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ORIGINAL ARTICLE

Pulmonary toxicity among cancer patients treated with a combination of docetaxel and gemcitabine: a meta-analysis of clinical trials

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Abstract
Purpose The combination of docetaxel and gemcitabine was tested in several studies in patients with lung, breast, and pancreatic cancers and other tumor entities. Some studies reported cases of severe or even fatal pulmonary toxicity that led to early termination of some trials. We created a meta-analysis model of published studies to identify explanatory factors for docetaxel–gemcitabine-dependent pulmonary toxicity.
Methods We searched MEDLINE/Pubmed, EMBASE, and Cochrane Clinical Trials database for prospective full-text studies that used a schedule of docetaxel and gemcitabine to treat a malignant disease. We performed a meta-analysis for proportions using the arcsine transformation and a meta-regression using a generalized linear mixed model based on a binomial distribution and a logit link.
Results We included 103 trials with 113 treatment arms comprising 5,065 patients (major entities included non-small cell lung cancer ($n = 2{,}550$), breast cancer ($n = 1{,}119$), pancreatic cancer ($n = 466$), and urothelial cancer ($n = 161$)). For the incidence of severe lung toxicity (common toxicity criteria [CTC] grades 3–5), we found a combined estimate of 2.70% (95% CI 2.26, 3.14). The estimate for the proportion of fatal cases was 0.35% (95% CI 0.21, 0.58).
We found that the sequence of the chemotherapy schedule had no influence on the incidence of severe pulmonary adverse events (F-test $F = 0.65$, df = 3,113, $P = 0.58$) nor did the study phase, treatment line or ethnicity of the participants. We found that patients with breast cancer, compared to lung cancer patients, developed severe lung toxicity less frequently (OR = 0.18, 95% CI (0.09, 0.36)).
Conclusion We could not demonstrate that a particular chemotherapy sequence of docetaxel–gemcitabine is associated with excess pulmonary toxicity. Patients with lung cancer are at a higher risk for severe pulmonary side effects with docetaxel–gemcitabine than are patients with breast cancer.

Keywords Neoplasms · Drug toxicity · Lung injury · Docetaxel · Gemcitabine · Meta-analysis

Introduction

Systemic chemotherapy or targeted therapy is the mainstay in the treatment of patients with advanced solid tumors. The prognoses for many patients are limited and due to side effects of chemotherapy regimens their quality of life may be negatively impacted. Pulmonary complications have been reported with many agents, but the incidence of these events is generally rare. However, some drugs or drug combinations attracted considerable attention because of their ability to cause pulmonary complications.

Several investigators have reported that the combination of docetaxel and gemcitabine is relatively well tolerated. For instance, in the treatment of lung cancer, investigators have

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replaced platinum agents with docetaxel–gemcitabine to avoid long hydration times and typical platinum-related toxicities (e.g., nausea, vomiting, and fatigue). However, both docetaxel and gemcitabine have long been known to cause pulmonary toxicity [1–8], and when given in combination, some studies have reported an excess of pulmonary toxicity that led to the premature cessation of four trials [33, 60, 65, 111]. Several deaths have also been reported in the literature due to pulmonary complications brought on by the docetaxel–gemcitabine combination. Contrarily, several studies, some of which are large controlled studies, did not provide any evidence for a significant risk of pulmonary toxicity with docetaxel–gemcitabine treatment [25, 37, 42].

The appearance of such pulmonary complications seems to be highly sporadic and hardly predictable. Some investigators have hypothesized that a particular schedule of administration may be associated with excess pulmonary toxicity. Based on the observations of their studies, Kouroussis et al. [65] and Vasey et al. [114] speculated that a weekly schedule may be hazardous, whereas Esteban [34] suggested that the administration of docetaxel on days 1 and 8 every 21 days, increases the risk. Kouroussis and coworkers [65] also found a low peripheral blood $CD4^+$ lymphocyte count due to corticosteroids and chemotherapy in many of the affected patients, and they suggested that this may have contributed to the toxicity. Asian investigators like Katakami [60] and Takeda [111] speculated that ethnic differences could be responsible for differences in the frequencies of the pulmonary side effects of docetaxel–gemcitabine. However, statistical proof of these hypotheses is lacking, pending the completion of additional studies.

We aimed to identify risk factors for pulmonary toxicity by extracting all the studies that administered docetaxel and gemcitabine in combination to create a meta-analysis model.

Methods

The process of data extraction, collection, and processing was based on the "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement" [9], an item-based guideline to ensure adequate reporting quality. We searched MEDLINE/Pubmed, EMBASE, and Cochrane Clinical Trials database in detail for prospective trials using the docetaxel–gemcitabine combination for the treatment of malignant diseases that were in full-text English publications. The search terms for MEDLINE/Pubmed were ("docetaxel" AND "gemcitabine"), limited by the type of article (i.e., clinical trial) and the language (i.e., English). We considered studies published through February, 2010. The following publications were excluded: studies that simultaneously used a third (or fourth) chemotherapeutic agent, studies with alternating or sequential dosing of the two agents (e.g., one of the two in every other cycle) and those that integrated large-field radiation therapy. The procedures for data extraction and inclusion of studies are outlined in Fig. 1.

Table 1 Classification of nominal variables

Tumor entity	• Lung cancer
	• Breast cancer
	• Pancreatic cancer
	• Urothelial cancer
	• Other
Study phase	• I
	• II
	• II, randomized
	•III
Line of treatment	• First-line
	• Any other line
Area of study accrual	• Europe
	• North America
	• Asia
	• Other geographic region or intercontinental trial
Treatment schedule	• Cycle length, 21 or 28 days
	Docetaxel once every cycle on day 1 or 8
	Gemcitabine two infusions every 3 weeks or three infusions every 4 weeks
	• Cycle length, 28 days
	Biweekly schedule of both substances
	• Docetaxel and gemcitabine twice every 3 weeks or three times every 4 weeks or continuously weekly
	• Any other type of schedule

We extracted the following nominal variables in detail and classified them as shown in Table 1: tumor entity, study phase, line of treatment, study location, and treatment schedule. Moreover, we extracted the following metric variables: proportion of female subjects, median age of studied population, and proportion of patients with an Eastern Cooperative Oncology Group (ECOG) performance score of 2. We used two endpoints of pulmonary toxicity as reported by the investigators: incidence of severe and fatal pulmonary toxicity (grades 3, 4, 5) and incidence of fatal pulmonary toxicity (grade 5). In the studies, the classification of side effects was either based on World Health Organization or Common Toxicity Criteria.

To perform a quantitative meta-analysis, we applied the double arcsine transformation to the observed proportions [10]. Based on this transformation, the inverse variance method was applied to obtain summary estimates using the

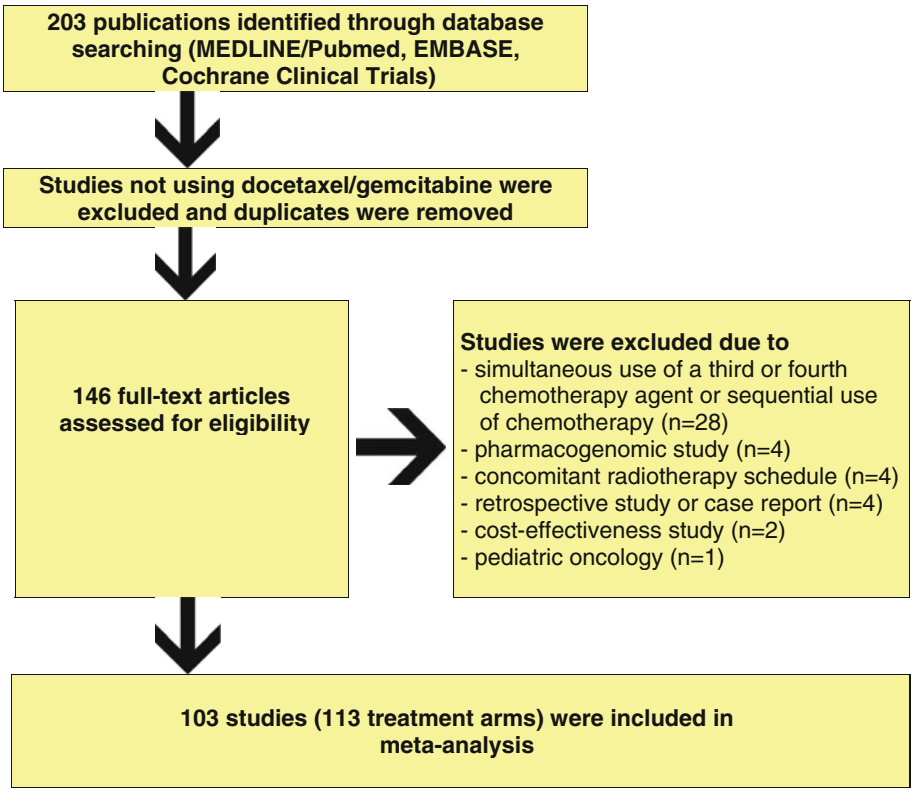

Fig. 1 Flow chart of identification, screening, eligibility and study inclusion

R-package meta [11]. Publication bias was assessed using Egger's method [12]. This method first computes the ratio of effect size and corresponding standard error. This standardized effect size is taken as the dependent variable in a linear regression model. The independent variable is the precision (1/standard error). The intercept of this regression model denotes the bias. If no publication bias is present the intercept will equal zero. Heterogeneity was assessed by a test of heterogeneity [13].

To take heterogeneity into account, a generalized linear mixed model based on a binomial distribution and logit link was applied. The random effects of this model account for the variability between studies and are quantified by the heterogeneity variance τ^2. Results of the meta-regression are presented as odds ratios together with a 95% confidence interval.

Results

We included 103 trials with 113 treatment arms using docetaxel–gemcitabine [14–116]. The trials were comprised of 5,065 patients. The numbers of included trials in the particular entities are shown in Table 2; the majority of studies were conducted in patients with lung cancer. Table 3 shows the absolute incidence of the toxicity endpoints within particular entities.

Table 2 Number of studies and participants in the different tumor entities

	Number of studies/arms	Number of patients
Non-small cell lung cancer	45/49	2,550
Small cell lung cancer	3/3	82
Breast cancer	19/19	1,119
Pancreatic cancer	13/15	466
Urothelial cancer	6/6	161
Other entities	17/21	687

Table 3 Incidence of severe and fatal pulmonary toxicity in different tumor entities

	n	Grades 3–5 pulmonary toxicity *n*	Fatal pulmonary toxicity *n*
Non-small cell lung cancer	2,550	104	13
Small cell lung cancer	82	8	0
Breast cancer	1,119	9	1
Pancreatic cancer	466	13	2
Urothelial cancer	161	5	1
Other entities	687	33	2

Table 4 Incidence of severe and fatal pulmonary toxicity according to the location of the studies

	n	Grades 3–5 pulmonary toxicity *n*	Fatal pulmonary toxicity *n*
Europe	3,190	79	9
North America	1,320	62	4
Asia	437	31	6
Intercontinental study or other location	118	0	0

Fifty-five trials reported no grade 3–4 pulmonary toxicity, whereas 48 trials reported such toxicity. We identified 15 trials with deaths from observed or suspected pulmonary adverse events [26, 33, 41, 45, 47, 57, 65, 68, 69, 80, 84, 91, 111, 114, 115]. We found seven trials with ≥20% grade 3–5 toxicity [23, 32–34, 49, 65, 115]. Four studies were closed prematurely due to unexpectedly frequent pulmonary toxicity [33, 60, 65, 111]. The wording of the pulmonary complication reflects different levels of diagnostic clarification: they were termed "dyspnea" or "shortness of breath" (18 studies), "pulmonary toxicity" ($n = 12$), "interstitial pneumonitis" ($n = 15$), "interstitial lung disease (ILD)" ($n = 3$), "acute respiratory distress syndrome (ARDS)" ($n = 5$), "lung injury" ($n = 3$), "pneumonia" ($n = 3$). More than one term was used in some studies.

Based on the regression method there was a significant publication bias. This could not be resolved by further searches and other efforts (bias = 1.788, $t = 3.3717$, df = 111, $P = 0.001$). This means that studies with a smaller case number are less likely to be published.

We found that the chemotherapy schedule had no influence on the incidence of severe (grade 3–5) pulmonary toxicity (F-test $F = 0.65$, df = 3,113, $P = 0.58$), nor did study phase or treatment line. Although there was a trend toward more Asian patients dying from pulmonary toxicity (6/437 Asians versus 13/4628 others, see Table 4), the model could not prove an increased risk associated with the ethnicity of the participants.

For the incidence of severe lung toxicity (grades 3–5), we found an overall estimate of 2.70% (95% CI 2.26%, 3.14%). We found strong heterogeneity between studies (Q-Statistic = 327.24, df = 112, $P < 0.0001$), which leads to an $I^2 = 65.8$, 95% CI (58.3, 71.9). Thus, 66% of the variability of the data is due to heterogeneity between the studies. As a result, a generalized linear mixed model was applied for the meta-analysis and the meta-regression. Based on this model, the combined estimate was given by 2.35% (95% CI 1.70, 3.25). The corresponding heterogeneity variance is given by $\tau^2 = 1.85$, indicating strong heterogeneity again. This implies that although the overall estimate is 2.35%, the true estimate of study-specific toxicity might be as low as 0.1% and as high as 33%, considering a 90% interval for the true effects.

Using the regression model, we found that relative to patients with lung cancer, patients with breast cancer developed severe lung toxicity less frequently (OR = 0.18, 95% CI (0.09, 0.36)). If lung cancer patients were tested against all other tumor entities, we could not detect an increased risk (OR = 0.98, 95% CI (0.49, 1.94)). If the model was corrected for the influence of age (median age) and the proportion of women, the statistical significance holds true for breast cancer versus lung cancer (OR = 0.08, 95% CI (0.01, 0.60)), but again no increased risk was found for lung cancer versus all other tumor entities (OR = 0.63, 95% CI (0.24, 1.63)).

The combined estimate for the proportion of fatal cases based on the random effects model was 0.35% with 95% CI (0.21, 0.58). In this setting, patients with lung cancer, compared to breast cancer patients, did not show significantly more fatal lung toxicity (OR = 0.20, 95% CI (0.02, 1.67)).

Discussion

In the present work, we collected and analyzed prospective studies using the combination of gemcitabine and docetaxel to identify risk factors for pulmonary toxicity.

We could not demonstrate that a weekly schedule of chemotherapy is a significant risk factor for pulmonary toxicity with docetaxel–gemcitabine. This was formerly hypothesized by Kouroussis [65] and Vasey [114] based on the observations made in their studies. In their phase I/II study, Kouroussis and coworkers [65] administered escalating doses of gemcitabine and docetaxel given for three consecutive weeks in cycles of 4 weeks to patients with advanced non-small cell lung cancer. There were six out of 26 patients suffering from severe pulmonary side effects, two of which died as a consequence. The group found a low $CD4^+$ lymphocyte count in several affected patients and speculated that there could be a cause-effect relationship between $CD4^+$ counts and pulmonary toxicity. Vasey and coworkers [114] randomized patients with ovarian cancer to three different schedules after they completed an induction phase with carboplatin. Two of the arms comprised gemcitabine and docetaxel, whereas one gave docetaxel three times weekly and the other in 3 weekly fractions every 4 weeks. One fatal case occurred with the weekly protocol and the authors hypothesized that weekly schedules cause more pulmonary toxicity. However, 17 patients suffered from grade 3–5 pulmonary toxicity within each of the two protocols, respectively, and the authors could not demonstrate statistical differences.

We found no influence of the line of treatment (first-line versus later) or the study phase on the risk of pulmonary toxicity. Although there was a trend for Asian patients to develop pulmonary side effects more frequently and two of the four prematurely closed studies were conducted in Japan [60, 111], the statistical model could not demonstrate that ethnicity is a risk factor. Katakami and colleagues [60] treated patients with advanced non-small cell lung cancer with docetaxel–cisplatin or docetaxel–gemcitabine. Patients treated with the latter combination (docetaxel three times weekly) suffered from excess pulmonary toxicity, leading to the early termination of the study. The authors speculated that Asian ethnicity may be associated with a higher incidence of pulmonary toxicity. A similar hypothesis was proposed by Takeda and coworkers [111]. The group conducted a study in pretreated patients with advanced non-small cell lung cancer and randomized between docetaxel only and gemcitabine–docetaxel. There were three treatment-related deaths with this combination schedule.

In the present analysis, we demonstrated that patients with breast cancer, relative to patients with lung cancer, had a lower risk for severe (grades 3–5) pulmonary toxicity under gemcitabine and docetaxel with an OR of 0.18 (95% CI 0.09, 0.36). The OR was 0.20 for the fatal cases but wide 95% confidence intervals (0.02, 1.67) prevented achieving formal statistical significance. Conclusions from these findings should be made with extreme caution as we know that lung cancer patients have typically been heavy smokers with structural lung damage, such as COPD or emphysema. As long as the process for diagnosing suspected pulmonary toxicity is vague and inconsistent and primarily dependent on the exclusion of alternative causes (bacterial pneumonia with or without ARDS, opportunistic infections, pulmonary arterial embolism, exacerbation of obstructive pulmonary disease, or insufficiently diagnosed pleural or pericardial effusion), that lung cancer patients tend to have more comorbidities than patients with breast cancer must be kept in mind.

The underlying studies of this meta-analysis reveal that the complication frequently starts with exertional dyspnea and elevated temperature [33, 60, 65]. The onset of symptoms may vary from cycle one to cycle six, so no consistent point of onset can be concluded from the studies. The investigators generally categorize two different courses of the complication [23, 33, 60, 65, 84, 115]. One group of patients suffered from milder pulmonary symptoms. Their treatment was usually discontinued and they improved quickly with corticosteroids. Alternatively, some patients—even after the cessation of docetaxel–gemcitabine and treatment with high doses of corticosteroids—progressively deteriorated until bilateral patchy infiltrations and severe hypoxemia were present, and intubation and mechanical ventilation were mandatory. Deaths typically occurred only in the latter group of patients. Radiological findings of affected patients revealed bilateral ground glass opacities and reticular, interstitial or patchy infiltrates [33, 60, 65, 115]. Biopsy or autopsy results were rare, but revealed diffuse alveolar damage [33, 115] with widespread type 2 pneumocyte hyperplasia, hyaline membrane formation, and fibrous thickening of alveolar walls. Even in cases of thorough clinical, laboratory, and histological workup, many authors agree that the cause of the complication cannot be separated unambiguously from other causes and processes (e.g., infections and lymphangiosis carcinomatosa).

The present study has several limitations:

1. Meta-analyses rely on a uniformity of populations, methods, and endpoints. However, in the clinical studies included in this analysis, not all investigators undertook an equal effort to elucidate the nature of the pulmonary symptoms of a patient. Thus, the different wording of the side effect (e.g., “dyspnea”, “pulmonary”, “pneumonitis”, “lung injury”, “ARDS”, and “interstitial lung disease”) reflects different degrees of diagnostic effort. Moreover, there is limited diagnostic proof for pulmonary toxicity with gemcitabine–docetaxel.
2. It could not be deciphered whether it is suitable to ascribe different mechanisms to the pulmonary complication. However, this is similar to many other adverse reactions reported in clinical studies (e.g., fatigue, asthenia, weight loss, and infections). Moreover, docetaxel and gemcitabine are different drugs that possibly comprise different mechanisms of pulmonary toxicity. A recommended analysis with maximal accuracy would test both drugs separately.
3. Studies with concurrent large-field radiotherapy were excluded. However, even after the completion of radiation therapy recall phenomena can occur. Radiation recall pneumonitis can be found up to several months after the last fraction of irradiation [8]. Only a few authors, such as Dunsford [33], Kouroussis [65] and Katakami [60], in their prematurely closed trials, stated that none of participants had irradiation to the thorax prior to treatment.
4. We could not be certain if concomitant drug intake plays a role in causing or alleviating pulmonary complications with the combination of docetaxel and gemcitabine.

In summary, we believe that a statistical analysis, such the study undertaken at present, should be interpreted with the appropriate amount of caution as the results can only generate hypotheses that then must be tested in prospective clinical trials.

Investigators should be aware of the pulmonary toxicity associated with docetaxel–gemcitabine chemotherapy. Due to sporadic incidences and lack of risk factors, patients treated with these drugs concomitantly must be carefully monitored for pulmonary toxicity. This must include an early cessation of treatment in suspected cases. Up to now, it is unclear to what degree corticosteroids are beneficial for the treatment. Moreover, no information exists on whether consecutive lung function tests or bronchoalveolar lavage facilitates an early diagnosis of this complication. Clinical studies with gemcitabine and docetaxel should include serial lung function and a diffusion capacity assessment as well as detailed schedules for the invasive assessment of suspected cases of pulmonary toxicity (e.g., bronchoalveolar lavage and biopsies).

Conflicts of interest None.

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