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ΤΡΙΜΕΛΗΣ ΕΠΙΤΡΟΠΗ

ΕΠΙΒΛΕΠΩΝ : ΝΙΚΟΛΑΟΣ ΚΟΥΛΟΥΡΗΣ ΚΑΘΗΓΗΤΗΣ ΕΚΠΑ

ΜΕΛΟΣ : ΑΝΤΩΝΙΑ ΚΟΥΤΣΟΥΚΟΥ ΚΑΘΗΓΗΤΡΙΑ ΕΚΠΑ

ΜΕΛΟΣ : ΠΕΤΡΟΣ ΜΠΑΚΑΚΟΣ ΑΝ. ΚΑΘΗΓΗΤΗΣ ΕΚΠΑ

ΠΕΡΙΕΧΟΜΕΝΑ

2.etoposide

D.ANTIMETABOLITES

1.gemcitabine

E.VINCA ALKALOIDS

F.PEMETREXED (antifolate)

G.TARGETED THERAPIES AND PULMONARY TOXICITIES

1. bevacizumab

2. gefitinib

3. erlotinib

4. afatinib

5. osimertinib

6. ALK inhibitors

H.IMMUNOTHERAPY

8.DISCUSSION

Abstract

Η επιδραση των νεοτερων κυτταροτοξικων-αντινεοπλασματικων φαρμακων, που χορηγουνται στην θεραπεια των ασθενων με καρκινο του πνευμονα, στην πνευμονικη λειτουργια, δεν μπορει να χαρακτηρισθει με ακριβεια, λογω της ταυτοχρονης η/και κατά συνεχεια χορηγησης και αλλων φαρμακων στα πλαισια της πολυπαραγοντικης θεραπευτικης αντιμετωπισης αυτων των ασθενων .

Για να είναι δυνατη η καλυτερη προσεγγιση του θεματος αυτου, αναζητηθηκαν σχετικες μελετες στο Medline, up to date, cohrane library. Χρησιμοποιηθηκαν οροι όπως οι δραστικες ουσιες των νεωτερων αντινεοπλασματικων φαρμακων και λεξεις κλειδια σχετικα με την τοξικοτητα των ουσιων αυτων στην αναπνευστικη λειτουργια, καθως επισης οι οροι δυσπνοια και πνευμονιτιδα.

Επισης αναφορες από τα αρθρα που αναζητηθηκαν, αναλυθηκαν ως επιπροσθετες πηγες αναζητησης.

Τα νεοτερα αντινεοπλασματικα φαρμακα φαινεται ότι επηρεαζουν την αναπνευστικη λειτουργια και ευθυνονται για την τοξικοτητα στον πνευμονα, με κυριο χαρακτηριστικο την ανεξηγητη δυσπνοια και την εμφανιση διαμεσου προτυπου πνευμονικης νοσου (ILD).

Είναι απαραιτητος ο αποκλεισμος υποκειμενων νοσηματων. Γενετικη προδιαθεση, αυτοανοσα νοσηματα και επιπροσθετα νοσηματα, μπορουν επισης να σχετιζονται με την εμφανιση πνευμονικης τοξικοτητας. Οι κλινικοι γιατροι θα πρεπει να είναι ενημεροι για πιθανη προσβολη του πνευμονα ως

επιπλοκη στην θεραπεια του καρκινου του πνευμονα και να εστιαστουν στην πρωιμη ανιχνευση και διαγνωση.

Abstract.

Pulmonary toxicity induced by novel antineoplastic agents has not been well characterized because of the simultaneous or sequential use of drugs and a multimodality therapeutic approach. To further investigate this topic, relevant studies were identified through Medline, up to date, cohrane library.

The generic names of novel antineoplastic agents and the key words pulmonary toxicity, dyspnea and pneumonitis were used for the search. References from the articles identified were also reviewed for additional sources. Most novel antineoplastic drugs may induce pulmonary toxicity. The most recognized patterns of lung toxicity consist of unspecified dyspnea and interstitial lung disease (ILD).

Exclusion diagnosis of possible underlying diseases is necessary. Genetic predisposition, autoimmune conditions or superimposed disease may also be involved in the development of lung toxicity. **Conclusion:** Clinicians should be aware of potential pulmonary toxicity as a complication in the treatment of cancer and focus on its early detection or prediction.

Introduction

The present study was aimed at determining the effect of chemotherapy on lung function in lung cancer patients.

Worldwide, lung cancer occurred in approximately 2.1 million patients in 2018 and caused an estimated 1.7 million deaths . In the United States, there will be approximately 230,000 new cases of lung cancer and over 140,000 deaths annually [1,101].

Lung cancer is the leading cause of cancer deaths worldwide and this makes it an attractive disease to review and possibly improve therapeutic treatment options. Both the absolute and relative frequencies of lung cancer have risen dramatically. Around 1953, lung cancer became the most common cause of cancer deaths in men. In 1985 it became the leading cause of cancer deaths in women, and now causes approximately twice as many deaths as breast cancer. There is good news that lung cancer deaths are declining in men and women presumably due to decreases in smoking. Now, however, nearly one-half of all lung cancer deaths occur in women [101].

Surgery, radiation, chemotherapy, targeted treatments, and immunotherapy separate or in combination are commonly used to treat lung cancer[1].

Rapid advances in understanding the molecular pathogenesis of NSCLC have demonstrated that NSCLC is a heterogeneous group of diseases. Although the

initial treatment of localized disease is the same, the molecular characterization of tumor tissue in patients with NSCLC serves as a guide to treatment both in those who present with metastatic disease and in those who relapse after primary therapy [101].

From the other side, the incidence of respiratory illnesses in general, has increased in the last 2-3 decades, thus leading to derangements of the lung functions, partly due to the increase in smoking, pollution, the life span and partly due to the use of various neoplastic drugs. At present, about 50% of the patients with cancer can be cured with chemotherapy, thus contributing to a cure in about 17% of the patients [4,5] · Particularly, the relationship between smoking, lung cancer and airflow obstruction is well recognised [1]. However, it is unclear whether the presence of airflow obstruction constitutes a significant risk factor for development of lung cancer, independently from smoking [2].

Furthermore, pulmonary function tests are valuable investigations in the management of patients with suspected or previously diagnosed respiratory disease[3].

They aid diagnosis, help monitor response to treatment and can guide decisions regarding further treatment and intervention.

The interpretation of pulmonary functions tests requires knowledge of respirat ory physiology· [3]

Indications for Pulmonary Function Tests

1. Investigation of patients with symptoms/signs/ investigations that suggest pulmonary disease e.g. • Cough • Wheeze • Breathlessness • Crackles • Abnormal chest x-ray
2. Monitoring patients with known pulmonary disease for progression and response to treatment e.g. • Interstitial fibrosis • COPD • Asthma • Pulmonary vascular disease
3. Investigation of patients with disease that may have a respiratory complications e.g. • Connective tissue disorders • Neuromuscular diseases
4. Preoperative evaluation prior to e.g. • Lung resection • Abdominal surgery • Cardiothoracic surgery
5. Evaluation patients a risk of lung diseases e.g. • Exposure to pulmonary toxins such a radiation, medication, or environmental or occupational exposure
6. Surveillance following lung transplantation to assess for • Acute rejection • Infection • Obliterative bronchiolitis

It is also important to address a number of concerns in evaluating a patient prior to surgery. These include determining if a patient is :

•Fit for a general anesthetic

•Appropriate for the planned surgical procedure

•Requires further treatment for any underlying respiratory problems (which may or may not have been identified prior to evaluation.

The ideal anticancer drugs can eradicate the cancer cells without harming the normal tissues, but unfortunately, no currently available agents meet this

criterion and the pulmonary toxicity which is caused by the administration of chemotherapy is usually irreversible and progressive.[4]

The initial site of damage seems to be the endothelial cells with an inflammatory type reaction resulting in drug induced pneumonitis.[6,7]

Pulmonary toxicity also induced by novel antineoplastic agents has not been well characterized because of the simultaneous or sequential use of drugs and a multimodality therapeutic approach. [8]

Most novel antineoplastic drugs may induce pulmonary toxicity. The most recognized patterns of lung toxicity consist of unspecified dyspnea and interstitial lung disease (ILD).[8]

Genetic predisposition, autoimmune conditions or superimposed disease may also be involved in the development of lung toxicity.

Clinicians should be aware of potential pulmonary toxicity as a complication in the treatment of cancer and focus on its early detection or prediction.[8]

Chemotherapy and pulmonary toxicity[9,104]

Although it is well recognised that several chemotherapeutic agents can cause cardiopulmonary toxicity [10-12], the exact pathologic mechanism, type, duration, severity and reversibility of pulmonary damage and its real

influence on postoperative outcome is still unclear.[13]

Chemotherapy has been demonstrated to be the cause of acute to subclinical lung impairment with various grades of interstitial and parenchymal involvement.[10,14]

Although the incidence of clinically significant pulmonary toxicity with most agents is low (<5%), the majority of adverse effects are subclinical, with the more common signs represented by abnormal radiological findings, the occurrence of restrictive ventilator defect and mostly by the decrease of lung transfer factor for carbon monoxide (DLCO) [7,15-18,71]

In another study [104], a progressive decline of FEV1 and FVC was observed after chemoradiation. In other studies early increases, yet not statistically significant, were observed in FEV1 and FVC after induction chemotherapy. The same observation has been noted in patients treated by chemotherapy alone. This observation might be due to the relief of obstruction in centrally located tumors. Yet, after long-term surveillance, a significant reduction in pulmonary function was apparent between 3 and 6 months, with no recovery until 36 months after radiation therapy. It has been suggested that FEV1 before treatment is important in lung damage development, and this risk increases in patients with low FEV1.

The majority of studies that investigated the toxic effects of chemotherapy have evaluated the cardiopulmonary function only at rest using conventional procedures (spirometry, determination of DLCO and echocardiography).[7,15]

Only few studies have been directed to evaluate cardiopulmonary function and reserve during exercise.[19]

INDUCTION THERAPY (IC)[18]

The most common use of neoadjuvant therapy is for patients with stage IIIA non–small cell lung cancer from N2 disease. The optimal care of these patients is controversial. A select group of patients, such as those with single-station N2 disease, those with micrometastatic disease, or those with non fixed or mobile N2 disease, may benefit from resection if they respond or are downstaged (rendered N2 negative) after neoadjuvant chemoradiotherapy.[20]

It is well known that the preoperative performance status of patients, their pulmonary function tests (PFTs), and their cardiac function are all important predictors of the risk for surgery [21-24] and could be impaired by chemotherapy agents.[25]

In fact, it is well known that the lung and the heart are a common target of chemotherapy toxicity, and a variety of treatments have been recognised as causative agents of cardiopulmonary damage.[10-12]

The type, severity and duration of lung damage is still unknown, but a prevalent interstitial injury, with the impairment of the alveolocapillary

membrane seems to be the most important feature after induction chemotherapy.[9,14] In most of the cases cardiopulmonary toxicity is not clinically evident and only radiological (chest CT scan) or functional (echocardiogram and cardiopulmonary function tests) tests provide the opportunity for detection of drug-associated toxicity prior to its clinical manifestation.[7,12,15]

Some studies have demonstrated that patients with lung cancer receiving platinum-based IC have favourable effects in spirometric performance with an increase in FEV1 and FVC probably by ameliorating bronchial obstruction caused by tumour extension.[9,17]

For lung volumes, only FEV1 was significantly affected both as absolute and percent predicted values. The small improvement in lung volumes is directly related to a cytoreductive effect of chemotherapy on the tumour mass, making the lung more expansible and reducing the restrictive ventilatory impairment.

The relationship between the radiological response to chemotherapy and the variation in lung volumes, stratified analysis showed a significant improvement in FEV1, FVC and VC only in subjects with a partial response (15—20% mean relative difference).

Some studies performed in patients with lung cancer showed that a reduction In DLCO after IC (induction chemotherapy) is a common finding; and it

represents an indicator of interstitial lung damage and a sensitive predictor of postoperative respiratory complications.[7,15,17,18]

The most sensitive lung function parameter of lung toxicity after IC is the reduction of DLCO, that is, the expression of the efficiency of alveolar—capillary membrane in gas exchanges. It has been related the increase in DLCO to an improvement in alveolar volume because we did not find changes in KCO (DLCO/alveolar volume) after IC. We know the ‘coefficient transfer’ KCO to be an expression of the integrity of the alveolar—capillary gas-exchange function depending on the diffusing capacity of the alveolar membrane, blood, pulmonary capillary volume and red cells.

All these factors can be affected by chemotherapy.[9]

In addition, Rivera and associates in 2009 , Leo and colleagues in 2004 , and others [17,18] have shown that reduced PFTs after induction therapy are associated with postoperative morbidity. The objective of this study was to examine the changes in the PFTs in patients who have undergone neoadjuvant therapy and to assess which test(s) may serve as a predictor of increased operative risk to help guide the preoperative decision as to who is at increased risk of surgery.

Although the mechanism of action is unclear, it is believed that pneumonitis leads to a pulmonary infiltrate that is often seen within days after the delivery

of chemotherapy.[18,25] There is a delayed type of hypersensitivity reaction that occurs that is thought to involve T lymphocytes.[26,27] In addition, when these agents are combined with radiation, there is lymphocytopenia that may also lead to interstitial infiltrates from opportunistic pulmonary infections, and although the FEV1% may increase, the Dlco% is often reduced.[28]

It has also been shown that those who undergo chemotherapy or chemoradiotherapy have increased risk as well .[18,29]

Once the true oncologic benefit of resection is established or estimated, the next factor that requires careful thought is assessment of the operative risk. This is based on the patient's physiologic profile. Preoperative neoadjuvant therapy clearly increases that risk. Chemotherapy alone and especially the combination of carboplatin and paclitaxel, a commonly used doublet by oncologists in North America and the one most commonly used in this series, is known to reduce the Dlco [28] without concurrent radiotherapy reduces pulmonary function.[28] Dose of chest irradiation was 6,600 cGy .

Radiotherapy[8]

Radiation can cause acute or chronic injury in non-neoplastic type I and II pneumocytes, endothelial cells and stromal fibroblasts.[30] At a pathological

level, pulmonary damage is present as ILD and/or fibrosis. The incidence of toxicity can occur early, within weeks after completion of treatment, or later within the first year.[31] The injury of normal lung tissue depends on the total dose,[32] dose received from the lung and mean lung dose.[33] Alterations in apoptotic and repair mechanisms can also explain the pathogenesis of radiation pneumonitis, as implied by the role of multiple cytokines (e.g. TGF-β, TNF-α, interleukin-1 (IL-1), IL-6 and PDGF) in the pathogenesis and early detection of toxicity. [34]

Initial DNA damage instigates the repair mechanisms or the process of inflammation and finally cell death and fibrosis. Pulmonary function tests should be used as markers or predictors of the incidence and severity of pneumonitis.

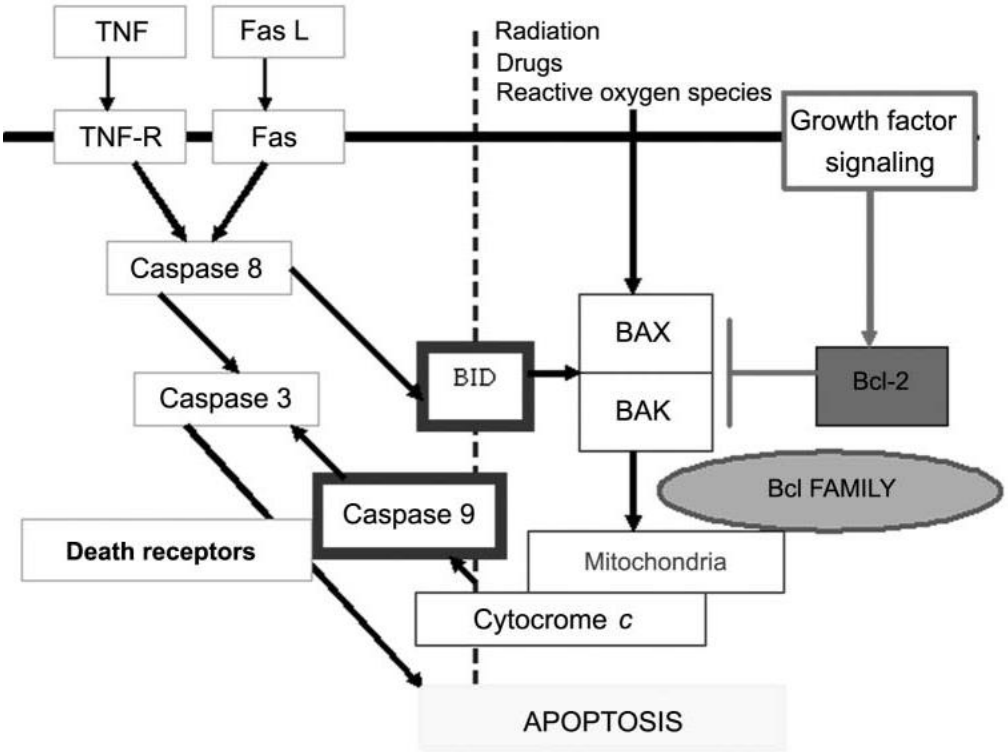
In another study [104] radiation therapy is associated with significant alterations in DLCO and KCO . The decrease in DLCO is a result of limited gas exchange reserve, caused by the potential toxicity of treatment. This decrease, may reflect interstitial and parenchymal damage leading to impairment in diffusion capacity of the alveolar membrane. Radiation results in the damage of endothelial, epithelial (type II pneumocytes) cells, by apoptosis and stimulation of stress response genes progressing to an acute exudative inflammation process, which occurs usually 1–6 months after completion of treatment . Also, early histological lesions with various grades of interstitial and parenchymal

involvement were observed after both chemotherapy and radiation therapy. Furthermore, the predictive value of clinical data such as the site of the radiated lung, the age of the patient and smoking history have been investigated in the contex of radiation pneumonitis.[35]

Multimodality Therapy in Lung Cancer and Pulmonary Toxicity

Apoptotic pathways initiated by antineoplastic drugs and radiation therapy [8]

(Charpidou *et al*: Therapy-induced Lung Toxicity (Review))



Multimodality therapy is the current standard in locoregionally advanced and metastatic lung cancer. Many cytotoxic agents are involved in pneumonitis but while traditionally bleomycin, adriamycin, cyclophosphamide, mitomycin C and methotrexate have been reported, these agents are of less importance in lung cancer because they are not commonly used. Among the third-generation agents used with radiation in current practice, docetaxel might be the most toxic. This drug has an unacceptable toxicity of serious (Grade 3) pneumonitis, in 47% of the patients, in concurrent administration with radiotherapy. [36]

When paclitaxel-induced pneumonitis is combined with radiotherapy, immunological as well as non-immunological mechanisms may be involved. A hypersensitivity reaction, as evidenced by increased lymphocytes and eosinophils, along with a decreased helper/suppressor T lymphocyte ratio, has been reported.[37] Protracted lymphocytopenia can be seen for up to three months and may indeed invite opportunistic infections to arise.

Chemotherapy with the cisplatin-irinotecan combination and concurrent radiotherapy correlates with increased of pulmonary fibrosis.[38] Serious pneumonitis (grade 3-4) has also occurred in 7.7% of patients treated with combination chemotherapy (cisplatin and vinorelbine) and radiation therapy according to one study.[39]

Pemetrexed, a new multitarget antifolate, is currently used in malignant pleura mesothelioma and in first and second line treatment of NSCLC.[40] When this agent is combined with platinum based chemotherapy and radiation, it may be associated with fatal pneumonitis.[41]

Classic chemotherapy agents [42] inhibit cell division and target rapidly proliferating cells. In contrast, the newer molecular targeted therapies are directed at specific molecules responsible for regulating cell activities, and the onset and presentation of their toxicities may therefore differ.

Understanding the mechanisms of action of the newer molecular agents may aid recognition of their associated toxicities, though the mechanisms of the toxicities are not completely understood.

Several of the monoclonal antibodies and tyrosine kinase inhibitors bind known membrane cell receptors. Others bind intracellular molecules and are multitargeted, and their toxicities may be more ubiquitous.

Our discussion is limited to toxicities that may be seen on computed tomographic (CT) studies of the chest, abdomen, and pelvis, because these are the imaging examinations most commonly used in the follow-up of cancer patients.

Cytotoxic chemotherapy agents usually interfere with RNA and DNA synthesis or cell division and, therefore, affect cell growth by various mechanisms of

action. Some of the most commonly used drugs include classic agents such as cyclophosphamide (an alkylating agent), cisplatin (a DNA intercalating agent), fluorouracil (5-FU; an antimetabolite), doxorubicin (an anthracycline), vincristine (a mitotic spindle inhibitor), and bleomycin. Some of the more recently developed cytotoxic agents include gemcitabine (another antimetabolite), oxaliplatin (a cisplatin analog), paclitaxel and docetaxel (the "taxanes," which are mitotic spindle poisons), and irinotecan (a topoisomerase inhibitor) (Table 1).

Table 1

Chemotherapeutic Drugs by Class Classic Cytotoxic Agents

Class	Agents
Alkylating agents	Busulfan, cyclophosphamide, ifosfamide, melphalan
Nitrosoureas	Carmustine
Platinum analogs	Carboplatin, cisplatin, oxaliplatin
Antimetabolites	Capecitabine, cytarabine, 5-FU, floxuridine, gemcitabine, methotrexate
Antitumor antibiotics	Bleomycin, dactinomycin, daunorubicin, doxorubicin
Taxanes	Docetaxel, paclitaxel
Vinca alkaloids	Vinblastine, vincristine, vinorelbine
Topoisomerase inhibitors	Etoposide, irinotecan, topotecan

Molecular therapies have developed as a result of an improved knowledge of cancer biology. They target cell surface antigens (as in the case of monoclonal antibodies) or various signaling molecules (as in the case of kinase inhibitors). Many of these agents affect multiple targets and, therefore,

have the potential to inhibit molecules that are critical to unsuspected pathways, causing toxicity that has not been previously observed.[43] While some of the toxicities of the cytotoxic agents and molecularly targeted therapies overlap, there is concern that the toxicities of the molecularly targeted agents are less predictable.

Targeted therapies can be classified according to their mechanism of action. Monoclonal antibodies are designed to bind to antigenic determinants of specific molecules, the expression of which is sometimes upregulated in malignancy, but the action of such antibodies does not necessarily rely on the activation of Immune effector cells. Several monoclonal antibodies are in clinical use.

Molecular targeted therapies are used either alone or in combination with standard chemotherapy agents. Combination chemotherapy regimens are designed to include agents with different mechanisms of action, so that cell growth is interrupted at two or more points of cell proliferation. The radiologist needs to be aware of the potential toxicities of both the conventional and the targeted agents when they are used in combination therapy.

Some newer molecularly targeted therapies do not inhibit membrane re ceptors but rather other intracellular molecules (ex. Metastatic renal cancer).

PULMONARY SYSTEM (Radiological Findings) [42]

Pulmonary infiltrates are the most common radiologic manifestation of both classic and new targeted chemotherapy toxicities. Toxicity from the classic chemotherapy agents typically results in bilateral interstitial infiltrates presenting with progressive dyspnea.

The newer EGFR-targeted agents can cause ground-glass infiltrates that should not be mistaken for tumor progression.

Pulmonary and interstitial infiltrates.[42]

Pulmonary infiltrates that develop in patients undergoing chemotherapy can result from progression of disease, infection, and inflammation caused by chemotherapy toxicity or cardiogenic and noncardiogenic causes of intersti tial edema. Knowledge about which chemotherapy agents are more likely to cause pulmonary toxicity may aid in judging the most likely cause. Chemotherapy-induced lung injury can manifest as early onset with infiltrates, pulmonary edema, hypersensitivity reaction, or pleural effusions or as late onset, after 2 months or more of therapy, with infiltrates or fibrosis.

Pulmonary toxicity may be seen with many of the newer cytotoxic chemothera peutic agents. Gemcitabine may cause diffuse ground-glass changes accompanied by thickened septal lines, interstitial infiltrates, or diffuse alveolar infiltrates, which may sometimes be associated with acute respiratory distress syndrome and rarely, death. [44-46] Paclitaxel-induced pulmonary toxicity is nonspecific and can manifest with bilateral reticular or ground-glass infiltrates or focal consolidation.[47]

These toxicities tend to manifest with dyspnea, cough, and hypoxemia, usually early after initiation of therapy. Oxaliplatin-induced pulmonary interstitial disease is an increasingly recognized entity. Interstitial pneumonitis with fibrosis occurs after 3–6 months of therapy.

Patients present with slow progressive cough and dyspnea that may rapidly progress to fibrosis and, rarely fatal pneumonitis.[47]

Pulmonary hemorrhage.

Major and fatal hemoptysis can occur in patients treated with bevacizumab for non–small cell lung cancer, reported in 5% of patients in an early clinical trial.[48] The mechanism is not known, but at retrospective review of CT scans from these patients, potential risk factors for pulmonary hemorrhage were identified as baseline tumor necrosis and cavitation.[49] In early clinical trials, investigators

identified squamous histologic appearance as a risk factor for pulmonary hemorrhage; this finding is now an exclusion criterion for bevacizumab therapy.[50] Bevacizumab is approved for use in colon, breast, lung, brain, and kidney cancer.

Capillary leak syndrome.

Capillary leak syndrome is characterized by an increase in vascular permeability, causing extravasation of fluids and proteins from capillary vessels into the soft tissues and resulting in interstitial edema. It is a systemic process leading to ARDS or noncardiogenic pulmonary edema in late stages. Diffuse air space disease with ground glass opacities is the most common finding on CT scans . Capillary leak syndrome is associated with several chemotherapy agents, including immune-mediated therapies such as interleukin 2 and interferon and has reported with gemcitabine.[51-52] Consideration of capillary leak syndrome in the differential diagnosis of new-onset interstitial pulmonary edema is crucial, since capillary leak syn drome may require the addition of corticosteroid therapy to diuretic therapy.[53,54]

Cytotoxic Drugs that Cause Pulmonary Toxicity [8]

Antineoplastic agents are also traditionally divided by their origin or mechanism of action.

The literature reports a number of chemotherapeutic agents that cause the serious side-effect of pulmonary toxicity. The third generation chemotherapies, specifically taxanes (docetaxel and paclitaxel) and/or gemcitabine, have been studied because of their broad use in the therapy of non-small cell lung cancer NSCLC .[36] The pattern of pulmonary toxicity by these agents is usually a non-specific interstitial pneumonitis, diffuse alveolar damage and pleural effusion.[55]

Table 1 – Current regimen of treatment for lung cancer.

Drug name	Generic name	Use
Xeloda	Capecitabine	anti-metabolites
Avastin	Bevacizumab	VEGF/VEGFR inhibitors
Tarceva	Erlotinib	EGFR inhibitors
Cytoxan	Cyclophosphamide	alkylating agents
Taxol	Paclitaxel	mitotic inhibitorsa
Taxotere	Docetaxel	mitotic inhibitors
Gemzar	Gemcitabine	antimetabolites
Erbitux	Cetuximab	EGFR inhibitors
Alimta	Pemetrexed	antimetabolites
Navelbine	Vinorelbine	mitotic inhibitors
Platinol	Cisplatin	alkylating agents
Trexall	Methotrexate	antimetabolites,antipsoriatics, antirheumatics
Ethyol	Amifostine	antineoplastic detoxifying agents
Iressa	Gefitinib	EGFR inhibitor
Neosar	Cyclophosphamide	alkylating agents
Platinol-AQ	Cisplatin	alkylating agents
Photofrin	Porfimer	miscellaneous antineoplastics
Onxol	Paclitaxel	mitotic inhibitors

http://www.drugs.com)

TAXANES (Plant alkaloids) [8,55]

Paclitaxel.

Like docetaxel, paclitaxel is derived itself from the bark of yew trees and is a spindle poison plant alkaloid.

Paclitaxel interferes with the normal function of microtubule growth and arrests microtubule function by ultra-stabilizing its structure. Binding to the β subunit of tubulin, paclitaxel prevents the disassembly of the resulting microtubule/ paclitaxel complex. Like docetaxel, paclitaxel also binds to Bcl-2 thus arresting its function of inhibiting apoptosis.

Paclitaxel is one of the most active chemotherapeutic agents in the treatment of breast, lung and ovarian carcinoma. Up to 30% of patients in early trials experienced a type I hypersensitivity reaction, characterized by dyspnea, chest tightness, bronchospasm, urticaria and hypotension.[56]

These symptoms occur within the first 2 or 3 min after the first dose of drug therapy, and may be due to IgE antibodies to paclitaxel or to its cremophor EL vehicle, or may be mediated by the release of histamine and other Vasoactive substances.

Premedication subsequently reduced the incidence of such reactions to 1% .

ILD in the form of non-specific or hypersensitivity pneumonitis has been

described in case reports, clinical studies and small series. Pulmonary infiltrates and symptoms were evident within 6 h following the drug infusion and the radiological signs resolved in 24–96 h while symptoms responded to steroids.[26]

It is noteworthy to mention that the incidence of interstitial pneumonitis is much higher if paclitaxel is given concurrently with radiation (47% of patients) or with other agents having the potential to cause lung toxicity, including gemcitabine (33% of patients).

A delayed-type hypersensitivity [8,55] reaction involving immunological and non-Immunological mechanisms has been proposed as a possible pathophysiological mechanism [57] for ILD.

A hypersensitivity reaction as shown by increased lymphocyte and eosinophil counts, along with a decreased helper/suppressor T lymphocyte ratio has been reported.[57]

Alternatively, it has been suggested that paclitaxel, especially when combined with radiotherapy, may lead to protracted lymphocytopenia for up to three months; this results in an immunodeficiency state, thus causing opportunistic infections that account, at least in part, for the interstitial infiltrates.[58,55]

Clinicians should we aware of the potential of paclitaxel to impair the PFTs.

Robert et al. studied patients with advanced non-small-cell lung cancer who were treated with paclitaxel, cisplatin and radiation. They found that FVC and especially DLCO decreased significantly.

No relationship was found between changes in PFTs and incidence of acute or late pulmonary toxicity. With regard to PFTs, paclitaxel may impair FVC and DLCO, which may decrease.

A prospective study from our group showed that the combination of paclitaxel and carboplatin induced an isolated decrease in DLCO in the absence of clinical or radiological evidence of toxicity. The change in DLCO was associated with a higher baseline DLCO and a lower FEV1,whereas it was unrelated to age, gender, smoking history or to cumulative dose of paclitaxel. In a subset of patients the decline in DLCO was present several months after the completion of chemotherapy.[28,55]

ILD in the form of nonspecific or hypersensitivity pneumonitis has been described in a number of case reports and clinical studies.[59,60-62,25,27] On the other hand, multi-therapeutic studies found the incidence of pneumonitis to be very low (1%), even with radiation therapy.[26] The symptoms and radiological findings of pulmonary infiltrates eventually resolved within 24-96 hours after steroid administration.[26]

In another dose escalation study, paclitaxel in combination with a fixed

dose of irinotecan in patients with advanced NSCLC was found to cause pneumonitis grade 1 to 3 . On the whole, the incidence of interstitial pneumonitis is much higher if paclitaxel is given concurrently with radiation (47% of patients) , or with other agents that may potentially cause lung toxicity, including gemcitabine (33% of patients).[63,64]

The mild interstitial pneumonitis that has been reported was managed with Low dose corticosteroids, which resulted in a good response,even when radiotherapy was administered.[25,59]

Other rare side-effects are DAD and lung fibrosis. DAD has been documented in two patients treated with paclitaxel and gemcitabine , and lung fibrosis has been seen in one patient treated with paclitaxel and carboplatin [8,65].

Docetaxel. [8,55]

Docetaxel is a taxane derivative with activity in many solid tumors including breast, gastric, ovarian and NSCLC.[66] Docetaxel disrupts the microtubular network in cells that is essential for mitotic and interphase cellular functions. Binding to free tubulin, docetaxel produces dysfunctional microtubular bundles which inhibit mitosis. The accumulation of such bundles leads to apoptosis.

Furthermore, docetaxel is known to inhibit Bcl-2 antiapoptotic protein, which further encourages apoptosis.

Hypersensitivity reactions seem to be common. [67,68] In one study, such reactions were observed in 42% of the patients and included dyspnea, pruritus, skin rashes, fever and hypotension, and may relate to the formulation of docetaxel with polysorbate-80 or to histamine release and may be blocked with the use of premedication.

Hypersensitivity pneumonitis in which chest computed tomography scans shows a typical ground glass appearance of the lung parenchyma bilaterally appear to be a frequent type of the injury.

Docetaxel can cause acute interstitial pneumonitis when used as monotherapy or in combination with other treatments.

The coadministration [8] of docetaxel and gemcitabine can be correlated with an incidence as high as 23% of interstitial pneumonitis. Patients receiving docetaxel combined with gemcitabine or estramustine have occasionally suffered from diffuse alveolar damage, which may even extend to adult respiratory distress syndrome (ARDS).

Docetaxel-related pneumonitis usually responds to steroids , which is also indicative of a hypersensitivity reaction. However severe cases have occasionally been reported in which the use of steroids was ineffective and

death ensued after long-term ventilatory support.[69]

Although in some cases, docetaxel has been connected to edematous states after subsequent cycles, pulmonary edema is rare.

A capillary leak syndrome [55] has also been suggested to explain the formation of pleural effusions in the absence of interstitial lung disease in patients receiving **docetaxel** .[70] This syndrome causes fluid retention and is associated with the cumulative docetaxel dose: >50% of patients receiving a total of 500 mg/m2 of the drug developed edema in a recent study.[70]

Diuretic treatment offers little help, while daily treatment with 40 mg of methyl-prednisolone the days before and after docetaxel administration, significantly delayed the onset of edema in a recent randomized study .

Platinum compounds(Alkylating agents) [71]

The administration of cisplatin and carboplatin, the 2 most commonly used platinum derivative agents, can lead to hypersensitivity reactions (HRs) in approximately 2% of patients, whereas the reported incidence of other DIPTs (drug induced pulmonary toxicities) 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.[71]

Because platinum agents usually are co-administered 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. [72]

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%.[73] In both of those studies, the difference in incidence was not statistically significant.

Topoisomerase inhibitors(Plants alkaloids)[55]

Topoisomerase inhibitors are chemical compounds that block the action of topoisomerase (I and II) which is a type of enzyme that controls the changes in DNA structure by catalyzing the breaking and rejoining of the phosphodiester backbone of DNA strands during the normal cell cycle.

Topotecan (Topoisomerase I inhibitors)

Topotecan is used primarily in the treatment of metastatic carcinoma of the ovary and as second-line treatment of small-cell lung cancer. Topotecan-related pulmonary toxicity appears to be very rare; bronchiolitis obliterans has been described in two cases.[74,75]

Etoposide (Topoisomerase II inhibitors)[71]

Etoposide may induce HRs (hypersensitivity reactions) with angioedema, bronchospasm, and hypotension, all of which require steroid administration. Interstitial lung disease (ILD) related to etoposide is rare, but several case reports have been published.

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.

The concomitant administration of other drugs, such as methotrexate, or thoracic radiation therapy may increase the risk of developing ILD.

Antimetabolites [8,55]

Gemcitabine.

Gemcitabine is a deoxycytidine analog (2',2'-difluoro-deoxycytidine) which interferes with DNA synthesis by inhibiting DNA and RNA polymerase. Inserting itself into the growing DNA, by competing with deoxycytidine triphosphate at the cytidine sites, gemcitabine arrests growth at the S-phase and induces apoptosis. This antimetabolite is used in a number of solid tumors including pancreatic, ovarian, breast and

esophageal as well as lung cancer.

The toxicity profile of gemcitabine is mild compared with other cytotoxics and usually involves myelosuppression which is dose limiting.[76]

Higher incidences of neutropenia can be seen more commonly in combination therapy rather than in first-line therapy.[77]

Although gemcitabine is considered to be a drug with a reasonable safety profile, cases of pulmonary toxicity have been reported. Studies with a large number of patients have shown an incidence of gemcitabine-related pulmonary toxicity of 4% and lower than 1% , respectively.

The clinical presentation is frequently sub-acute and nonspecific.

Symptoms may even appear weeks after the last given dose and may include progressively worsening dyspnea, fevers, chills and night sweats. Transient dyspnea has been reported to arise within hours after the administration of gemcitabine in about 8-10% of patients. More often, this transient dyspnea is associated with bronchospasm and is usually a self-limiting event. The dyspnea might be due to underlying disease such as lung cancer (40% of Study population) or pulmonary manifestations of other malignancies. However, severe dyspnea associated with this drug has occurred in about 3-5%. Most of these cases could be managed by withdrawing gemcitabine and concomitant administration of diuretics and

corticosteroids.

Additional and rare gemcitabine-related pulmonary toxicities include alveolar hemorrhage (AH), [47,71] diffuse alveolar damage (DAD), acute respiratory distress syndrome,(ARDS), noncardiogenic pulmonary edema, hemolytic uremic syndrome (HUS) , and capillary leak syndrome.

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%. [78]

The onset of symptoms (dry cough, fatigue, malaise).[79-81] occurs 3 to 12 weeks after the beginning of treatment. The radiologic findings are represented by diffuse or patchy ground-glass attenuation, reticular nodules, and interstitial thickening.[71]

In most patients, the histologic findings at autopsy reveal hyperplasia of type II pneumocytes, patchy AH, hyaline membrane formation, and fibrosis, [81] all findings that are consistent with acute lung injury.

Additionally, this drug appears to have a direct toxic effect on the endothelial cells of the pulmonary capillaries, which causes a capillary leak syndrome. It appears that this capillary event is often mild as patients are asymptomatic and have normal pulmonary function. In these cases, the withdrawal of the drug is sufficient and the use of corticosteroids is not warranted.

The incidence rate of ARDS associated with gemcitabine has been reported to be as low as 0.002%.

Although in general serious toxicity is not common with gemcitabine, it has been observed to cause some fatalities . More deaths are due to gemcitabine used in combination with other cancer therapies.

A retrospective analysis which investigated patients with advanced NSCLC who received gemcitabine and cisplatin followed by surgery and/or radiation found that diffusion capacity for carbon monoxide (DLCO) decreased significantly after treatment.

Other lung function indices, such as forced vital capacity (FVC) and Forced expiratory volume in one second, remained unaffected.

To reiterate, combination chemotherapy with docetaxel and gemcitabine is associated with a higher incidence of interstitial pneumonitis .

Additionally, diffuse alveolar damage or ARDS has been seen in those receiving docetaxel combined with gemcitabine .

Discontinuation of therapy and the administration of corticosteroids (ie, prednisone 60 mg daily) may improve DIPT (drug induced pulmonary toxicity) within a few days.

Vinca alkaloids (Plants alkaloids) [71]

Vinca alkaloids are a set of anti-mitotic and anti-microtubule alkaloid agents originally derived from the periminkle plant Catharanthum roseus (Vinca rosea) and other vinca plants. They block beta-tubulin polymerization in a dividing cell.

Vinca alkaloids rarely induce DIPT when administrated as single agents, but pulmonary toxicity is reported in combination with MMC (Mitomycin-C, is no longer in use) as described above.[82] The only DIPTs that have been reported after administrationof 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. [83]

Pemetrexed (Antifolate -Antineoplastic Agent) [71]

No significant pulmonary toxicity has been reported for pemetrexed in phase 3 studies [84,85], and only sporadic case reports have indicated the possible occurrence of pemetrexed-related interstitial pneumonia.[86]

Targeted Therapies and Pulmonary Toxicity [8,106]

Several studies of the last decade have indicated the pivotal role of angiogenesis and EGFR activation in tumor growth and metastatic dissemination . This has led to an ‘explosion’ of targeted therapies in lung cancer treatment.

New single and multitarget agents have been developed. EGF tyrosine kinase inhibitors (TKIs) have been used as salvage treatment in refractory NSCLC.[40,87,88] Anti-EGFR agents — Gefitinib (Iressa), erlotinib (Tarceva), afatinib (Giotrif) and osimertinib (Tagrisso) are orally active small molecule inhibitors of the epidermal growth factor receptor (EGFR) tyrosine kinase (TK). They are primarily used in the treatment of advanced non-small cell lung cancer (NSCLC).

Approximately 1 percent of patients treated with gefitinib or erlotinib and 3 percent of patients treated with osimertinib develop lung toxicity, usually within the first two to three months of therapy. The risk is higher in patients with preexisting lung disease and in smokers. Approximately one-third of patients who develop interstitial lung disease (ILD) while being treated with gefitinib die of this complication. The mortality rate among patients receiving osimertinib appears to be lower; in one review of 813 cases, 27 developed

ILD/pneumonitis, and 4 cases (15 percent of the total) were fatal . The mortality rate in patients who develop ILD while receiving erlotinib is not well characterized but is likely similar to gefitinib, based on available information.

VEGF-TKIs (namely sorafenib and sunitinib) and monoclonal antibodies against the VEGF receptor VEGFR (bevacizumab) [8,89] are combined with chemotherapy in standard first-line treatment or in phase II and III first- and second-line clinical trials in NSCLC.

Pulmonary infiltrates are among the most common adverse reactions of the EGFR-targeted inhibitors gefitinib and erlotinib. [42,90] The overall prevalence of pulmonary toxicity with gefitinib is 1%, and it is higher in Asia than in the US. [91]

Clinically, patients present with acute onset of dyspnea, with or without cough; symptoms may appear as early as 1 week to 1 month after initiation of therapy. CT findings include airspace consolidation or extensive bilateral ground-glass infiltrates.[92] The mechanism of pulmonary toxicity is unknown but it is has been suggested that repair of damaged epithelial cells requires activation of EGFR-mediated pneumocytes, which is inhibited by gefi tinib and erlotinib . Four radiologic patterns have been described on CT scans: (a) a nonspecific area with ground-glass attenuation, (b) multifocal areas of air space consolidation, (c) patchy distribution of ground-glass

attenuation accompanied by interlobular septal thickening, and (d) extensive bilateral ground-glass attenuation or airspace consolidations with traction bronchiectasis. The most common pattern is a nonspecific area of ground-glass attenuation, and the pattern associated with the highest mor tality rate is extensive bilateral ground glass airspace consolidation, thought to represent diffuse alveolar damage. [92]

Treatment with gefinitib and erlotinib has been correlated with interstitial pneumonitis in 1% and 0.8% of treated patients. [8] The pathogenesis of ILD is likely to be an effect of EGFR involvement in the repair process and not a result of biotransformation or chemical injury as with radiotherapy and chemotherapy. [93,94]

Monoclonal antibodies are used in the treatment of various hematopoietic malignancies and solid tumors. Most recently, bevacizumab has been used in lung cancer [40] and has been correlated with serious and fatal hemoptysis , while bleeding episodes have not been reported in patients with colorectal, renal, breast or prostate cancer [95]. Squamous NSCLC histology, a central location of the tumor and proximity to large vessels may present risk factors for pulmonary bleeding adverse events. [89]

Bevacizumab (Monoclonal antibody) [37,71]

Bevacizumab is a monoclonal antibody that targets the VEGF receptor, which normally promotes the proliferation of additional blood vessels to support tumor growth and the development of metastases.

Tyrosine kinases within the receptor are transmembrane molecules that are activated by the binding of a ligand (eg, epidermal growth factor, VEGF) with the extracellular domain of the receptor. The interaction of ligand and receptor results in activation (phosphorylation) of the intracellular domain, which in turn phosphorylates any number of intracellular molecules (so-called second mes sengers) that instruct the cell to grow and divide.

Tyrosine kinase inhibitors (TKIs) prevent the phosphorylation of the second messengers, thereby interrupting the unregulated intracellular signaling pathway(s).

Examples of TKIs include gefitinib (Iressa) and erlotinib (Tarceva), which bind to the mutationally modified intracellular adenosine triphosphate–binding domain of the EGFR and are used in the treatment of patients with non–small cell lung cancer.

The most common bevacizumab-related DIPTs are hemoptysis and pulmonary hemorrhage.[71,89]The occurrence of these events is associated most

frequently with the presence of tumor cavitation and with a diagnosis of squamous cell carcinoma.

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. [71]

The incidence of thromboembolic complications reported for bevacizumab differs among studies.

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).

Recently, a retrospective study in colorectal cancer that investigated the prophylactic use of acetylsalycilic acid during treatment with bevacizumab indicated 87 that there was no increase in hemorrhagic risk.

Further assessments are needed to prove the efficacy of acetylsalycilic acid in reducing the risk of thrombosis in NSCLC patients treated with bevacizumab.

Bevacizumab [55] is an IgG1 recombinant humanized monoclonal antibody to

vascular endothelial growth factor (VEGF) that blocks binding of human VEGF to its receptors. Bevacizumab has been approved for first-line treatment of advanced colorectal cancer in combination with other agents.

Severe pulmonary toxicity has not been usually reported in patients receiving bevacizumab. Nevertheless, hemoptysis was encountered frequently in a randomized phase II study in patients with non-small-cell lung cancer. Although hemoptysis can be a symptom of lung cancer, the incidence was significantly higher among patients receiving bevacizumab (20% versus 6%).

Such bleeding episodes have not been reported in patients with colorectal, renal, breast or prostate cancer.

In all cases tumors were centrally located and in the proximity of major blood vessels. Furthermore, squamous histology may possibly present a risk factor for major bleeding and have been excluded from the ongoing trial.

Gefitinib [55]

Gefitinib is an oral selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase that may be effective in some patients with advanced non-small-cell lung, ovarian, breast, head and neck, and colon cancers

Pulmonary toxicity consists of ILD, i.e. diffuse alveolar and/or interstitial damage, usually occurring during the first 3 months of treatment. The estimated worldwide incidence of ILD is low (about 1%; 2% in the Japanese post-marketing experience and 0.3% in a US expanded access program). ILD presents as an acute onset of dyspnea, with cough or low-grade fever, becoming severe in a short period of time. About one third of the cases are fatal. Alveolar hemorrhage and lung fibrosis are rare. Risk factors for toxicity include Japanese ethnicity, prior thoracic radiation or chemotherapy, smoking history, pre-existing idiopathic pulmonary fibrosis and pulmonary infections. The pathophysiology of gefitinib-induced lung injury needs to be clarified, but some mechanisms may be considered. EGFR promotes the regeneration of the alveolar epithelial cells and is up-regulated in acute lung injury. Consequently, the EGFR inhibitor, gefitinib, may impair normal repair and thereby exacerbate any lung injury, especially in patients with pulmonary comorbidities.[93]

Gefitinib-associated DIPT [71] consists mainly of ILD: AIP with DAD AH and pulmonary fibrosis have been reported. It usually occurs within the first 90 days of treatment , and the median time of clinical onset was 24 days in Japan and 42 days in the United States.

In a Japanese multi-institutional study [71] 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. 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 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 especially in those patients who have pre-existing pulmonary fibrosis.

Erlotinib.[71]

Pulmonary toxicity is rare; only one case of interstitial pneumonitis has been reported.

Worldwide, the rate of erlotinib-induced lung toxicity is approximately 1%, [96,97] although single-center studies have reported a higher incidence among Japanese patients.[98]

In addition, in a retrospective Japanese study, the occurrence of adverse reactions was observed earlier with erlotinib than with gefitinib

The most common pulmonary toxicity from erlotinib is acute or subacute onset of dyspnea with rapid progression to respiratory failure and ARDS .

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

The risk factors for developing lung toxicity include, age, smoking history, and the concomitant administration of chemotherapy and radiotherapy; 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.

In 1 case report, the occurrence of lung toxicity secondary to erlotinib was observed in patients with preexisting usual interstitial pneumonia.

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.

Afatinib [106]

Afatinib is a highly selective irreversible inhibitor of the ErbB family, including ErbB1 (EGFR), ErbB2 (HER2), and ErbB4. Afatinib, 40 mg daily, was administered to patients with NSCLC in two randomized trials, and the following ILD rates were reported.

Osimertinib [106]

Across clinical trials, ILD/pneumonitis has occurred in approximately 2 to 3 percent of patients treated with osimertinib approximately 15 percent of cases (one in six) have been fatal .

The United States prescribing information for osimertinib recommends withholding the drug for any patient who presents with worsening of respiratory symptoms (eg, dyspnea, cough, fever), which may indicate ILD, and that the drug be permanently discontinued if ILD is confirmed.

In Lung LUX 3, among 230 patients treated with afatinib, there were three cases of potential ILD (1 percent), and of the four deaths on treatment, two were from

respiratory decompensation .

In Lung LUX 6, one of 242 patients receiving afatinib developed grade 4 ILD but recovered following treatment with antibiotics and glucocorticoids . In a dose-escalation trial of 253 patients with EGFR, there were six cases of potential pneumonitis-like events; all six cases resolved or were resolving following drug discontinuation.

The risk of ILD/pneumonitis may be higher when osimertinib is administered after an immune checkpoint inhibitor. In a retrospective study of 26 patients who received different types of EGFR TKIs administered before or after an anti-programmed cell death 1 (PD-1) antibody (eg, nivolumab, pembrolizumab), three out of seven patients treated with osimertinib after an anti-PD-1 agent developed ILD (42.8 percent), whereas treatment with a first or second-

-generation agent after treatment with an anti-PD-1 agent, or with osimertinib before an anti-PD-1 antibody did not increase the risk for ILD . Patients who developed ILD were treated with systemic glucocorticoids after discontinuation of EGFR TKI treatment and had resolution of their ILD.

ALK inhibitors [106]

Crizotinib, ceritinib, alectinib, brigatinib, and lorlatinib are orally active

inhibitors of the anaplastic lymphoma kinase (ALK); all are approved for treatment of advanced or metastatic non-small cell lung cancer if the tumor contains a characteristic EML4-ALK fusion oncogene. All drugs in this class have been associated with development of ILD/pneumonitis.

IMMUNOTHERAPY [99,102,103,105]

Immune checkpoint inhibitors (ICIs) are newer, immunotherapy-based drugs that have been shown to improve survival in advanced non-small cell lung cancer (NSCLC). Unlike traditional chemotherapeutic agents, ICIs work by boosting the body's natural tumor killing response. However this unique mechanism of action has also led to the recognition class-specific side effects. These therapies are sometimes associated with often subtle, potentially fatal immune-related adverse events (irAEs).

Labeled immune-related adverse events, these toxicities can affect multiple organ systems including the lungs. Immune-mediated lung injury because of ICI use, termed checkpoint inhibitor pneumonitis (CIP), occurs in about 3%-5% of patients receiving ICIs, however the real word incidence of this entity may be higher, especially now that ICIs are being used in nonclinical trial settings.

Immune checkpoints are surface proteins on T cells and other immune cells that act as negative regulators of immune activation by various antigens, including tumor antigens. Immune checkpoint inhibitors (ICIs) are a class of immunotherapeutic agents that harness the intrinsic immune response

against tumor antigens by removing the brake on T-cell activation by antigen-presenting cells (APCs). However by the same process, these agents may also promote T-cell attack on self-antigens, which clinically manifests as a set of unique toxicities labeled immune-related adverse events (irAEs).

In NSCLC several trials have demonstrated improvement in survival outcomes for patients with NSCLC with progressive disease after traditional chemotherapy, therefore generating interest in the use of ICIs in both early and late stage NSCLC.

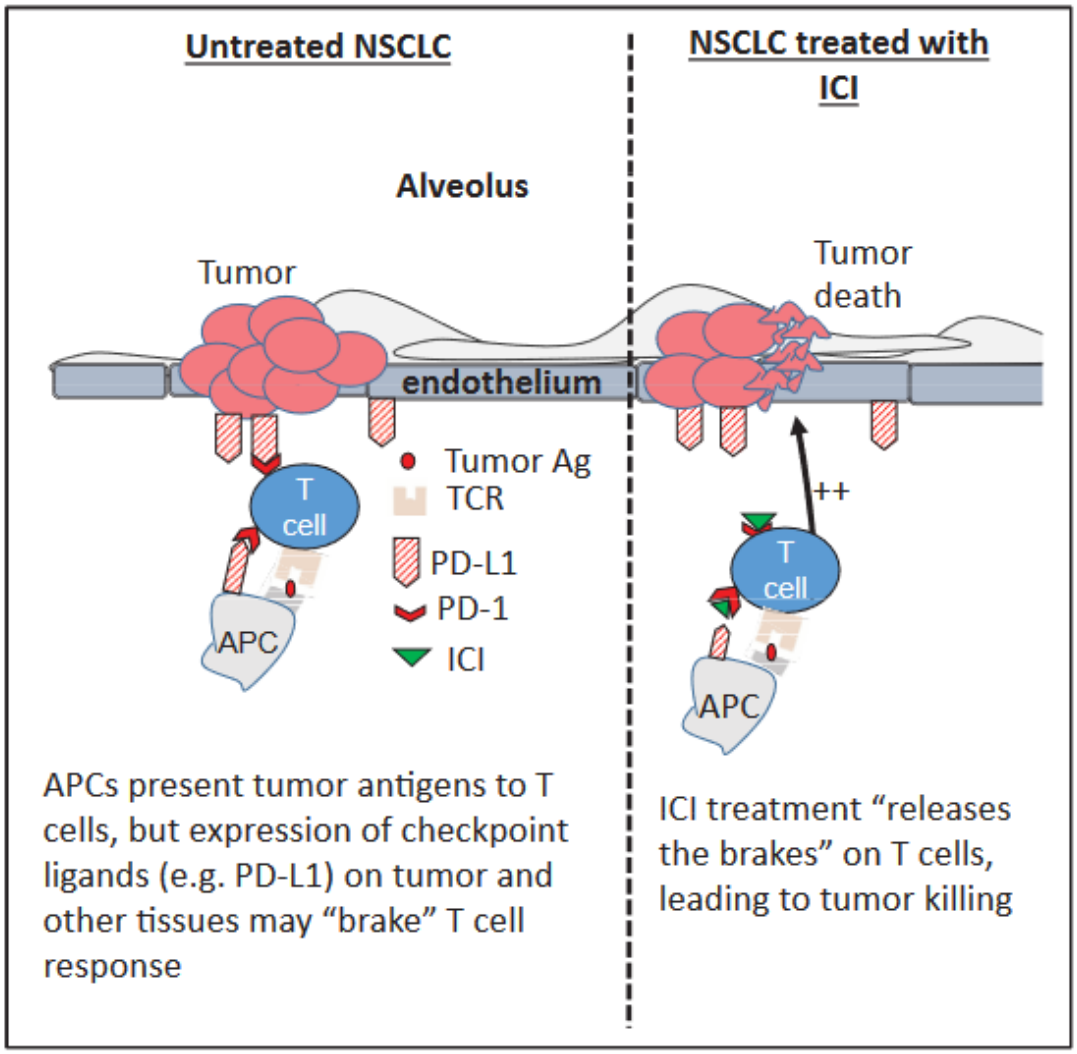


Figure 1 – *Schematic showing the actions of checkpoint PD-1 and its ligands PD-L1 in untreated and ICI-treated NSCLC. Ag = antigen; APC = antigen-presenting cell; ICI = immune checkpoint immunotherapy; NSCLC = non-small cell lung cancer; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1; TCR = T-cell receptor.*

Monoclonal antibodies targeting PD-1(eg. nivolumab, pembrolizumab), CTLA-4 (ipilimumab), or PD-L1(eg, durvalumab, atezolizumab, avelumab) have

been studied in late phase clinical trials and demonstrated significant improvements in PFS and OS compared with second-line chemotherapy. Based on these results, anti-PD-1/PD-L1 therapies are now the preferred second-line therapy for advanced NSCLC and even as first-line therapy in certain scenarios.

However, along with tumor killing, ICIs can also cause a spectrum of toxicities that may be mediated by their immunologic mechanisms of action (ie,irAEs). Reported toxicities include colitis, hypophysitis, pneumonitis, thyroiditis, inflammatory arthritis and more. [100]

Checkpoint inhibitor pneumonitis (CIP) that occurs as a result of anti-PD-1/PD-L1 ICIs remains a rare but concerning complication. CIP is defined as the development of dyspnea and /or other respiratory signs / symptoms (including cough and desaturation with excertion) in the presence of new infiltrates on chest imaging and in the absence of new infection (based on expectorated sputum and /or BAL microbiology).

In a large retrospective cohort of patients treated with ICIs across tumor types, the overall incidence of CIP was 5% and 86% of cases improved with corticosteroids.

There have been no prospective trials [102] aimed at evaluating optimal treatment strategies for patients with CIP. Current guidelines56-58 and recommendations

are therefore based on case reports or small case series. The mainstay of management of CIP is corticosteroid therapy. High doses (typically 1-4 mg/kg) of prednisone/equivalent corticosteroids are initiated once a formal diagnosis has been made. Current guidelines recommend a dose of 1 mg/kg/d of prednisone for lower-grade (ie, grade 2) CIP and 2-4 mg/kg/d for higher-grade (ie, grade 3-4) CIP. Patients who remain without clinical improvement after 48 to 72 hours of corticosteroids are considered steroid refractory.

CIP is responsible for a spectrum of lung injuries from the acute phase (acute interstitial pneumonia) to the organizing (organizing pneumonia) and fibrotic phases (non specific interstitial pneumonia). In addition, changes consistent with hypersensitivity pneumonitis (HP) and nonspecific ground-glass opacities can also be seen.

DISCUSSION

Most novel antineoplastic agents have the potential to induce pulmonary toxicity, which involves primarily the lung parenchyma; the airways, pleura or pulmonary circulation are less frequently affected. The exact incidence of lung toxicity remains currently unclear; this is related to confounding factors, including pulmonary comorbidities and prior or concurrent use of other treatment modalities, such as radiation and antineoplastic drugs. The

clinical presentation of many drug-induced effects is similar; however, some present acutely, while others are insidious in their onset. In most instances the symptoms are confined to the lungs, while occasionally they may be part of a systemic syndrome. The most recognized clinical patterns consist of dyspnea without further specification and ILD, which requires the same diagnostic approach as in ILD of other causes. Lung toxicity may respond to appropriate treatment, however, fatalities have been reported.

Assessing the true incidence of DIPT (drug induced pulmonary toxicity) is quite challenging because of the complexity of its diagnosis and the limited number of cases reported.

According to a study assessed the incidence of severe DIPT in approximately 3% to 5% of patients with lung cancer but it rates as high as 10% have been reported in studies of combined chemotherapy and radiotherapy.

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.

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 maybe released into circulation. However, experiments on animals that were exposed to pneumotoxic agents (ie, para quat, bleomycin) revealed inconsistent patterns of serums changes in ACE levels 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 antineoplas tic 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.

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 93 pneumonia, and collagen vascular disease.

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.

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.

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.

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 recom mended to exclude infections; echocardiography, blood natriuretic peptide levels, and response to diuretics can assess the cardiac origin of pulmonary edema.

A single antineoplastic agent can generate different clinical, radiologic, and histologic patterns of DIPT and ILD represents the most frequent complication (70%).

Once other etiologies are excluded, and when radiologic and histologic findings are suggestive, the probability of DIPT is very high. The iden tification 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.

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.

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