR	
V or I	<1	1.9	5.6	19	NR	
D vs	9	2.9	7.9	29.7	NR	[44]
Pemetrexed	9	3.4	8.3	29.7	NR	
D every 3 weeks vs	10.5	3.3	6.3	26.9	NR	[55]
D every week	12.6	3.4	9.2	39.5	NR	

**Significant difference ($p < 0.05$).*

BSC: Best supportive care; D: Docetaxel; I: Ifosfamide; NR: Not reported; V: Vinorelbine.

neoadjuvant group received docetaxel 100 mg/m^2 every 3 weeks for three cycles followed by surgery or radiotherapy. Overall survival and the time to progression did not differ between the docetaxel and control groups. No unexpected toxic effects were noted with docetaxel and radiation pneumonitis was not more common in those allocated with neoadjuvant docetaxel following radiotherapy.

Two interesting Phase II studies of docetaxel as neoadjuvant or adjuvant therapy were reported. Betticher and colleagues reported a Phase II trial of cisplatin (40 mg/m^2 days 1 and 2) and docetaxel (85 mg/m^2 day 1) every 3 weeks in 90 patients with Stage IIIA N2 (N2 proved by mediastinoscopy) NSCLC [46]. Three cycles were conducted before surgery, with an objective response of 60%. However, 87% of these patients underwent surgery. Overall median survival of the entire group was 27.6 months, but in patients with pathological N0 or 1 (downstaging with chemotherapy), the 3-year survival was 61%. Toxicity was manageable with no grade 4 nonhematological side effects. Postoperative mortality was 3% whereas the postoperative morbidity was 17%, as expected in first-line surgery.

The Phase II South Western Oncology Group (SWOG) 9504 study included 83 patients with nonresectable Stage IIIA N2 or IIIB NSCLC [47]. Treatment consisted of concomitant chemotherapy (cisplatin and etoposide) and thoracic radiotherapy for up to 61 days, followed by three cycles of docetaxel 75 mg/m^2. A total of 57% of patients reported grade 4 neutropenia, and 9% febrile neutropenia; however, three patients died of late pulmonary complications. Median survival was remarkable at 26 months, and survival rates at 1, 2 and 3 years were 76, 54 and 37%, respectively, higher than those reported for other SWOG studies. These results were recently confirmed by a Phase III trial of a cisplatin/etoposide/thoracic radiotherapy regimen followed by three cycles of docetaxel [48].

Docetaxel: treatment with radiotherapy

Most studies of taxanes with radiation found the combination to be supra-additive but sequence-dependent, with the taxane having to be administered before radiation [49]. When docetaxel was administered in a 3-week schedule, toxicity was mainly neutropenia, but the most commonly used schedule was docetaxel, 20–30 mg/m^2/week concurrent with radiation over 6 weeks [50]. The association of weekly platinum and docetaxel with radiotherapy is also feasible, with acceptable toxicities [51]. Nevertheless, docetaxel and concurrent thoracic radiotherapy have not yet been sufficiently studied in large Phase III trials and caution must be reserved for this regimen due to possible toxicities (esophagitis, pneumonitis) [52].

Docetaxel: treatment with targeted therapies

Due to the recent developments in new, targeted therapies, several studies of an association between chemotherapy and targeted therapies (erlotinib, gefitinib, celecoxib, bortezomib) have been conducted, and notably with docetaxel [53]. The results are actually disappointing but the optimal timing of the association is not yet known and the results are too preliminary to draw conclusions from.

Docetaxel: weekly treatment

Several Phase II trials have assessed weekly docetaxel in advanced NSCLC, with doses of 25–40 mg/m^2/week for 3 weeks in a 4-week schedule, or every week for 6 weeks in an 8-week schedule, both as first- or second-line, single agent or in combination with platinum [54,55]. These studies yielded activity in the same range between the 3-week and weekly schedules. The recently published Phase III trial by Schuette and colleagues randomized 208 previously treated NSCLC patients to two treatment arms: docetaxel 75 mg/m^2 every 3 weeks and docetaxel 35 mg/m^2 days 1, 8 and 15 (weekly) every 4 weeks [55]. The principal objective was median survival, with a clear trend in favour of the weekly arm (9.2 vs 6.3 months, but not statistically significant), without a difference in the objective response rate (10 vs 7.4%). However there were significantly fewer grade 3/4 hematological toxicities (leukopenia, anemia and thrombocytopenia). The Distal 01 Study reported by Gridelli and colleagues compared docetaxel 75 mg/m^2 every 3 weeks and docetaxel 33.3 mg/m^2 weekly for 6 weeks (with 2 weeks rest) in second-line treatment of NSCLC [56]. QoL was the main objective and did not differ between the two arms; survival and response rate were similar, but haematological toxicities were greater in the 3-week arm. Similar results were found in a French, randomized, second-line Phase II study [57]. Based on the results of another recent Phase II study, this weekly schedule seems most appropriate for elderly or frail patients (performance status 2) [58].

Expert commentary

Docetaxel is now established as an important part of our chemotherapeutic strategies against NSCLC. In combination with a platinum in the

Highlights

Mechanisms of action

- Docetaxel binds to and stabilizes microtubules, causing cell cycle arrest and apoptosis. Taxanes selectively bind to the β-subunit of polymerized tubulin at sites distinct from those of vinca alkaloids. Docetaxel targets the same site as paclitaxel, but with a twofold higher affinity.

Pharmacokinetic properties

- The pharmacokinetics of docetaxel can be described by a linear three-compartment model after an intravenous administration at doses greater than 70 mg/m^2. More than 90% of docetaxel binds to plasma proteins, predominantly α_1-acid glycoprotein. Docetaxel is metabolized primarily by cytochrome P450 3A4 and 3A5 enzymes in the liver. 96% is eliminated in the feces via the biliary tract; 4% is eliminated unchanged in the urine.

Cinical efficacy

- The efficacy of docetaxel has been demonstrated in monotherapy in non-small cell lung cancer, in several Phase I and II studies as well as in three Phase III trials. The association between cisplatin/docetaxel has demonstrated its efficacy in the most important Phase III trial performed to date in Stage IV non-small cell lung cancer versus cisplatine vinorelbine.

Safety & tolerability

- The dose-limiting toxicity is neutropenia. Fluid retention, hypersensitivity, neurological or dermatological toxicity are quite uncommon.

Dosage and administration

- 75 mg/m^2 in a 60-min perfusion, every 3 weeks, in monotherapy or in association with cisplatin. For weekly administration, the recommended dose is 30–40 mg/m^2 for 3 weeks, every 4 weeks.

first-line setting, docetaxel has demonstrated good efficacy with acceptable and manageable toxicities for Stage IV NSCLC. As a single agent, the weekly schedule is particularly recommended for elderly patients and those with poor performance status, with a striking balance between efficacy and low toxicity profile. In the second-line setting, docetaxel proved efficacious along with pemetrexed. Based on the evidence of a well-conducted Phase II trial, in the initial stage, docetaxel can be considered as a major advance in the pre- or postoperative setting. In Stage IIIB NSCLC, further studies are needed to determine the exact role of docetaxel in association with concurrent thoracic radiotherapy. Nevertheless, after concurrent chemoradiotherapy (with cisplatin and etoposide), adjuvant docetaxel seems to have interesting efficacy in a Phase II and III trial. Docetaxel is also the best drug for use in nonplatinum combinations, especially in association with gemcitabine

Outlook

Chemotherapy remains an important therapeutic strategy in the treatment of NSCLC, either with curative or palliative intent. Several drugs can be used in Stage IV disease: docetaxel and paclitaxel, gemcitabine, vinorelbine, irinotecan, cisplatin and carboplatin. As a single agent or in association with platinum salts or gemcitabine, docetaxel is established in the first-line setting, with a clear efficacy and a low toxicity profile, and as a single agent in the second-line setting. It is therefore possible to have several chemotherapeutic strategies against Stage IV disease. NSCLC is becoming, in some patients, a chronic disease (like breast cancer) and an early evaluation for prognosis is required to determine the best chemotherapy doublets, using data from pharmacogenomic and proteomic studies, and the best association (sequential or concurrent) with biological therapies. In the early stage, chemotherapy is a real advance in association with local treatment based on either surgery or thoracic radiotherapy. Although there is only one published Phase III trial with docetaxel in the early stage, data in well-conducted Phase II trials with docetaxel are very promising.

Due to the progress with chemotherapy, anaesthesia, surgery, thoracic radiotherapy and biological therapies, survival rates are increasing, showing a 15–20% increase in 5-year survival. These results could be considered as disappointing, but on the whole, the number of cured NSCLC patients is greater each year than the number of cured lymphomas and Hodgkin patients.

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