REVIEW

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Docetaxel-induced interstitial pneumonitis following non-small-cell lung cancer treatment

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Abstract Interstitial pneumonitis has been described infrequently following administration of docetaxel, used alone or in combination with other chemotherapeutic agents or concurrent irradiation, for non-small-cell lung cancer (NSCLC). This toxicity is of special relevance in NSCLC, as clinical severity and differential diagnosis may be especially challenging. It seems to be due to type I and type IV hypersensitivity reactions to the drug. Clinical and radiographic features are nonspecific and diagnosis is made by exclusion. The rate of grade III–IV docetaxel-induced pneumonitis, ranging from 7 to 47%, depends on several factors, including total dose, chemotherapy schedule and especially concomitant docetaxel treatment with gemcitabine and radiotherapy. Although the usual outcome is cure, it sometimes eventually progresses to pulmonary fibrosis despite steroid treatment. This toxicity must be taken into account when planning treatment strategies for NSCLC in order to reduce its rate and to achieve prompt diagnosis and treatment.

Key words Docetaxel • Interstitial pneumonitis • Non-small-cell lung cancer

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Introduction

Docetaxel-induced interstitial pneumonitis is an understudied and poorly diagnosed toxicity. As an example, in a reliable oncology book such as *Cancer: Principles and Practice of Oncology* (7th edition), in the lung toxicity chapter there are only 2 references to docetaxel as a causative drug [1]; in a weighty database such as "Micromedex. Healthcare series. 2006", there are only 2 reported cases of docetaxel-induced pneumonitis [2]; and finally, in the broadest review of taxane-induced pneumonitis found in Up-to-date version 14.3, 22 references to paclitaxel can be found *vs.* only five for docetaxel [3].

Several cases of docetaxel-induced interstitial pneumonitis have been reported since 2000, either when docetaxel is administered as monotherapy regimen or in combination with other agents and/or irradiation, in a wide range of malignancies, including non-small-cell lung cancer (NSCLC), breast cancer [4, 5], prostate cancer [6], bladder cancer [7] and others, such as gynaecologic neoplasms [8].

Docetaxel-induced interstitial pneumonitis in NSCLC

Docetaxel-induced pneumonitis is of special relevance in NSCLC as clinical and radiographic findings can be confounded or added to with primary tumour progression, opportunistic infection, toxicity induced by other drugs or radiation, or worsening of underlying co-morbidities associated to smoking habit and lung cancer (chronic pulmonary disease and emphysema), making diagnosis challenging.

The first report of docetaxel pulmonary toxicity was made in 1998 by Etienne et al. from the Pneumology Service, Hospital de la Croix Rouge in Lyon, France [9]. Since then, there have been several reported cases after different schedules and dosages of docetaxel for NSCLC, including palliative monotherapy treatment [10], in combination with ifosfamide [11] or gemcitabine [12–17], or after definitive treatment in concurrent chemoradiotherapy [18], with or without induction or consolidation chemotherapy treatment [19–24].

On the basis of an extensive literature search (which only found case reports and phase II studies commenting on lung toxicities), an overview of mechanisms of lung damage, common clinical and radiographic features, response to corticosteroids and outcome of docetaxel-induced interstitial pneumonitis for treatment of NSCLC will be discussed below.

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Pathophysiology

Similar to paclitaxel-induced damage, the proposed docetaxel lung toxicity mechanisms include type I and type IV hypersensitivity reactions to the drug. Type I appears to be due to basophil histamine release and mediated by IgE. This response induces acute dyspnoea, bronchospasm, hypotension and erythematous rash, develops in up to 30% and diminishes to 1–3% with steroid premedication. Type IV, T-cell-mediated tissue injury presents as an acute–subacute clinical course (from a few hours to 2 weeks) of bilateral pulmonary infiltrates and is usually transient. Its rate and response to steroids is poorly established [3, 9]. Mechanisms of action based on hypersensitivity reaction to Taxotere are supported by pathology studies on lung biopsy series reported by Read et al. [8]. There are controversial data concerning lung cross-toxicity between paclitaxel and docetaxel [25, 26].

Clinical and radiographic features

Clinical and radiographic taxane-induced pneumonitis findings are nonspecific and similar to interstitial pneumonitis of other aetiology. Symptoms usually have an insidious onset and include fever, malaise, chest pain, cough and dyspnoea, with several degrees of respiratory failure and impaired pulmonary function tests. Chest X-ray and CT scan show bilateral pulmonary interstitial infiltrates.

Although definitive diagnosis is established by lung biopsy, an exclusion diagnosis is generally made on the basis of clinical and radiographic features, absence of infectious disease, non-response to antibiotics and good outcome with corticosteroids [2, 3].

Toxicity staging is complex due to different grading scales (CTC-NCI and acute or late RTOG toxicity scale), applied according to previous treatment with chemotherapy alone or in combination with radiotherapy. Even more, these scales combine subjective symptoms (cough and dyspnoea severity), radiographic findings (patched pattern and pulmonary fibrosis), pulmonary function test abnormalities grading, response to treatment (cough recovery) and treatment needs (continuous or intermittent oxygen therapy and assisted ventilation).

Incidence rate and related factors

The rate of grade 3–4 interstitial pneumonitis ranges from 7 to 47%, depending on several factors that influence toxicity development. These factors include the total delivered dose, schedule and especially concurrent treatment with gemcitabine and radiotherapy.

Total amount of delivered drug

From the literature review it is difficult to establish a docetaxel-induced interstitial pneumonitis causative dose due to diversity of docetaxel doses and schedules employed in monotherapy regimens as well as in combination with other drugs and/or irradiation. Although a 23% interstitial pneumonitis incidence caused a premature ending of a phase I study with weekly docetaxel and gemcitabine for NSCLC, this high pulmonary toxicity rate did not seem to be related to docetaxel dose [14].

Treatment schedule

Interstitial pneumonitis appears to be more related to Taxotere schedule than dose. Weekly schedules cause lower myelosuppression but more pneumonitis than three weekly administration. This issue was suggested by Chen et al. in a randomised trial with 3 different docetaxel schemas in platinum-resistant NSCLC patients: 35 mg/m^2 on day 1, 8 and 15 every 4 weeks, 40 mg/m^2 on days 1 and 8 every 3 weeks and 75 mg/m^2 on day 1 of 3 weeks. A near significant statistical difference (p=0.05) was found in pneumonitis incidence for weekly schedules [27].

Gemcitabine association

Most reports on combination chemotherapy-induced interstitial pneumonitis are with docetaxel and gemcitabine association, probably due to additive toxicity. As is shown in Table 1, the rate in published series ranges from 2.5 to 37%. These different rates may be explained by distinct dosages, schedules and toxicity grades investigated [12–17].

Radiotherapy association

The rate of radiation-induced pneumonitis in NSCLC treatment is a clearly established issue. Factors that can add to the development of pulmonary toxicity include lung architecture, pre-existing co-morbidities, radiation dose, volume of irradiated lung, dose fractioning and concurrent delivery of drugs with additive lung toxicity. The V20, defined as the volume of normal lung that receives more than 20 Gy, is a predictor of the risk of radiation pneumonitis [1, 28].

There are several reports on pulmonary toxicity due to concomitant docetaxel and radiotherapy as definitive treatment for stage III NSCLC, either with docetaxel and radiotherapy as exclusive definitive management [18] or as part of a treatment plan including induction chemotherapy [19] or consolidation therapy [20, 21]. Docetaxel-induced pneumonitis has also been reported after docetaxel as consolidation chemotherapy following

Table 1 Docetaxel and gemcitabine induced pneumonitis

Author [Ref.]	Number of patients	Schedule (dose in mg/m^2)	Grade	Pneumonitis (%)
Hainsworth [12]	39	DOC 30, GEM 800; days 1, 8 and 15; 4 weeks	4	1 (2.5)
Chen [13]	36	DOC 30, GEM 800; days 1 and 8; 3 weeks	4	2 (5.5)
Kouroussis [14]	26	DOC 40, GEM 1000, days 1, 8 and 15; 4 weeks	3–4	6 (23)
Fernandez [15]	19	DOC 35, GEM 1250, days 1 and 8; 3 weeks	2–4	7 (37)
McNeill [16]	42	DOC 35, GEM 800, days 1, 8 and 15; 4 weeks	3–4	3 (7)
Popa [17]	32	DOC 40, GEM 1000, days 1 and 8; 3 weeks	3	6 (18)

DOC, docetaxel; *GEM*, gemcitabine

concurrent radiotherapy with cisplatin and etoposide or vinorelbine, probably due to an additive recall toxicity [22–24]. Nevertheless, in a recent study in which 3 induction courses of cisplatin and gemcitabine were followed by concurrent weekly docetaxel with radiotherapy, no grade 3–4 toxicity was found and only 14% grade 1–2 pneumonitis was reported [29]. Taking all published data into account (see Table 2), the overall pneumonitis rate ranges from 9 to 47%, possibly due to different irradiation and chemotherapy schedules and doses employed in different series [18–24].

Treatment and outcome

Spontaneous resolution constitutes the usual outcome of docetaxel-induced interstitial pneumonitis, although it can sometimes eventually progress to pulmonary fibrosis. According to published data on grade 3–4 toxicity and patient deaths reported in several series [9–14, 18, 19, 21, 23, 24], the mortality rate is about 30% (18 patient deaths out of 59 cases of severe toxicity).

Once toxicity occurs, withdrawal of the offending agent is the cornerstone of therapy. There is no consensus about response to corticosteroids in published series, although apart from 2 studies [8, 10], the vast majority of authors suggest a good outcome or resolution on steroid treatment [4, 7, 9, 15, 21].

Conclusion

Docetaxel-induced interstitial pneumonitis constitutes an underestimated toxicity due to several contributing factors, including: complex evaluation criteria, suspicion diagnosis, added clinical features with primary tumour or infection, additive toxicity with radiotherapy and other cytotoxic agents, concomitant treatment (NSAIDs and steroids) and the absence of well analysed pulmonary toxicity (need of systematic radiographic studies and pulmonary function tests). In order to minimise the incidence and severity of docetaxel-induced interstitial pneumonitis in NSCLC, some recommendations can be made:

1. Taking into account acute and subacute pulmonary toxicity when establishing treatment plan with docetaxel, with special consideration to concomitant administration with gemcitabine and radiotherapy for NSCLC.
2. Including interstitial pneumonitis in differential diagnosis on appearance or worsening of respiratory symptoms.

Table 2 Docetaxel and radiation induced pneumonitis

Author [Ref.]	Number of patients	Schedule (CT dose in mg/m^2 and RT in Gy)	G3–4 pneumonitis (%)
Onishi [18]	32	Concurrent CT+RT: DOC 20/weeklyx6; RT 60–66	15 (47)
Vergnenegre [19]	40	Induction CT: CDDP+NVB Concurrent CT+RT: DOC 25/weeklyx6; RT 66	3 (7.5)
Jang [20]	16	Concurrent CT+RT: DOC 75+CDDP 60/three-weeklyx3; RT 69 Consolidation CT: DOC+CDDP	2 (12.5)
Sakai [21]	32	Concurrent CT+RT: DOC 30+CBDCA/bi-weeklyx4; RT 60 Consolidation CT: DOC+CBDCA	3 (9)
Bedano [22]	73	Concurrent CT+RT: CDDP+VP; RT 59 Consolidation CT: DOC 75/three-weeklyx3	7 (9.5)
Gandara DR [23]	83	Concurrent CT+RT: CDDP + VP; RT 61 Consolidation CT: DOC 75/three-weeklyx3	6 (7.2%)
Sekine I [24]	59	Concurrent CT+RT: CDDP + NVB; RT 60 Consolidation CT: DOC 75/three o four-weeklyx3	4 (6.7%)

CT, chemotherapy; *RT*, radiotherapy; *DOC*, docetaxel; *NVB*, vinorelbine; *CDDP*, cisplatin; *CBDCA*, carboplatin; *VP*, etoposide

3. Establishing incidence with radiographic studies and pulmonary function test performed at baseline, during and after antineoplastic treatment.
4. Reducing or withholding drug administration and initiating corticoid treatment when docetaxel-induced interstitial pneumonitis is suspected.

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