Review Article

Pulmonary Toxicity Related to Systemic Treatment of Nonsmall Cell Lung Cancer

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Physicians who are responsible for the delivery of systemic treatment in lung cancer should be aware of the potential risk of drug-induced pulmonary toxicity (DIPT), because such toxicity may develop in the context of a multifactorial clinical condition. First, most patients with lung cancer may suffer from other non-neoplastic, smoking-related lung diseases, such as emphysema and chronic obstructive lung disease, which may generate pathologic changes in lung parenchyma. In addition, lung cancer itself may worsen the respiratory function, inducing atelectasis and lymphangitic carcinomatosis. The superimposed iatrogenic damage may lead to respiratory failure and, sometimes, death. The risk of DIPT from chemotherapeutic agents has been widely examined in the past; and, currently, the potential for lung toxicity has been extended by the introduction of molecular targeted therapies. Because there are no univocal criteria with which to recognize DIPT, the diagnosis often is made by exclusion; consequently, it is hard to establish an early diagnosis. The objective of this review was to describe the major DIPTs associated with antineoplastic agents against nonsmall cell lung cancer to help physicians with this difficult diagnostic challenge. ***Cancer*** **2011;117:3069–80.**

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Chemotherapeutic agents that are used against nonsmall cell lung cancer (NSCLC) may induce pulmonary toxicity (drug induced pulmonary toxicity [DIPT]). To date, the newly adopted, molecular-targeted therapies (epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors and antiangiogenetic agents), used either alone or in combination, have increased the potential for DIPT.[1]

The diagnosis of DIPT may be complicated, because its clinical, histologic, and radiologic findings are nonspecific.[2] However, the identification of DIPT is crucial, because patients with NSCLC who are candidates for systemic therapy already may have compromised respiratory function caused by several pre-existing conditions. Most of patients with lung cancer suffer from other non-neoplastic, smoking-related lung diseases (ie, emphysema, chronic obstructive lung disease), which may generate pathologic changes in lung parenchyma; and lung cancer itself may worsen the respiratory function, inducing atelectasis and lymphangitic carcinomatosis.

Moreover, in patients with early stage NSCLC, elective surgery leads to a loss of lung volume (parenchyma amputation) and to perioperative functional alterations (atelectasis, diaphragm dysfunctions, ventilatory depression, alterations in pulmonary gas exchange, cough, and clearance of secretions). In this context, an assessment for the potential risk of DIPT is advisable when choosing between neo-adjuvant chemotherapy and adjuvant chemotherapy, and an early diagnosis of DIPT is essential to avoid respiratory insufficiency during treatment. In addition, radiation therapy, which is indicated for patients who have locally advanced, unresectable NSCLC, may induce acute and chronic changes in lung parenchyma, especially if it is administered concomitantly with chemotherapy.

The objective of the current report was to review the different potential DIPTs related to NSCLC treatment. For each of the commonly used drugs, we reviewed the available information about the incidence of DIPT, symptoms and their onset, risk factors, radiologic and histologic patterns, therapy, and outcomes, and we propose a diagnostic algorithm to aid clinicians in the early detection of DIPT.

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Table 1. Description of Parenchymal Patterns of Drug-Induced Pulmonary Toxicity

Parenchymal Pattern	Clinical Presentation	Chest X-Ray	HRCT	Histopathology
NSIP-like	Insidious onset of dyspnea, dry cough, fever	Reticular infiltration and diffuse, homogeneous opacities	Patchy or diffuse ground-grass opacities; fibrosis, reticular pattern, traction bronchiectasis, honeycombing with basal distribution (in advanced ILD)	Mild-to-moderate interstitial chronic inflammation, abnormal type II pneumocytes, interstitial fibrosis
AIP-like	Dyspnea, dry cough, fever, ARDS (possible)	Bilateral patchy or homogeneous air-space consolidation mainly in the middle and lower zones	Bilateral consolidation and ground-glass opacities; traction bronchiectasis (in advanced ILD)	DAD: acute phase (interstitial and alveolar edema, hyaline membrane formation) and organizing phase (type II pneumocyte hyperplasia, organizing fibrosis)
HP-like	Dyspnea, fever, fatigue, myalgias, arthralgias, skin rush	Diffuse, reticular infiltrates and nodules most in upper and middle zones	Bilateral ground-glass opacities and/or small, poorly defined, centrilobular nodular opacities; lobular areas of air trapping	Mixed mononuclear cell infiltration with interstitial, but not alveolar, eosinophils, evolving in fibrosis; eosinophils in both interstitium and alveoli (as in eosinophilic pneumonia); blood eosinophilia is observed in $<$40% of cases in the pattern like eosinophilic pneumonia
BOOP-like/ COP-like	Progressive dyspnea, dry cough, fever	Peripheral, bilateral, scattered, heterogeneous, and homogeneous opacities in both upper and lower lobes	Poorly defined, nodular areas of consolidation; peribronchial or subpleural, centrilobular nodules and "tree-in-bud opacities"; bronchial dilatation	Immature fibroblastic plugs (Masson bodies) within the respiratory bronchioles, alveolar ducts, and adjacent alveolar spaces
Alveolar hemorrhage	Dyspnea, ARDS (possible), hemoptysis (rare)	Bilateral homogeneous and heterogeneous opacities	Bilateral, scattered, or diffuse ground-glass areas	Mononuclear cells and erythrocytes cells in the interstitium and alveoli; type II alveolar epithelial cell hyperplasia, intra-alveolar organizing pneumonia, fibrinoid necrosis
Noncardiogenic pulmonary edema	Dyspnea, cough, ARDS (possible)	Diffuse alveolar-filling infiltrates with no cardiomegaly	Interstitial thickening, alveolar opacities	Interstitial thickening; protein-rich exudate and hemosiderin-containing macrophages in the alveoli

HRCT, indicates high-resolution computed tomography; NSIP, nonspecific interstitial pneumonia; ILD, interstitial lung disease; AIP, acute interstitial pneumonia; ARDS, acute respiratory distress syndrome; DAD, diffuse alveolar damage; HP, hypersensitivity pneumonia; BOOP, bronchiolitis obliterans organizing pneumonia; COP, cryptogenic organizing pneumonia.

MATERIALS AND METHODS

A bibliographic search of the literature available on PubMed was performed. The selection criteria for the search included the presence of DIPT for each of the antineoplastic agents used against NSCLC. We included clinical trials, meta-analyses, and case reports to be as exhaustive as possible in the description of DIPT.

Published articles reporting on DIPT have used different clinical, radiologic, or histologic criteria for its definition. For the purpose of the current review, we defined DIPT as any pulmonary complication that involved parenchyma, airways, or lung vessels and any systemic disease that involved the lung. The possible parenchymal patterns of DIPT are defined in Table 1 according to symptoms and histologic and radiologic patterns. The main features of clinical DIPT syndromes related to airways disease, lung vessels, and systemic diseases are summarized in Table 2.

Specific Pulmonary Toxicity of Different Antineoplastic Agents

Pulmonary toxicity of cytotoxic agents

Platinum compounds

The administration of cisplatin and carboplatin, the 2 most commonly used platinum derivative agents, can lead to hypersensitivity reactions (HRs) in approximately

Table 2. Description of Clinical Syndromes of Drug-Induced Pulmonary Toxicity Related to Airway Diseases, Lung Vessel Diseases, and Systemic Syndromes

Clinical Syndrome	Description
Airway diseases	
Hypersensitivity reaction	Acute onset of bronchospasm, dyspnea, cough, hypotension, skin rush during drug administration or minutes to hours later
Lung vessel diseases	
Pulmonary thromboembolism	Acute onset of dyspnea, thoracic pain, hypoxia
Pulmonary hemorrhage	Acute onset of dyspnea, hemoptysis (uncommon), ARDS (possible), bland pulmonary hemorrhage
Systemic syndromes	
Capillary leak syndrome	Dyspnea, cough, noncardiogenic pulmonary edema, associated with peripheral edema, pleural effusion, and intravascular hypovolemia
Hemolytic-uremic syndrome	Dyspnea, cough, associated with microangiopathic hemolytic anemia, thrombocytopenia, renal failure, noncardiogenic pulmonary edema, and, in some patients, alveolar hemorrhage with subsequent ARDS

ARDS indicates acute respiratory distress syndrome.

2% of patients, whereas the reported incidence of other DIPTs is not statistically significant. HRs related to platinum compounds generally are type I and can occur after multiple cycles of chemotherapy. The symptoms associated with platinum compounds are urticaria, rush, angioedema, bronchospasm, and hypotension. The treatment of severe HRs includes infusion interruption and the administration of corticosteroids, antihistamines, and epinephrine. In addition, treatment discontinuation is recommended.[3]

Because platinum agents usually are coadministered with other cytotoxic agents, it may be observed sporadically that some pulmonary adverse events related to platinum administration have been attributed to other drugs. It was reported that the combination of gemcitabine plus carboplatin, compared with gemcitabine alone, leads to an increased risk of lung toxicity (13% vs 11% for grade 3/4 lung toxicity), and a role for carboplatin in this increase cannot be excluded.[4] In a phase 3 trial that compared gemcitabine plus cisplatin versus cisplatin alone, it was reported that, in the cisplatin-alone arm, the incidence of grade 3 dyspnea was 3%, and the incidence of grade 4 dyspnea was 2%.[5] In both of those studies, the difference in incidence was not statistically significant.

Gemcitabine

The most frequent form of pulmonary toxicity described for gemcitabine is dyspnea. Grade 4 dyspnea is reported in approximately 3% of patients, and it can be associated with bronchospasm in approximately 0.6% of patients.[5] Generally, dyspnea occurs within hours after the administration of gemcitabine, and it is self-limiting.

Additional and rare gemcitabine-related pulmonary toxicities include alveolar hemorrhage (AH),[6] diffuse alveolar damage (DAD),[7] acute respiratory distress syndrome (ARDS),[8] noncardiogenic pulmonary edema,[9] hemolytic uremic syndrome (HUS),[10] and capillary leak syndrome.[11] A pooled analysis from a large database indicated that the incidence of severe gemcitabine-induced pulmonary toxicity can vary from 0.02% to 0.27%.[12]

The onset of symptoms (dry cough, fatigue, malaise) occurs 3 to 12 weeks after the beginning of treatment.[13-15] The radiologic findings are represented by diffuse or patchy ground-glass attenuation, reticular nodules, and interstitial thickening.[16] In most patients, the histologic findings at autopsy reveal hyperplasia of type II pneumocytes, patchy AH, hyaline membrane formation, and fibrosis,[7,8,15] all findings that are consistent with acute lung injury.

Potential risk factors have been identified in the concomitant administration of other agents (paclitaxel, docetaxel, ifosfamide, and granulocyte-colony–stimulating factor), previous lung disease, and chest radiation.[6] In an early clinical phase 2 study, thoracic radiotherapy (total dose, 60 grays [Gy]) was administered concomitantly with gemcitabine (1000 mg/m^2 per week) to patients with locally advanced NSCLC. That study was interrupted after the inclusion of 8 patients because of severe toxicity (3 patients died, 10%-20% died of pneumonitis, and 50% died of esophagitis).[17] Since that experience, other studies have tried to assess the optimal dose of gemcitabine to take advantage of its radiosensitization effect and to avoid toxicity.[18] The suggested dose of gemcitabine combined with radiotherapy can vary from 100 mg/m^2 to 375 mg/m^2 per week, depending on the radiotherapy dose, the type of treatment planning (2-dimensional or 3-dimensional), and the radiation volume.[19]

The risk of gemcitabine-induced recall phenomenon is rare, although some instances of recall pneumonitis in patients who received previous radiation therapy have been reported. Dry cough and dyspnea are early symptoms, and ground-glass opacities in the irradiated areas have been observed on computed tomography (CT) scans. This risk of recall pneumonitis should be taken into

account even after an extended time after previous radiotherapy (from weeks to months).[20] Discontinuation of therapy and the administration of corticosteroids (ie, prednisone 60 mg daily) may improve DIPT within a few days.[21]

Etoposide

Etoposide may induce HRs with angioedema, bronchospasm, and hypotension, all of which require steroid administration.[22] Interstitial lung disease (ILD) related to etoposide is rare, but several case reports have been published.[23] The clinical onset is characterized by nonspecific symptoms, such as progressive dyspnea with severe hypoxemia, nonproductive cough, and, in some patients, fever, which normally appears after a prolonged treatment but may occur even after 1 week.

The features observed on chest x-ray and CT scans include bilateral, diffuse interstitial and alveolar infiltrates; and, at lung biopsy, the predominant pattern is represented by diffuse alveolar, septal, and parenchymal fibrosis; DAD; focal hyaline membrane formation; AH; and atypical bronchial epithelial hyperplasia.[23] The concomitant administration of other drugs, such as methotrexate, or thoracic radiation therapy may increase the risk of developing ILD.[24]

Mitomycin-C

Mitomycin-C (MMC) is no longer used for the treatment of NSCLC; however, in some of the recently published combined-modality trials in early stage NSCLC that were initiated more than 15 years ago, MMC still was part of triplet combinations.[25,26] With this agent, pulmonary toxicity may occur in 4% of patients or even more, especially if its administration is associated with other agents,[27] such as vinca alkaloids, platinum agents, and radiotherapy.[28,29]

Three different clinical patterns of toxicity may occur: 1) chronic interstitial pneumonitis with fibrosis (when MMC is administered alone or in combination with radiotherapy and other agents).[28] The onset of symptoms (progressive dyspnea, dry cough, and rare fever) usually occurs 3 to 12 months after the beginning of treatment, but it also may occur after a single administration.[29] This syndrome may respond promptly to drug discontinuation and corticosteroid administration but, in spite of the treatment, it can also evolve to progressive pulmonary insufficiency, as described in some patients.[30,31] 2) Acute pneumonitis (typical of MMC combined with vinca alkaloids) is accompanied by a rapid onset (within hours) of dyspnea and bronchospasm, which can evolve clinically into ARDS and may require intubation.[32] Supportive care, bronchodilators, and steroid administration normally improve dyspnea within days, although evolution to chronic pulmonary insufficiency is common in these patients.[27,33] 3) Pulmonary toxicity may be induced by MMC-related HUS. Patients affected by HUS develop microangiopathic hemolytic anemia, renal failure, noncardiogenic and pulmonary edema; and some patients develop AH with subsequent ARDS and respiratory failure.[34] This syndrome usually occurs late, often more than 1 year after the beginning of treatment. The prognosis for these patients is poor despite intensive-care treatment, high-dose corticosteroid therapy, and plasmapheresis.[35]

Vinca alkaloids

Vinca alkaloids rarely induce DIPT when administrated as single agents, but pulmonary toxicity is reported in combination with MMC, as described above.[36] The only DIPTs that have been reported after administration of single-agent vinorelbine are rare instances of acute interstitial pneumonia (AIP), dyspnea, and bronchospasm (within hours from the infusion). These DIPTs are usually responsive to bronchodilators and steroids.[37]

Taxanes

Paclitaxel is approved for the treatment of several different cancers, including NSCLC. Initial clinical data indicated that up to 30% of patients developed HRs; however, this rate decreased to approximately 1% when patients were premedicated with antihistamines and steroids.[38] Unlike reactions to platinum compounds, nearly 95% of all reactions to taxanes occur during the first or second cycle, and symptoms develop within the first 10 minutes of the infusion. The treatment of severe HRs (characterized by dyspnea, hypoxemia, bronchospasm, urticaria, arterial hypotension, and erythematous rashes[39]) includes administration of epinephrine, diphenhydramine, albuterol, and hydrocortisone as well as treatment discontinuation.[3]

Paclitaxel-related interstitial pneumonitis occurs in 1% of patients, but its incidence increases if it is administered concomitantly with gemcitabine and radiotherapy.[40,41] Symptoms are nonspecific (dry cough, dyspnea, hypoxemia) and occur from hours to weeks after the infusion.[6] An x-ray may reveal patchy infiltration and a reticulonodular pattern, and high-resolution CT (HRCT) can reveal patchy areas with ground-glass opacities.[42] The

histology is characterized by interstitial inflammation, hyaline membrane formation, fibrosis, and abnormal type II pneumocyte proliferation, which is suggestive of a direct toxic effect, whereas the presence of eosinophils in both blood and bronchoalveolar lavage (BAL) supports the hypothesis of a hypersensitivity pathogenesis.[6,41,43]

Most patients improve with drug discontinuation, supportive care, and steroids, although fatal events have been reported.[6,41]

HRs are less frequent with docetaxel than with paclitaxel, because docetaxel is dissolved in ethanol and water rather than cremaphor. Docetaxel can induce fluid retention caused by capillary leakage as a consequence of the induced damage to endothelial cells with consequent capillary hyperpermeability, leading to noncardiogenic pulmonary edema, peripheral edema, pleural effusion, and ascites.[44] The incidence of this complication is 3% in monotherapy and 23% in association with gemcitabine.

Interstitial pneumonitis has been reported after docetaxel administration and can be suspected in the presence of fever, dry cough, and dyspnea. On physical examination of the chest, fine, bilateral crackles can be detected even in patients who have normal chest x-rays. Patients with severe AIP and hypersensitivity pneumonia (HP) with ARDS-like symptoms that occurred within 8 to 21 days after the last dose of docetaxel have been described: symptoms develop acutely over 1 or 2 days and may progress rapidly to respiratory failure, which requires mechanical ventilation.[45] Docetaxel-induced pneumonitis typically presents with a pattern like that observed in nonspecific interstitial pneumonia, and it is remarkable in its long duration.[6]

The association of docetaxel with other chemotherapeutic agents or radiotherapy may increase the incidence of grade 3/4 DIPT.[46] Pneumonitis rates as high as 7% to 10% have been reported, especially during or after concurrent radiotherapy,[47] and a rate as high as 23% was reported with the coadministration of gemcitabine.[48] Although mild pneumonitis tends to resolve spontaneously or after low doses of steroids,[6] in severe cases, treatment discontinuation and the use of steroid therapy are not always effective to avoid insufficiency and death.

Pemetrexed.

No significant pulmonary toxicity has been reported for pemetrexed in phase 3 studies,[49,50] and only sporadic case reports have indicated the possible occurrence of pemetrexed-related interstitial pneumonia.[51]

Pulmonary Toxicity of Targeted Therapies

Anti-EGFR therapies

Gefitinib

In 2 second-line, phase 2 studies that included more than 400 patients who received gefitinib monotherapy, 2 patients experienced ILD-type events (interstitial pneumonia and pneumonitis).[52,53] Both were Japanese patients who received gefitinib 500 mg daily. One patient recovered from DIPT after withdrawal from treatment. In the other patient, the pneumonitis occurred 3 days after withdrawal from gefitinib treatment (because of severe fatigue), and it was ongoing at the time the patient died of disease progression. Two phase 3 trials (Iressa NSCLC Trial Assessing Combination Treatment 1 [INTACT1] and INTACT2) that compared gefitinib and placebo in combination with standard chemotherapy as first-line treatment of advanced NSCLC did not report any increased lung toxicity in the gefitinib arm.[54,55]

In the Iressa Pan-Asia Study (IPASS study), carboplatin/paclitaxel was compared with gefitinib monotherapy as first-line treatment for advanced pulmonary adenocarcinoma in nonsmokers and former light smokers. ILD events occurred in 16 of 609 patients who received gefitinib (2.6%), including 3 fatal outcomes, and in 8 of 608 patients who received carboplatin/paclitaxel (1.4%), including 1 fatal outcome.[56]

A subsequent observational study that included more than 185.000 patients who received gefitinib reported an incidence of ILD of 1.5% to 2% among Japanese patients versus 0.3% in the rest of the world.[57] Despite this low incidence, gefitinib-induced DIPT may be fatal up to 30% of patients.[58]

Gefitinib-associated DIPT consists mainly of ILD: AIP with DAD,[59,60] AH,[61] and pulmonary fibrosis[62,63] have been reported. It usually occurs within the first 90 days of treatment,[6] and the median time of clinical onset was 24 days in Japan and 42 days in the United States.[58]

In a Japanese multi-institutional study of 102 patients with gefitinib-induced ILD, the radiologic findings were classified into 4 patterns: 1) parenchymal areas with ground-glass attenuation; 2) multifocal areas of airspace consolidation; 3) patchy distribution of ground-glass attenuation with associated interlobar septal thickening; and 4) extensive, bilateral, ground-glass attenuation or airspace consolidations with traction bronchiectasis.[64] The first and the last patterns were the most common (47.1% and 23.5%, respectively). The mortality rate was significantly higher in patients who had pattern

number 4, which was consistent with the radiologic features of DAD.

Smoking and pulmonary fibrosis have been reported as risk factors for developing gefitinib-induced DIPT,[63] whereas it remains uncertain whether previous radiotherapy confers an increased risk. In some patients, even an early diagnosis with discontinuation of therapy and treatment with corticosteroids may be ineffective,[65] especially in those patients who have pre-existing pulmonary fibrosis.[58,66]

Erlotinib

Worldwide, the rate of erlotinib-induced lung toxicity is approximately 1%,[67,68] although single-center studies have reported a higher incidence among Japanese patients.[69] In addition, in a retrospective Japanese study, the occurrence of adverse reactions was observed earlier with erlotinib than with gefitinib.[70] The most common pulmonary toxicity from erlotinib is acute or subacute onset of dyspnea with rapid progression to respiratory failure and ARDS.[71] CT findings reveal diffuse, ground-glass opacities; and the classic DAD pattern has been described histologically. In only 1 patient, a pattern similar to bronchiolitis obliterans organizing pneumonia (BOOP) was reported.[71]

The risk factors for developing lung toxicity include age,[72] smoking history, and the concomitant administration of chemotherapy and radiotherapy[73]; however, to date, no conclusive evidence is available. Erlotinib-related toxicity may be increased if it is combined with other agents; in particular, some cases of ILD have been described in association with gemcitabine.[74]

In 1 case report, the occurrence of lung toxicity secondary to erlotinib was observed in patients with pre-existing usual interstitial pneumonia.[75] On the basis of existing data, patients with pre-existing pulmonary fibrosis should not be excluded from receiving erlotinib; however, strict treatment monitoring is recommended for such patients, and an accurate assessment of the lung parenchyma before starting treatment is strongly advised.

Cetuximab

Cetuximab-related lung toxicities include acute HR and ILD. HRs after cetuximab administration are more common than after gefitinib or erlotinib, whereas the occurrence of ILD is less frequent.[76] Overall. the results from phase 2 studies have indicated that adding cetuximab to chemotherapy does not exacerbate the side effects of platinum-based doublets.[77]

A phase 3 trial that compared cisplatine/vinorelbine with or without cetuximab in chemotherapy-naive patients who had advanced EGFR-positive NSCLC revealed grade 4 dyspnea and respiratory failure in 2% of patients in the cetuximab arm versus 1% in the chemotherapy-alone arm without any increase in treatment related-deaths.[78] Grade 4 infusion reactions were observed in $<$ 1% of patients in the cetuximab arm, whereas no HRs were reported in the chemotherapy arm.

In another phase 3 trial that compared the carboplatin/taxane doublet with or without cetuximab in patients with advanced NSCLC, the authors did not report any pulmonary toxicity. Drug-related grade 3 or 4 HRs that led to therapy discontinuation occurred in 4.6% of patients in the cetuximab arm versus 0.6% of patients in the chemotherapy-alone arm.[79]

Occasionally, BOOP has been described in patients who received cetuximab for the treatment of metastatic colorectal cancer.[80]

Antiangiogenic therapies

Bevacizumab

The most common bevacizumab-related DIPTs are hemoptysis and pulmonary hemorrhage.[81,82] The occurrence of these events is associated most frequently with the presence of tumor cavitation and with a diagnosis of squamous cell carcinoma.[83] Pulmonary hemorrhage appears to be associated with the presence of cavitation and with centrally located tumors, although it remains unclear whether histology alone is the main risk factor for bleeding or is a surrogate for other risk factors.[84]

In a phase 2 study, life-threatening or fatal hemoptysis occurred in 4 of 13 patients who had squamous histology versus 2 of 54 patients who had adenocarcinoma, and the overall incidence of fatal pulmonary hemorrhage was 9.1%.[84] This observation led to the exclusion of patients who had squamous cell carcinoma, cavitation, or hemoptysis from receiving bevacizumab in the subsequent phase 3 studies. With these exclusion criteria, in a study that evaluated the addition of bevacizumab to carboplatin and paclitaxel, the incidence of life-threatening pulmonary hemorrhage decreased to 1.9%, and the incidence of fatal hemorrhage was 1.2%.[81]

In another phase 3 trial patients, with advanced, nonsquamous NSCLC were assigned randomly to receive either cisplatin/gemcitabine plus low-dose bevacizumab (7.5 mg/kg), high-dose bevacizumab (15 mg/kg), or placebo.[86] Grade 3 or greater pulmonary hemorrhage was observed in 2 patients in the placebo arm (0.6%), 5

patients in the low-dose bevacizumab arm (1.5%), and 3 patients in the high-dose bevacizumab arm (0.9%). Four of those 10 events occurred in patients who had centrally located tumors.[85]

The incidence of thromboembolic complications reported for bevacizumab differs among studies[84,86]; in the above-mentioned Eastern Cooperative Oncology Group 4599 trial, a risk for thrombosis/embolism of 5% was reported in the bevacizumab arm versus 3% in the control arm, and 1 death secondary to pulmonary embolism was documented in the bevacizumab arm.[81] In the cisplatin and gemcitabine study with either placebo or bevacizumab, no increase in the incidence of arterial or venous thromboembolic events was reported.[85]

The concomitant risk of bleeding and thrombosis can be explained by the endothelial perturbations induced by the inhibition of vascular endothelial growth factor, which causes abnormal apoptosis and loss of integrity of endothelial cells (hemorrhage) and also a decrease in the platelet inhibitors prostaglandin I-2 and nitric oxide (thrombosis).[86] Recently, a retrospective study in colorectal cancer that investigated the prophylactic use of acetylsalycilic acid during treatment with bevacizumab indicated that there was no increase in hemorrhagic risk.[87] Further assessments are needed to prove the efficacy of acetylsalycilic acid in reducing the risk of thrombosis in NSCLC patients treated with bevacizumab.[86]

Sunitinib and sorafenib

The efficacy and safety of multiple vascular endothelial growth factor receptor-tyrosine kinase inhibitors, such as sunitinib and sorafenib, still is under evaluation. In a recent phase 3 study that compared the carboplatin/paclitaxel doublet alone or with sorafenib, no significant difference in the rates of dyspnea, pulmonary embolism, or pulmonary hemorrhage were observed in either arm, whereas only the risk of bleeding was significantly greater in the sorafenib arm.[88]

DISCUSSION

Assessing the true incidence of DIPT is quite challenging because of the complexity of its diagnosis and the limited number of cases reported. A recent study assessed the incidence of severe DIPT in approximately 3% to 5% of patients with lung cancer,[89] but it rates as high as 10% have been reported in studies of combined chemotherapy and radiotherapy.[1]

Table 3. Suggested Risk Factors for Developing Drug-Induced Pulmonary Toxicity

Antineoplastic Agent	Risk Factors
Platinum-based agents	Not reported
Gemcitabine	Pre-existing lung disease; concomitant treatment with paclitaxel, docetaxel, and granulocyte-colony–stimulating factors
Mitomycin-C	Concurrent use of vinca alkaloids (acute pneumonia with bronchospasm); concurrent use of other chemotherapeutic drugs, irradiation, and oxygen supplementation (interstitial pneumonia with pulmonary fibrosis)
Vinka alkaloid	Concurrent treatment with mitomycin-C (acute pneumonia with dyspnea and bronchospasm)
Etoposide	Concurrent treatment with other chemotherapeutic agents and radiotherapy
Paclitaxel	Radiotherapy; concurrent treatment with gemcitabine
Docetaxel	Concurrent chemotherapy; radiotherapy
Pemetrexed	Not reported
Gefitinib	Pre-existing pulmonary fibrosis, history of heavy smoking
Erlotinib	History of smoking, age, pre-existing lung disease, concurrent chemotherapy (gemcitabine), radiotherapy
Cetuximab	Not reported
Bevacizumab	Squamous cell histology, presence of cavitation, recent surgery, centrally located tumor, use of anticoagulant (risk of bleeding)
Sunitinib and sorafenib	Not reported

To add complexity, the incidence of pulmonary complications related to some agents can vary according to ethnicity, particularly for the incidence of diffuse ILD among Japanese patients compared with the rest of the world after treatment with EGFR inhibitors. The reasons for this significantly higher incidence among Japanese patients remain unknown.[90] Suggested risk factors for the development of DIPT related to each agent are reported in Table 3.

The analysis of possible predictive factors for DIPT suggests that vascular lung damage may be detected by increased plasma levels of angiotensin-converting enzyme (ACE). This hypothesis is based on the finding that ACE is localized on the plasma membrane of pulmonary endothelial cells, and, when the membrane is damaged, ACE may be released into circulation. However, experiments on animals that were exposed to pneumotoxic agents (ie, paraquat, bleomycin) revealed inconsistent patterns of serum changes in ACE levels[91]; thus, at the moment, ACE cannot be considered a valid predictive factor of DIPT.

There also are conflicting data about the value of the serial assessment of diffusing lung capacity (DLCO) during chemotherapy: On 1 hand, it offers the opportunity of an early diagnosis and an early withdrawal of the antineoplastic agent; whereas, conversely, it has been noted that a decrease in the DLCO value it rarely correlated to clinically relevant lung disease, and it may improve at the end of the chemotherapy.[92] The relatively small number of studies and these contrasting results do not validate the use of DLCO measurements for predicting DIPT, and further prospective studies are needed to establish their reliability.

Symptoms often are nonspecific, including dry cough, dyspnea, fever, and chest pain. In patients with immunosuppression secondary to chemotherapy, a differential diagnosis should be made with viral, bacterial, and fungal pneumonia and also with cancer progression, radiation-related injury, cardiovascular causes (fluid overload, heart failure), pulmonary embolism, idiopathic interstitial pneumonia, and collagen vascular disease.[93]

The onset of symptoms sometimes is acute (immediately after drug administration) and may help in suspecting DIPT; however, the onset often may be delayed and may be related mainly to the total cumulative dose of the administered agent. This should be taken into account to avoid the risk of underestimating the possibility of DIPT. In most cases, HR and hypersensitivity-like inflammatory interstitial pneumonias have an early onset (days to weeks), whereas interstitial pneumonitis with fibrosis has a late-stage occurrence (months to years).

At the time when a patient is becoming symptomatic, a chest x-ray may be negative (ie, docetaxel); and, in these patients, a thoracic HRCT is highly recommended to make an early diagnosis of DIPT because of its greater sensitivity for detecting parenchymal abnormalities.[94] When diffuse parenchymal lung disease is suspected, the use of clinical criteria and HRCT has a sensitivity of 72% to 77%, whereas its specificity is higher (72%-84%) as a result of the ability to exclude other diseases.[95] In 1 study that compared the efficacy of HRCT versus chest-x-rays in detecting DIPT, abnormal findings were detected in 74% of patients on chest x-rays and in 100% of patients on HRCT scans.[96]

However, because clinical and radiologic criteria are not always sufficient to diagnose DIPT, further investigations are needed to make a differential diagnosis. Blood cultures, sputum analysis, and urinalysis are recommended to exclude infections; echocardiography, blood natriuretic peptide levels, and response to diuretics can assess the cardiac origin of pulmonary edema.[95]

Table 4. Patterns of Drug-Induced Pulmonary Toxicities Reported for Each Antineoplastic Drug

Antineoplastic Agent	Pulmonary Toxicity
Platinum-based agents	Hypersensitivity reactions; not other toxicities reported
Gemcitabine	Dyspnea, rarely associated with bronchospasm (rare in hypersensitivity pneumonitis)
	Acute interstitial pneumonia with DAD (possible ARDS)
	Noncardiogenic pulmonary edema (possible ARDS)
	Alveolar hemorrhage
	Hemolytic-uremic syndrome
	Capillary leak syndrome
Mitomycin-C	Interstitial pneumonia with fibrosis
	Acute pneumonitis with dyspnea and bronchospasm (if concurrent treatment with vinca-alkaloids)
	Hemolytic-uremic syndrome
Vinka alkaloid	Dyspnea and bronchospasm
	Acute interstitial pneumonia
	Noncardiogenic pulmonary edema
Etoposide	Hypersensitivity reaction with bronchospasm
	Acute interstitial pneumonia with diffuse alveolar damage
	Alveolar hemorrhage
Paclitaxel	Acute hypersensitivity reaction with bronchospasm and dyspnea
	Acute interstitial pneumonia
	Hypersensitivity pneumonitis
Docetaxel	Capillary leak syndrome with noncardiogenic pulmonary edema
	Acute hypersensitivity reaction with bronchospasm (rare)
	Chronic interstitial pneumonia
	Acute interstitial pneumonia with possible ARDS
	Hypersensitivity pneumonia with possible ARDS
Pemetrexed	No consistent lung toxicity has been reported
Gefitinib	Interstitial pneumonitis with fibrosis
	Acute interstitial pneumonia with DAD
	Alveolar hemorrhage
Erlotinib	Acute interstitial pneumonia with DAD
	BOOP-like pattern (rare)
Cetuximab	Hypersensitivity reactions
	Interstitial lung disease (rare)
	BOOP-like pattern (rare)
Bevacizumab	Pulmonary hemorrhage
	Hemoptysis
	Thromboembolic events (rare)
Sunitinib and sorafenib	The risk of pulmonary hemorrhage is under evaluation

DAD indicates diffuse alveolar damage; ARDS, acute respiratory distress syndrome; BOOP, bronchiolitis obliterans organizing pneumonia.

In this context, the histologic findings, even if they are not always conclusive, can help the clinician to exclude other pathologic conditions (ie, lymphangitic carcinomatosis, vasculitis, pneumonia) and to support the diagnosis. A definitive diagnosis can be reached with lung biopsy, but this approach is not always possible, because it depends on

Table 5. Diagnostic Procedure in Patients With Suspected Drug-Induced Pulmonary Toxicity

Step 1	**Symptoms:** Must be consistent with those described for DIPT	**Onset:** Temporally plausible with the administration of drug according to the literature	**Evaluation of risk factors** (for possible risk factors, see Table 3)
Symptoms and onset consistent with DIPT are sufficient to proceed to further investigations; the presence of risk factors should increase the suspicion of DIPT			
Step 2	**Radiologic investigation of chest:** Chest x-ray and computed tomography scan (for patterns, see Table 1)	**Histology:** Open lung biopsy (rarely possible); transbronchial biopsy; bronchioalveolar lavage (for patterns, see Table 1)	**Differential diagnosis:** To exclude other etiologies; further examinations should be performed according to the hypothesis (ie, research of infections, echocardiography)
Once other etiologies are excluded and when radiologic and histologic findings are suggestive, the probability of DIPT is very high			
Step 3	Withdrawal of suspected antineoplastic agent	Beginning of therapy (high-dose corticosteroids)	Drug rechallenge is not recommended
Regression of symptoms with the withdrawal of the suspected toxic drug and patient recovery after therapy make the diagnosis of DIPT almost certain; however, cases of progressive DIPT resistant to therapy and with fatal outcome have been reported			

DIPT indicates drug-induced pulmonary toxicity.

the general conditions of the patient and on the invasiveness of the procedure. The clinical utility of fiberoptic bronchoscopy with BAL and transbronchial lung biopsy remains to be determined; however, it is less risky, and it may allow the collection of useful information. In particular, BAL can assess the presence of infections, malignant cells (suggestive of lymphangitic carcinomatosis), and AH.

A single antineoplastic agent can generate different clinical, radiologic, and histologic patterns of DIPT, as reported on Table 4, and ILD represents the most frequent complication (70%).[90] Once other etiologies are excluded, and when radiologic and histologic findings are suggestive, the probability of DIPT is very high. The identification of the drug that caused the toxicity is sometimes complicated by the coadministration of multiple agents, sometimes concomitant with radiotherapy; thus, it can be hard to detect the specific agent that is responsible for DIPT. Moreover, in some patients, the association of 2 drugs enhances the pulmonary toxicity of the single agent (ie, paclitaxel, vinca alkaloids).

Readministration of the suspected drug with recurrence of symptoms may be the only potential approach to establish a diagnosis, but it is not recommended, because it can induce severe DIPT. In these patients, the recommendation is to withhold all antineoplastic drugs that have the potential for lung toxicity.

There are no recommended guidelines for the treatment of DIPT, and the usual approach consists of withdrawal of the suspected drug and the prompt administration of high-dose of corticosteroids. For less severe cases of pneumonitis, the administration of methylprednisolone 60 mg every 6 hours has been proposed; however, if severe respiratory failure occurs, then methylprednisolone 1 g daily commonly is given for 3 days with gradual dose reduction.[97,98] In patients with HR who have hypoxia, hypotension, and circulatory collapse, mechanical ventilation, bronchodilators, epinephrine, vasopressors, and intravenous fluid administration are indicated.[3,6] The response to corticosteroids is the key to confirming the suspected diagnosis of DIPT, although even this treatment sometimes is not sufficient to avoid progressive pulmonary impairment or death (ie, mitomycin, docetaxel).

In conclusion, there is no single diagnostic procedure that can result in a clear diagnosis of DIPT. A relatively high level of clinical suspicion may be obtained when all results from clinical assessment and instrumental diagnostic procedures are globally considered, because DIPT is a diagnosis of exclusion. To help clinicians with this challenge, we propose a "step-by-step" diagnostic procedure (Table 5). Scientifically recognized databases of DIPT already are available on the web (ie, www.pneumotox.fr accessed September 2010) and represent a useful diagnostic tool for the clinician, especially if online updates are pursued consistently.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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