

# Chemotherapy-induced pulmonary toxicity in lung cancer management

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Chemotherapy is the cornerstone of therapy in many stages of lung cancer. Many diagnostic options have to be taken into account when a patient suffering from lung cancer presents with nonspecific, respiratory, clinical manifestations. A multidisciplinary diagnostic approach is then warranted. The top priority is to rule out those life-threatening causes, such as lung infection, that could be properly treated if a right diagnosis is early. To reach a definite diagnosis frequently requires that one or more diagnostic, pneumologic techniques are performed. Regarding to drug-induced pulmonary disease, prevention is mandatory. In this review we have tried to highlight the risk and characteristics of cytostatic-induced pulmonary toxicity caused by those agents that have been commonly employed to treat lung cancer for the last decades. When treating lung cancer patients, a high clinical suspicion of chemotherapy-induced lung toxicity should be kept in mind since an early withdrawal of the offending drug is the most efficacious therapy.

Key words: Lung cancer, chemotherapy, lung toxicity.

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## INTRODUCTION

Oncologists have often to face a broad differential diagnosis when lung cancer patients under cytos-

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Toxicidad pulmonar inducida por citostáticos en el tratamiento del cáncer de pulmón

La quimioterapia es la opción terapéutica más eficaz en diversos estadios del cáncer de pulmón. El clínico se enfrenta ante un amplio abanico de posibilidades diagnósticas cuando un paciente afecto de cáncer de pulmón presenta manifestaciones clínicas respiratorias inespecíficas. En tal circunstancia es obligada una aproximación diagnóstica multidisciplinaria. La prioridad fundamental es la exclusión de aquellas etiologías susceptibles de un tratamiento eficaz y que representen una amenaza vital para el paciente como es el caso de la infección pulmonar. La confirmación de un diagnóstico etiológico definido va a requerir frecuentemente la adopción de uno o varios procedimientos diagnósticos mediante la práctica de determinadas técnicas neumológicas específicas que deben ser individualizadas en cada caso. En relación a la toxicidad pulmonar inducida por medicamentos, es prioritaria una actitud preventiva. En esta revisión se subrayan los aspectos fundamentales de la toxicidad pulmonar causada por aquellos citostáticos que se han venido utilizando durante las últimas décadas en el tratamiento del cáncer de pulmón. Dado que la retirada precoz del agente causante es la medida terapéutica más eficaz, el oncólogo debe ~~mantener siempre un alto índice de sospecha~~ para la detección de una posible toxi-

tatic treatment present with nonspecific respiratory symptoms and radiographic shadowing<sup>1-3</sup>. Because of their own prognostic and therapeutic implications the following etiologies have to be firstly considered in the initial diagnostic approach: lung infection, either by conventional pathogens or atypical microorganisms, malignancy-related thromboembolic pulmonary disease, local tumor progression, iatrogenic intra-alveolar hemorrhage, radiotherapy-induced adverse effects, transfusion reactions, postoperative complications

in those patients that have undergone thoracic surgery, oxygen toxicity, and eventually drug-induced pulmonary toxicity. In that last case, most patients are also receiving many drugs, other than cytostatics, that sometimes may cause lung toxicity<sup>4</sup>.

For most clinicians the diagnosis and treatment of pneumonia in a non-immunocompetent patient is often the top priority from a practical point of view. However, it is worthwhile to be aware of other entities that may overlap the clinical presentation of pulmonary infection, as it has been recently emphasized<sup>5</sup> (table 1).

Usually, a multidisciplinary approach is warranted to try to elucidate the cause of new clinical pulmonary findings in lung cancer patients that are treated with chemotherapy, especially when a multimodality therapeutic program is going on. An algorithmic approach to evaluation of pulmonary infiltrates and nonspecific respiratory symptoms and signs in lung cancer patients on chemotherapy is schematically shown in figure 1. The increasing use of combined chemotherapy and concurrent or alternating radiotherapy makes it even more dif-

ficult for clinicians a right diagnostic approach in these circumstances. The progressive trend of lung cancer to be diagnosed in people aged > 70 years has raised the subject of an alleged increase of drug toxicity in that population<sup>6</sup>. Probably, the multiple underlying diseases which are often present in many elderly patients may afford a better explanation for this finding that age per se. Sometimes physicians have to confront with the dilemma of slowly resolving pulmonary infiltrates in lung cancer patients receiving antibiotics for a confirmed diagnosis of pneumonia. Clinicians have to keep in mind that a slower than usual radiologic resolution of pneumonia may be found in the elderly, in those cases of severe pneumonia with extensive pulmonary shadowing, and with some etiologies such as Legionella<sup>5,7</sup>. The aim of this article is to review the subject of chemotherapy-induced lung toxicity with a more specific emphasis in those cytostatics that have recently been more commonly used in the therapeutic approach of lung cancer (table 2). Since a variety of mechanisms have been postulated in chemotherapy-induced-pulmonary toxicity but the actual pathogenesis remains speculative<sup>8</sup>, we have focused only in clinically relevant data of the subject. The role of biological response modifiers, hormonal agents, and other non-cytostatic agents in causing adverse respiratory effects is then beyond the scope of this review. Related topics as the radiation sensitizer action of different cytostatics, the interactions of radiotherapy with antineoplastic agents in producing lung damage, and the perioperative considerations of thoracic surgery following chemotherapy have been addressed in other in-depth reviews<sup>9-11</sup>.

#### GENERAL CONSIDERATIONS

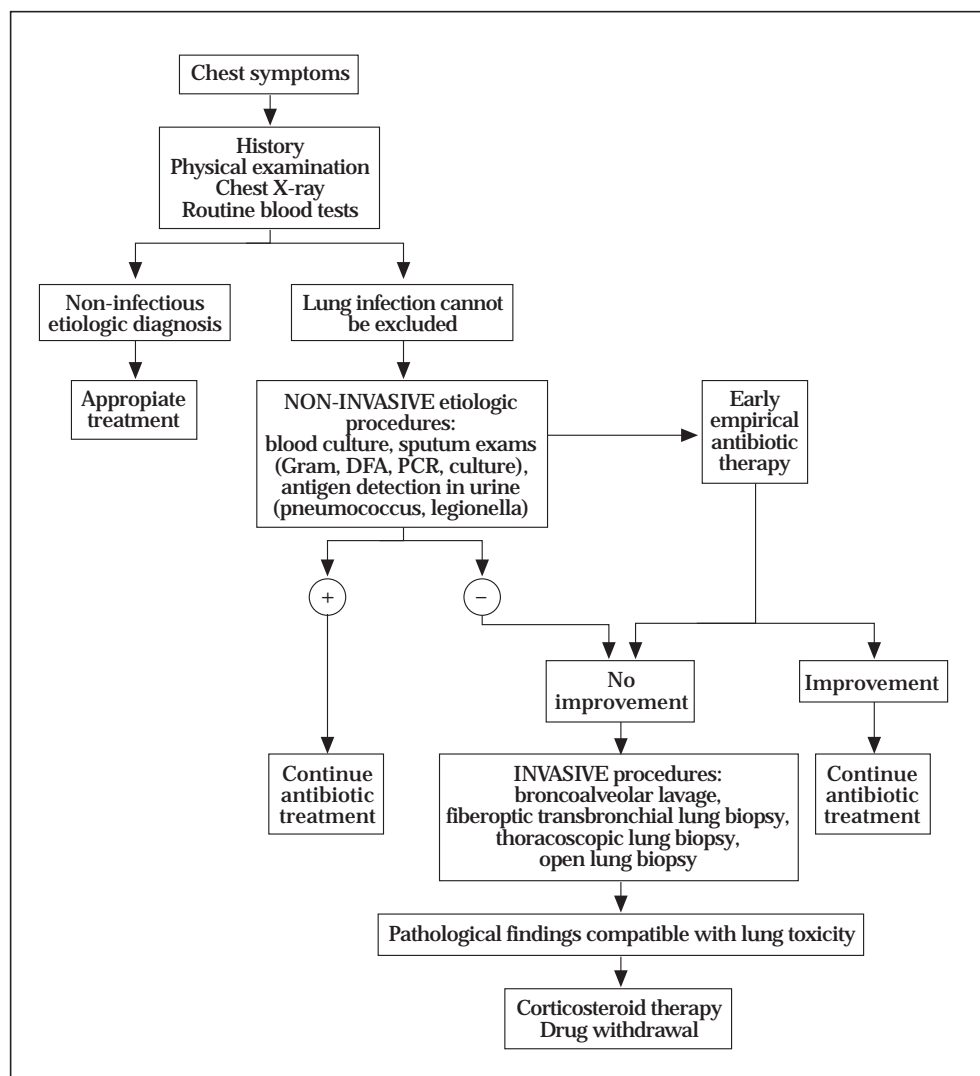
##### Clinical features

Although a certain clinical or radiographic presentation may occasionally be suggestive of pulmonary toxicity caused by a determined cytostatic, it can be in general stated that clinical and radiologic findings are usually not distinctive for any particular chemotherapeutic agent<sup>1-4,8</sup>. Since clinical and radiographic manifestations are protean, it must be emphasized that a high index of clinical suspicion is needed to establish a right diagnosis and institute an appropriate therapy. Affected patients may present with dyspnea, cough, malaise, and sometimes fever. The onset of clinical symptoms is often progressive but a subacute or even abrupt clinical presentation is also possible. In those cases of insidious, progressive pulmonary injury, a relationship between dose and duration of chemotherapy and the onset of lung

TABLE 1. Noninfectious pulmonary diseases mimicking pneumonia

Acute an chronic eosinophilic pneumonia
Acute inhalation pulmonary injury
Acute chest syndrome associated with adult sickle cell disease
Allergic bronchopulmonary aspergillosis
Alveolar proteinosis
Blood transfusions reactions
Bronchiolitis obliterans organizing pneumonia (BOOP)
Bronchioloalveolar-cell carcinoma
Diffuse alveolar hemorrhage syndromes
Drug-induced or toxic pneumonitis
Exogenous lipid pneumonia
Inflammatory abdominal diseases
Inflammatory pseudotumor (plasma-cell granuloma)
Hypersensitivity pneumonia (extrinsic allergic alveolitis)
Kaposi's sarcoma
Lobar atelectasis
Malignant haemopathies: leukemia, lymphomas, fungoides mycosis
Noninfectious causes of adult respiratory distress syndrome (ARDS)
Oxygen toxicity
Postcardiac injury syndromes
Postpartum antiphospholipid antibodies syndrome
Pulmonary torsion
Pulmonary vasculitis (Wegener's granulomatosis, Churg-Strauss syndrome, others)
Radiotherapy-induced pneumonitis
Systemic lupus erythematosus
Sarcoidosis
Thromboembolic pulmonary disease: lung infarcts, Dressler syndrome

From Roig J, et al. Arch Bronconeumol 1998<sup>5</sup>.



**Fig. 1. Lung cancer: algorithmic approach to differential diagnosis of new pulmonary infiltrates after following chemotherapy.**

toxicity is not always clear. Those chemotherapeutic agents that have been associated with acute pneumonitis, adult respiratory distress syndrome (ARDS), progressive pulmonary fibrosis, pleural disease, and an hypersensitivity reaction that may cause respiratory symptoms, are shown, respectively, in tables 3, 4, 5, 6 and 7.

The terminology used in many chemotherapy-induced lung toxicity case reports may be sometimes confusing. Some authors prefer to emphasize the pathological findings, other the clinical picture in a general way, and others chose very specific patophysiological terms such as non-cardiogenic pulmonary edema, acute respiratory failure or acute respiratory distress syndrome (ARDS). In order to clarify these concepts for those readers that are not skilled in pulmonary disease it is worthwhile to remember that neither non-cardiogenic pulmonary edema nor acute respiratory failure are equivalent to ARDS since the diagnosis of this

**TABLE 2. Lung cancer: chemotherapeutic agents associated with pulmonary toxicity**

<b>Alkylating agents</b>
Cyclophosphamide
Nitrosureas
Ifosfamide
Procarbazine
<b>Antimetabolites</b>
Methotrexate
Gemcitabine
<b>Cytotoxic antibiotics</b>
Mitomycin
Doxorubicin*
<b>Antimicrotubule agents</b>
Vinca alkaloids
Paclitaxel
Docetaxel
<b>Miscellaneous</b>
Topotecan
Irinotecan
Etoposide
Teniposide

\* Lung edema secondary to congestive heart failure.

**TABLE 3. Lung cancer: chemotherapeutic agents associated with acute pneumonitis**

Cyclophosphamide
Docetaxel
Etoposide
Gemcitabine
Ifosfamide
Ipomeanol
Irinotecan
Methotrexate
Mitomycin
Paclitaxel
Procarbazine
Vinca alkaloids

last entity requires other additional criteria to be established. The microscopic diagnosis of diffuse alveolar damage usually corresponds to the early histopathological expression of any ARDS, whatever its cause is.

**Imaging techniques**

Many different types of radiographic abnormalities have been reported<sup>12</sup>. In general, the chest radiograph findings lag behind the onset of clinical symptoms. Chest CT scan may help to define the extent and characteristics of the opacities<sup>13</sup>. High-resolution CT scan may occasionally detect subtle parenchymal abnormalities when the chest radiograph is still normal. On the basis of the differences found in magnetic resonance characteristics, a possible role for magnetic resonance spectrometry could be suggested but further studies are clearly warranted to support this concept<sup>14</sup>. The clinical utility of nuclear scintigraphy to both improve sensitivity and to try to correlate the extent of disease with the inflammatory activity is well established<sup>15</sup>. However, gallium scans, as any imaging technique, have inherent limitations in specificity. We think that, when considering a diagnosis of pulmonary drug toxicity, the most important role of any radiologic technique is to detect a new abnormality, whatever it is, either in clinically symptomatic patients or as a radiologic finding in a subclinical phase.

**Pulmonary function tests**

An early diagnosis of lung toxicity, even before radiographic shadowing appears, may also be suggested

**TABLE 4. Lung cancer: chemotherapeutic agents associated with ADRS**

Gemcitabine
Methotrexate
Mitomycin
Paclitaxel
Vinca alkaloids + mitomycin

**TABLE 5. Lung cancer: chemotherapeutic agents associated with progressive pulmonary fibrosis**

Cyclophosphamide
Etoposide
Methotrexate
Mitomycin
Nitrosureas

if pulmonary function testing shows an unexplained decrease in carbon monoxide diffusing capacity (DLCO) in patients that complain about dyspnea of unknown cause<sup>16</sup>. In contrast to the decreased DLCO usually found in the more common pattern of interstitial lung involvement, an increased DLCO may be sometimes noticed in those rare cases of diffuse alveolar hemorrhage<sup>17</sup>. In severe cases, hypoxemia and an increased alveolar-arterial (A-a) gradient are usually observed. Pulmonary function testing also may help to evaluate the degree of restrictive ventilatory alteration that is often found and to monitorize the functional outcome in a non-invasive way.

**Other techniques**

Fiberoptic bronchoscopy with bronchoalveolar lavage may be helpful in ruling out an infectious etiology and in supporting the diagnosis of chemotherapy-induced pneumonitis<sup>18</sup>. A nonspecific lymphocytic predominance with imbalance of the CD4/CD8 ratio is often observed in certain drug-induced pneumonitis but it should be kept in mind that the clinical usefulness of this finding in diagnosing drug toxicity is clearly limited. In certain cytostatic-induced pulmonary toxicities, such as cyclophosphamide or busulfan, characteristic bizarre pneumocytes in sputum or lavage fluid can be identified. The clinical relevance of a few preliminary studies that suggested the usefulness of determining serum markers for cytostatic-induced lung toxicity has not been confirmed so far<sup>19,20</sup>.

**Pathology**

Some attempts have been made to try to correlate

**TABLE 6. Lung cancer: chemotherapeutic agents associated with pleural disease**

Cyclophosphamide
Docetaxel*
Doxorubicin**
Methotrexate
Mitomycin
Procarbazine
Vinblastine + mitomycin

\*Trasudative pleural effusion caused by fluid retention syndrome;  
 \*\*Trasudative pleural effusion caused by congestive heart failure.

**TABLE 7. Lung cancer: chemotherapeutic agents associated with an hypersensitivity reaction that may cause respiratory symptoms**

Docetaxel
Etoposide
Gemcitabine
Ifosfamide + mesna
Irinotecan
Methotrexate
Mitomycin
Paclitaxel
Procarbazine
Topotecan
Vinca alkaloids

te radiographic findings with the underlying histopathologic process<sup>12</sup>. In those cases of chemotherapy-induced lung toxicity in which a biopsy procedure has been performed, many pathologic patterns, most of them showing a variable degree of an inflammatory component, have been reported<sup>21</sup>. A variety of interstitial pneumonias, usually chronic or nonspecific interstitial pneumonia, and many other histologic patterns have been observed (table 8). In cases with a protracted course, different degrees of non-reversible interstitial or alveolar duct fibrosis are found after acute abnormalities have evolved to a late proliferative phase.

**Diagnosis**

In summary, the diagnosis of lung toxicity caused by cytostatics in lung cancer patients should be based on clinical history, especially from a chronological point of view, nonspecific clinic findings, and the reasonable exclusion of infection and other less common causes of infiltrative lung disease, either patchy or diffuse. As stated before, a multidisciplinary diagnostic approach is mandatory, and the possible need of invasive techniques, such as bronchoalveolar lavage, transbronchial, thoracoscopic or open pulmonary

**TABLE 8. Lung cancer: tissue reactions in chemotherapy-induced pulmonary toxicity**

Chronic interstitial pneumonia
Diffuse alveolar damage
Bronchiolitis obliterans organizing pneumonia (BOOP)
Obliterative bronchiolitis
Hypersensitivity pneumonia*
Lung fibrosis
Pulmonary edema
Pulmonary hemorrhage
Pulmonary hypertension
Pulmonary veno-occlusive disease

\* Presence of poorly formed granulomas in methotrexate-induced lung toxicity.

biopsy, has to be considered in some cases in an individualized way.

**TREATMENT**

More benign, early detected cases may resolve after cessation of the incriminated cytostatic agent<sup>1-4</sup>. Therefore, the most appropriate treatment for many cases of cytostatic-induced lung toxicity is withdrawal of the offending drug. In the usually more severe case a short course of corticosteroid therapy is warranted. However, the outcome is variable depending on the offending agent and the degree of established lung damage. After an improvement of symptoms is observed, tapering of the dosage has to be instituted on an individualized basis. Lung transplantation has exceptionally been considered in very selected cases for patients cured of a malignancy who had developed chemotherapy-induced fibrosis<sup>22,23</sup>.

**ALKYLATING AGENTS**

Table 9 shows a summary of pulmonary toxicity caused by alkylating agents.

**Cyclophosphamide**

Two patterns of cyclophosphamide-induced pulmonary toxicity have been clearly identified<sup>24</sup>. Early-onset acute pneumonitis is reversible and responds to discontinuation of the drug or, in more severe cases, to corticosteroid therapy. Clinical features of late-onset pneumonitis are those of progressive pulmonary fibrosis with associated pleural thickening on chest radiograph. These patients do not respond neither to cessation of cyclophosphamide nor to institution of corticosteroid therapy. The incidence of pulmonary injury associated with this cytotoxic agent is not exactly determined but it is thought to be lower than 1%.

A syndrome of water retention with marked hypervolemia and hyponatremia may be induced by high-dose intravenous cyclophosphamide therapy<sup>25</sup>. Secondary pleuropulmonary findings may then rarely be observed, especially in older patients that receive a fluid overload to prevent hemorrhagic cystitis. In an experimental study cyclophosphamide-induced lung toxicity was shown to be potentiated by hyperoxia<sup>26</sup>. Radiation therapy and cyclophosphamide seem to be a particularly toxic combination for the lung.

**Nitrosureas**



TABLE 9. Lung cancer: alkylating agent-induced lung toxicity

Agent	Clinical presentation	Respiratory features	Incidence	Outcome
Cyclophosphamide	Acute Chronic	AP CPF	< 1%	AP: usually recovery CPF: high mortality rate even after corticosteroid treatment
Nitrosurea	Rarely acute Usually chronic, dose-related (total dose > 1,000 mg/m <sup>2</sup> )	AP CPF	< 20%-30% with dose > 1,000 mg/m <sup>2</sup> Increased risk with concomitant COPD	Mortality may be high if diagnosis is delayed
Procarbazine	Acute	HR Rarely AP or pleuritis Very rarely involvement of respiratory muscles in cases of peripheral neuropathy	Very rare	Usually recovery
Ifosfamide	Acute	HR (mesna related) Acute encephalopathy respiratory depression* Rarely AP	CNS depression in < 12%	Usually recovery

\* Special concern in advanced COPD and SAS; AP: acute pneumonitis; CPF: chronic pulmonary fibrosis; HR: hypersensitivity reaction; COPD: chronic obstructive pulmonary disease; SAS: sleep apnea syndrome; CNS: central nervous system.

Bischloroethylnitrosourea (BCNU) and cyclohexylchloroethylnitrosourea (CCNU) have been infrequently used in a few combination chemotherapy regimens for small-cell lung cancer. Pulmonary toxicity, resulting in alveolitis and fibrosis, has been reported after BCNU and CCNU therapy, usually in cumulative doses greater than 1,000 mg/m<sup>2</sup><sup>27-29</sup>. Interestingly, preexisting lung disease and abnormal pulmonary function tests, two relatively common findings in lung cancer, have been identified as risk factors for the development of BCNU-induced lung toxicity in a malignant glioma series<sup>28</sup>. In that subset of population a 20%-30% incidence of lung toxicity has been reported<sup>27-29</sup>. Although toxicity is usually dose-related, an acute form of pneumonitis can occur at either end of the dose schedule<sup>30</sup>.

However, most cases present with the clinical features of an insidious chronic pulmonary fibrosis. Enhanced oxygen toxicity has been reported after BCNU therapy<sup>31</sup>.

#### Ifosfamide

Hypersensitivity reactions, that may imply respiratory manifestations, are possible when ifosfamide is administered, as usual, in conjunction with mesna. The risk of CNS depression following ifosfamide therapy (about 12%)<sup>32</sup> has to be taken in consideration in those patients that suffer from advanced chronic obstructive lung disease, a common association in lung cancer, since

somnolence may worsen hypercapnia and enhance encephalopathy. A word of caution is also needed in the case of underlying central or obstructive sleep apnea syndrome, since the prevalence of the last one in general population is relatively high. Direct pulmonary toxicity is very rare but possible<sup>33</sup>.

#### Procarbazine

This nonclassic alkylating agent, sometimes used in small-cell lung carcinoma, may cause rarely an hypersensitivity reaction including lung infiltrates that may force discontinuation of the drug<sup>34-36</sup>. Pleural effusion has been occasionally reported<sup>37</sup>. Since procarbazine is used primarily in combination therapy, most reported cases of hypersensitivity have occurred in patients receiving other cytotoxic drugs. Procarbazine is one of the drugs that occasionally may cause neuropathies that could impair respiratory muscle function<sup>38</sup>.

#### PLATIN COMPOUNDS

Platin-based regimens have been the goldstandard of combined chemotherapy for the last decade. The lack of any direct pulmonary toxicity is a characteristic of both cisplatin and carboplatin therapies. Two cases of noncardiogenic pulmonary edema associated with hemolytic uremic syndrome had been allegedly attributed to cisplatin in a 1991 report<sup>39</sup>. In our opinion, the absence of new references so far and the fact that

TABLE 10. Lung cancer: antimetabolite agent-induced lung toxicity

Agent	Clinical presentation	Respiratory features	Incidence	Outcome
Methotrexate	Usually subacute, but hypersensitivity acute and pneumonitis chronic also possible	Usually acute  ARF and chronic fibrosis also possible Rarely acute encephalopathy* with respiratory depression (associated with high-dose therapy)	2%-8%	Complete recovery after corticosteroid therapy in early diagnosed cases
Gemcitabine	Acute	BHR HR AP Rarely ARDS, PVOD	< 1%	Usually complete recovery except in ARDS

\* Special concern in advanced COPD and SAS; ARF: acute respiratory failure; BHR: bronchial hyperreactivity; HR: hypersensitivity reaction; AP: acute pneumonitis; ARDS: adult respiratory distress syndrome; PVOD: pulmonary veno-occlusive disease.

both patients suffered from acute cisplatin nephropathy and that the noncardiogenic edema seemed to be triggered by a red blood cell transfusion make this association very doubtful. Adverse lung effects have not been reported so far with the new orally available platinum-containing anticancer drugs.

ANTIMETABOLITES

Table 10 shows a summary of pulmonary toxicity caused by antimetabolites.

Methotretxate

The role of this folate antagonist as a therapeutic agent seems to be nowadays more in the field of autoimmune disease than in that of lung cancer<sup>40</sup>. Although a subacute clinical presentation is most common, acute and chronic forms also occur. Pulmonary toxicity may be diagnosed as early as a few days and as late as many years of treatment<sup>41</sup>. The incidence of pulmonary toxicity has been a matter of controversy but present studies estimate a rate of 2% to 8%. Difficulties found in comparing the incidence and characteristics of methotrexate-induced lung toxicity among series promoted the scoring system published by Searles et al in 1987<sup>42</sup>. In a large study on methotrexate induced lung injury following treatment for rheumatoid arthritis a few risk factors were identified: age greater than 60 years, hypoalbuminemia, diabetes mellitus, and rheumatoid pleuro-pulmonary involvement<sup>43</sup>. The most frequent pulmonary manifestation is hypersensitivity pneumonitis, with peripheral blood eosinophilia that may be observed in up to 40%-50% of patients. Lymphocytic predominance with an increase in CD4+ T cells and CD4/CD8 ratio in bronchoalveolar lavage fluid, and a characteristic pathologic pattern of poorly defined granulomatous infil-

tration with interstitial mononuclear infiltrates have also been consistently reported<sup>44</sup>. A fulminant presentation of respiratory failure has been well described, even after intrathecal administration in non-pulmonary malignancies. The unusual radiographic finding of hilar adenopathy has been very occasionally reported. Acute chest pain caused by pleuritis without parenchymal involvement may rarely occur<sup>45</sup>. While the drug has been used to control severe corticosteroid-dependent bronchial asthma, methotrexate-induced bronchial hyperreactivity has been paradoxically reported. A reversible pulmonary non-Hodgkin's B-cell lymphoma may appear in patients under methotrexate therapy. Characteristically, it may regress after cessation of the drug. An interesting association with Epstein-Barr virus infection has been reported<sup>46</sup>. Acute encephalopathy that may present with confusion and even coma has been reported with high-dose therapy. Respiratory implications in severe COPD, in a manner similar to ifosfamide, must be remembered by clinicians. Piritrexim, a methotrexate analog that has been occasionally used in upper respiratory tract tumors, which are commonly associated with lung cancer, may also cause pulmonary toxicity<sup>47</sup>.

Fluoruracil

The use of fluorinated pyrimidines in lung cancer has been mostly restricted to Japanese studies. To the best of our knowledge, significant pulmonary toxicity has not been reported so far. Fluoruracil administration could enhance the risk of mitomycin-induced thrombotic microangiopathy with acute respiratory distress syndrome<sup>8</sup>.

Gemcitabine

This pyrimidine analog shows a good activity against

TABLE 11. Lung cancer: antibiotic agent-induced lung toxicity

Agent	Clinical presentation	Respiratory features	Incidence	Outcome
Mitomycine	Acute Chronic, dose-related (total dose > 30 mg/m <sup>2</sup> )	AP Rarely ARF Very rarely thrombotic microangiopathy with ARDS	3%-12%	Fatality rate of 40% even after corticosteroid treatment  Increased risk of ARDS if oombined therapy with vinca alkaloids Increased risk of microangiopathy if associated with fluoruracil (highest mortality)
Doxorubicine	Late, dose-related (total dose > 500 mg/m <sup>2</sup> )	CHF	< 10%	Poor outcome if severe CHF is already present at diagnosis

ARF: acute respiratory failure; BHR: bronchial hyperreactivity; HR: hypersensitivity reaction; AP: acute pneumonitis; ARDS: adult respiratory distress syndrome; CHF: congestive heart failure.

a wide range of solid tumors, including lung cancer. Consequently, it has become one of the most widely used cytostatics in the therapeutic approach of lung tumors. One benign respiratory side effect of gemcitabine is dyspnea, which may start within a few hours of administration of the drug and is thought to be related to bronchospasm<sup>48-52</sup>. A potentially more serious event is the appearance of parenchymal infiltrates that sometimes may be associated with acute respiratory distress syndrome<sup>53-56</sup>. A few fatalities attributed to diffuse alveolar damage and ARDS have been reported. Since that drug shows an structure and metabolism quite similar to cytosine arabinoside (ara-C) a capillary leak phenomena has also been allegedly incriminated in gemcitabine-induced pulmonary toxicity. Rare instances of pulmonary veno-occlusive disease and hemolytic uremic syndrome have been reported<sup>57,58</sup>. A recent German study reported a worrying 7.1% percentage of unexplained non-cardiogenic pulmonary distress «most likely related to gemcitabine» in a series of 56 patients<sup>56</sup>. A more extensive retrospective study based on 4,448 trial patients shows a 0.45% incidence of serious pulmonary toxicity<sup>50</sup>. Although high dose steroid pretreatment has allowed succesful rechallenge with gemcitabine after initial severe pulmonary toxicity in a few instances, this approach does not seem to be prudent since a potential risk of repeated toxicity with reexposure can not be definitely avoided. Although many pulmonary toxicities caused by gemcitabine are mild, oncologists must be aware of possible life-threatening cases in order to administer corticosteroid therapy in a timely fashion<sup>59</sup>. Concern about an increased risk of severe pulmonary toxicity in patients treated with a combination of gemcitabine and docetaxel has been reported<sup>60,61</sup>.

ANTIBIOTICS

Table 11 shows a summary of pulmonary toxicity caused by antibiotics.

Mitomycin

Although mitomycin-induced pulmonary toxicity is unpredictable the reported global range of significant pulmonary reactions from mitomycin is 3%-12% and more likely to occur at higher dosages<sup>62-68</sup>. Mitomycin lung toxicity can not be prevented with corticosteroid pre-medication. An acute or subacute pneumonitis, sometimes with bronchospasm and acute respiratory failure, and also a more chronic, progressive form, have both been described. Chronic pneumonitis seems to be related to the total dose of the drug administered and it is very uncommon when the cumulative dose is less than 30 mg/m<sup>2</sup>. Most cases of mitomycin-induced lung damage occur when a vinca alkaloid is administered concomitantly<sup>8</sup>. In that population life-threatening reactions, such as severe noncardiogenic edema and adult respiratory distress syndrome with diffuse alveolar damage, have been reported<sup>63,64,66</sup>. When mitomycin is administered as part of a combination neoadjuvant chemotherapy, lung toxicity may be enhanced by high concentrations of oxygen during surgery<sup>69,70</sup>. It has been suggested that the administered oxygen concentration should not exceed a FiO<sub>2</sub> of 0.5. Pleural involvement is an uncommon radiographic finding. Type I and type II cells atypia is also possible, a cytological finding similar to those that may be observed after busulfan or cyclophosphamide therapy. Once pulmonary toxicity has been diagnosed withdrawal of the drug and the institution of corticosteroid therapy may not avoid a progressive respiratory failure in up to 40% of cases. Pulmonary toxicity has also been reported with the new mitomycin analogs, such as KW-2149<sup>71</sup>.



TABLE 12. Lung cancer: antimicrotubule agent-induced lung toxicity

Agent	Clinical presentation	Respiratory features	Incidence	Outcome
Vinca alkaloids	Acute	HR AP	Dyspnea in < 5% of patients receiving vinorelbine	Usually recovery. Rarely ARDS with high mortality if associated with mitomycin
Paclitaxel	Acute	HR AP	HR < 1% with pretreatment AP rare if dosage < 350 mg/m <sup>2</sup>	Usually recovery with mandatory pretreatment Risk of ARDS if high dose therapy or concomitant radiotherapy
Docetaxel	Acute or chronic	AP Fluid retention syndrome	AP very rare Increased risk of water retention if dose > 400 mg/m <sup>2</sup>	Usually complete recovery

HR: hypersensitivity reaction; AP: acute pneumonitis.

The most severe form of pulmonary reaction from mitomycin is a thrombotic microangiopathy with renal failure, hemolytic anemia, and noncardiogenic pulmonary edema<sup>72</sup>. This entity overlaps the «hemolytic uremic syndrome» and causes an adult respiratory distress syndrome in approximately 50% of cases.

Blood transfusions and 5-fluorouracil have been allegedly incriminated in the appearance of this distinctive syndrome<sup>8</sup>. The syndrome is unusual, especially if a low cumulative dose is administered, but the prognosis is poor since the overall case-fatality rate is about 70%<sup>8</sup>.

Doxorubicin. Daunorubicin. Epirubicin

Abnormal pulmonary findings in patients receiving anthracycline antibiotics are usually secondary to primary cardiac toxicity<sup>1-4</sup>, which has been reported in up to 10% of patients and seems to be related to cumulative dose. The risk of congestive heart failure seems to remain low until a total dose of 450 to 550 mg/m<sup>2</sup> has been reached. However, severe congestive myocardiopathy is possible even after a single dose and it has been suggested that the risk of congestive heart failure begins to increase at total doses of doxorubicin above 350 mg/m<sup>2</sup> or 700 mg/m<sup>2</sup> of daunorubicin<sup>73</sup>. Doxorubicin may rarely produce pleural disease.

#### VINCA ALKALOIDS

Table 12 shows a summary of pulmonary toxicity caused by antimicrotubule agents, including vinca alkaloids and taxanes.

When used alone, the vinca alkaloids are very rare causes of direct lung toxicity<sup>74,75</sup>. Most reported cases are associated with combined mitomycin chemotherapy or radiotherapy<sup>63,64,66</sup>. Acute pulmonary edema after intravenous vinblastine

infusion has been noted<sup>76</sup>. Dyspnea of unclear etiology has been observed following administration of vindesine used in combination with mitomycin-C<sup>77</sup>. Vincristine is one of the drugs that can impair respiratory muscle function<sup>38</sup>. Although sensory neuropathies are usually the most common manifestation, motor or sensorimotor neuropathies may also occur. Involvement of respiratory muscles is rare but possible.

#### Vinorelbine

Vinorelbine is now probably the most widely used vinca alkaloid in the treatment of lung cancer<sup>74</sup>. Dyspnea has been reported to occur in up to 5% of patients. An acute bronchospasm, similar to an hypersensitivity reaction, or an subacute clinical presentation with dyspnea and cough have both been observed. The last one usually occurs within one hour after treatment and the chest radiograph occasionally may show a patchy interstitial shadowing<sup>75</sup>.

#### TAXANES

##### Paclitaxel

Paclitaxel has emerged as one of the most efficacious cytostatics in the therapeutic approach of lung cancer. Before premedication with corticosteroids up to 30% of patients in early trials suffered from dyspnea caused by bronchospasm and other symptoms, such as rash and hypotension, secondary to anaphylaxis<sup>78-80</sup>. The mechanism seems to be a direct injury to basophils that causes an immediate histamine release. The routine administration of antihistaminics, corticosteroids, and H<sub>2</sub> blockers, before paclitaxel intravenous infusion, has decreased the incidence of that hypersensitivity to about 1%. Interestingly, parenteral desensitization to paclitaxel has been reported with successful

results.

A different type of pulmonary damage is that derived from direct pulmonary toxicity, which seems to be dose-related<sup>81-86</sup>. With doses less than 350 mg/m<sup>2</sup> lung

toxicity seems to be extremely rare. Transient pulmonary infiltrates have been occasionally reported. More serious pulmonary toxicities have been observed with

high dose paclitaxel therapy, particularly when combined with other cytostatics in the setting of patients that undergo bone marrow transplantation.

The use of concurrent lung irradiation and paclitaxel therapy deserves a few comments<sup>87-93</sup>. Compared to other radiosensitizer cytostatics, a higher than usual enhancement of radiation-induced lung damage has been reported. At least in one study, this combination modality therapy was associated, to some extent, with an increased risk of postoperative complications in stage III lung cancer patients<sup>94</sup>.

However, differences in drug combinations and radiation doses among studies suggest that larger, prospective studies are warranted before any definite conclusion is reached. A recall pneumonitis may be very uncommonly observed in patients previously treated with radiotherapy.

#### Docetaxel

A very unusual acute diffuse interstitial pneumopathy has been described<sup>95</sup>. As stated before, a few cases of lung toxicity caused by combined therapy with docetaxel and gemcitabine have been reported<sup>60,61</sup>. Hypersensitivity mechanisms are thought to be incriminated since recovery is rapid after steroid therapy.

The appearance of a pleural effusion, often moderate, in patients that are being treated with docetaxel, should not be misdiagnosed as a pleuropulmonary side-effect of the drug. A fluid retention syndrome, sometimes causing weight gain as well as pleural effusion and ascitis, is a characteristic and unexplained toxicity of that drug. The incidence and severity of this fluid-retention syndrome increases at cumulative doses of 400 mg/m<sup>2</sup> or greater.

#### CAMPTOTHECINS

##### Topotecan. Irinotecan

The topoisomerase I inhibitors, topotecan and irinotecan, have been used in the treatment of refractory or relapsed small-cell lung cancer.

A very low rate of reversible pulmonary toxicity, basically mild to moderate dyspnea, has been

observed with topotecan. In a phase II study of topotecan in malignant mesothelioma, one out of 22 patients had a grade 2 pulmonary toxicity<sup>96</sup>.

Transitory dyspnea in up to 22% of patients, coughing, and rhinitis are possible respiratory adverse effects when irinotecan (CPT-11) is administered. More serious events such as dyspnea with radiographic infiltrates and fever show an incidence range of 1% to 3%<sup>97,98</sup>. However in a large phase II Japanese trial with a dose of 100 mg/m<sup>2</sup> weekly up to 8% of patients had pulmonary toxicity. In another Japanese trial of 16 patients that received the irinotecan as a second-line therapy with the same weekly schedule, 2 patients had extensive pulmonary shadowing (13%)<sup>100</sup>. In concurrent chemoradiotherapy for lung cancer, CPT-11 has been identified in multivariate analysis as a significant risk factor associated with eventual development of pneumonitis<sup>101</sup>.

#### EPIPODOPHYLLOTOXINS

##### Etoposide. Teniposide

These topoisomerase II inhibitors keep a significant role in the treatment of small-cell lung cancer. Although etoposide (VP-16) shows a distinctive low risk profile of general toxicity a very few cases of biopsy-proven pulmonary toxicity have been reported<sup>102-105</sup>. A fatality after following oral therapy has also been observed<sup>103</sup>. A very rare hypersensitivity reaction including loss of consciousness, non-specific chest pain, and bronchospasm is also possible after etoposide infusion<sup>104</sup>.

Teniposide (VM-26) was reported to have produced an acute lung injury in one case but the significance of that report is unclear since the patient had previously received BCNU<sup>1</sup>.

#### IPOMEANOL

Ipomeanol (IPO) has been administered to non-small cell lung cancer patients in a phase I trial with a reported preliminary rate of serious (grade 4) pulmonary toxicity of about 2%<sup>106</sup>.

#### CONCLUSION

Chemotherapy-induced lung toxicity may have a substantial impact on the prognosis of lung cancer patients that follow cytostatic therapy. Although the incidence is in general low, oncologists must be aware of this entity since if it remains unrecognized the likelihood of a fatal outcome is clearly increased.

Several lines of evidence support the notion that

an early diagnosis of any drug-induced pulmonary toxicity is mandatory to improve survival. The clinical relevance of such an early diagnosis is supported by the need of an immediate withdrawal of the offending drug and the early institution of corticosteroid therapy in severe cases. The challenging setting of lung cancer patients that present with respiratory symptoms and clinical findings of unknown etiology should be approached from a multidisciplinary point of view.

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Palabras clave: cáncer de pulmón, quimioterapia, toxicidad pulmonar.

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