Review

Therapy-induced Toxicity of the Lungs: An Overview

ANDRIANI G. CHARPIDOU, IOANNIS GKIOZOS, SOTIRIOS TSIMPOUKIS, DESPOINA APOSTOLAKI,
KALLIOPI D. DILANA, ELENI M. KARAPANAGIOTOU and KOSTAS N. SYRIGOS

*Oncology Unit, Third Department of Medicine, Athens School of Medicine,
Sotiria General Hospital, Athens, Greece*

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. 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.*

Pulmonary toxicity occurs as a complication in the treatment of lung cancer. With the current trends in lung cancer therapy, pulmonary toxicity is unavoidable. It is estimated that the frequency of this complication is anywhere between 10-30% depending on the type of treatment.

Anticancer agents for lung cancer have been implicated in lung injury and interstitial lung disease (ILD). ILD comprises histopathological patterns of acute lung injury (ALI), nonspecific interstitial pneumonitis (NSIP), diffuse

Correspondence to: Kostas N. Syrigos, MD, Ph.D. Ass. Professor and Head, Oncology Unit, Third Department of Medicine, Athens Medical School, Sotiria General Hospital, Building Z, 152 Mesogion Avenue, 115 27, Athens, Greece. Tel: +30 210 7475034, Fax +30 210 7781035, e-mail: knsyrigos@usa.net/ksyrigos@med.uoa.gr

alveolar damage (DAD), bronchiolitis obliterans with organizing pneumonia, eosinophilic pneumonia, and pulmonary hemorrhage (1). The clinical manifestations of disease range from cough and low-grade fever to serious severe dyspnea and respiratory failure. Understanding of the mechanisms involved is limited although it is considered to be a multistep process. Simultaneous or sequential use of drugs and a multimodality therapeutic approach make assessment of toxicity to a specific agent difficult.

This review focuses on cell injuring mechanisms, potential pulmonary toxicity of the novel antitumor agents for lung cancer (cytotoxic and targeted therapies) and future developments in the early detection or prediction of the candidates for ILD from the therapy.

To further investigate this topic, relevant studies were identified through Medline. The generic names of novel antineoplastic agents (docetaxel, gemcitabine, paclitaxel, irinotecan, gefinitib, erlotinib and bevacizumab) were used in the search. The key phrases pulmonary toxicity, dyspnea, pneumonitis, apoptosis and radiotherapy were used for better results. The references from the articles identified were also reviewed for additional sources.

Pathogenesis

Chemotherapeutic agents appear to affect both normal and neoplastic cells. Drug-associated lung injury results either from cellular dysfunction generating the cell-death mechanism (apoptosis) or by impairing the cell and tissue repair sequence.

Apoptotic dysfunction. The normal activation of apoptosis seems to play an important role in the remodeling of lung tissue after acute lung injury, for the clearance of excess epithelium and mesenchymal cells from resolving lesions (2, 3).

The type II pneumocyte is the stem cell of the alveolar epithelium and is primarily responsible for re-epithelization and the restoration of the integral alveolar architecture. During normal cell turnover or lung damage, these cells

divide and differentiate into the predominant alveolar type I pneumocytes (4). Widespread loss of integrity of non-neoplastic pneumocytes type I and II appears to be the primary cause of DAD (5).

Activation of the apoptotic procedure follows two fundamental pathways: the death receptor and the mitochondrial pathway. These two are intimately connected *via* caspase 8 and BID (BCL-2-interacting domain). Caspases, a family of cysteine proteases, can activate degradation enzymes that destroy the cell. The first pathway is initiated by cell surface receptor-mediated activation of caspase (Figure 1). The death receptors (Fas, tumor necrosis factor receptor-1 and tumour necrosis factor receptor-2) interact with soluble proteins or membrane-bound proteins such as the Fas ligand (FasL). FasL is a cell surface molecule expressed predominantly in activated T-lymphocytes and natural killer cells (6, 7). It is accumulated in soluble form at sites of tissue inflammation and has the potential to initiate the apoptosis of leukocytes, epithelial cells and other parenchymal cells (7-9). On the other hand, the mitochondrial pathway is composed of members of the B-cell leukemia (Bcl) family of proteins. The Bcl family has both proapoptotic members, such as Bcl-2 associate X protein (BAX), Bcl-2 associate K protein (BAK) and BID, and antiapoptotic members, such as B-cell leukemia 2 (Bcl-2). When cells are exposed to an apoptotic stimulus, for example anticancer drugs, radiation and reactive oxygen radicals, proapoptotic proteins are activated through posttranslational modifications or changes in their conformation. These proteins increase the permeability of the outer membrane of the mitochondria resulting in the release of cytochrome *c*. In the cytosol, cytochrome *c* activates a caspase cascade that ultimately leads to cell death (10).

Impaired repair. Members of the epidermal growth factor (EGF) family [*i.e.* EGF, transforming growth factor alpha (TGF-α)] are likely to be important regulators of epithelial repair by virtue of their ability to stimulate cell migration, proliferation, differentiation and survival. EGF belongs to a family of growth factors that exert their biological effect by binding to a transmembrane tyrosine kinase receptor epidermal growth factor receptor (EGFR also known as c-erB1). In the normal lung, the distribution of EGF and EGFR has been demonstrated by immunohistochemistry, with expression observed in the basal cell layer of the bronchial epithelium (11, 12) and in occasional type II alveolar pneumocytes (13).

Angiogenesis also plays a key role in wound healing. Normal wound repair generates an angiogenic response to deliver nutrients and inflammatory cells to the injured tissue. The mediators of wound angiogenesis include soluble factors such as vascular endothelial growth factor (VEGF), TNF-α, TGF-β, fibroblastic growth factor (FGF) and platelet-derived growth factor (PDGF) which have been identified in several wound models (14).

As EGF signaling and angiogenesis may represent an important mechanism that helps coordinate the process of recovery from lung injury (15, 16), it is possible that their inhibition would partly reduce the ability of pneumocytes to respond and repair. The alteration of repair mechanisms and/or abnormal apoptotic function leads to disruption of the alveolar-capillary membrane and clinical, pathological and radiographic manifestations of ALI.

Radiotherapy

Radiation can cause acute or chronic injury in non-neoplastic type I and II pneumocytes, endothelial cells and stromal fibroblasts (17). 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 (18). The injury of normal lung tissue depends on the total dose (19), dose received from the lung and mean lung dose (20). 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 (21). 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. 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 (22).

Novel Cytotoxic Drugs that Cause Pulmonary Toxicity

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 (23). The pattern of pulmonary toxicity by these agents is usually a non-specific interstitial pneumonitis, diffuse alveolar damage and pleural effusion (24).

Docetaxel. Docetaxel is a taxane derivative with activity in many solid tumors including breast, gastric, ovarian and NSCLC (25). 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.
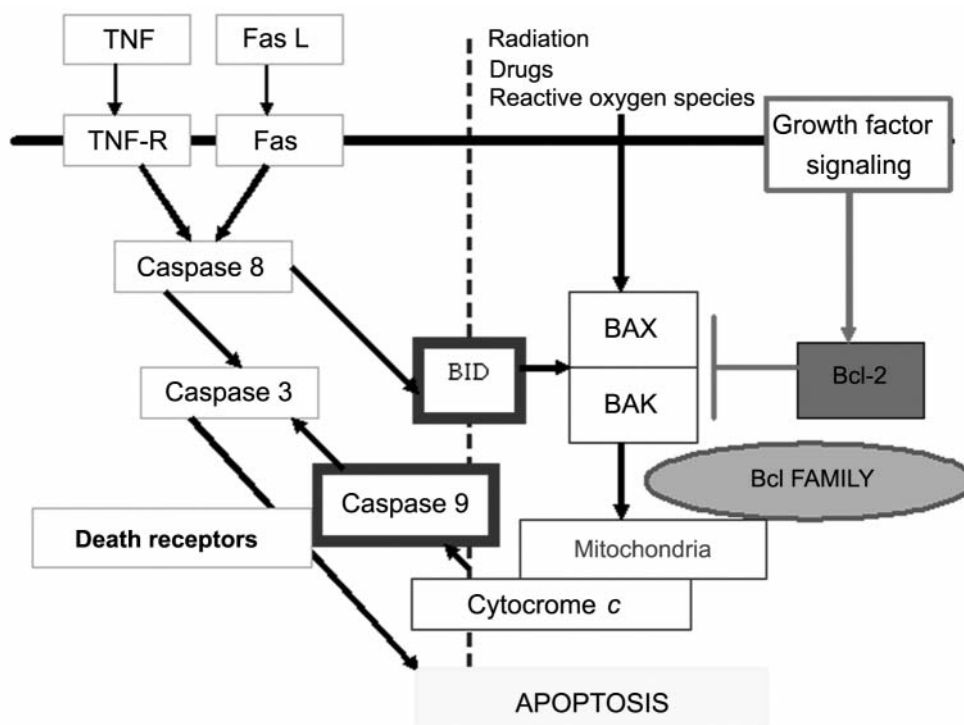
Figure 1. *Apoptotic pathways initiated by antineoplastic drugs and radiation therapy.*

Hypersensitivity reactions seem to be common (26, 27). 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 (28). 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 (24, 29, 30).

Docetaxel can cause acute interstitial pneumonitis when used as monotherapy or in combination with other treatments (29-35). The coadministration of docetaxel and gemcitabine can be correlated with an incidence as high as 23% of interstitial pneumonitis (36). Patients receiving docetaxel combined with gemcitabine or estramustine have occasionally suffered from diffuse alveolar damage (33, 37), which may even extend to adult respiratory distress syndrome (ARDS). Docetaxel-related pneumonitis usually responds to steroids (30, 31), 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 (33, 34, 38).

Although in some cases, docetaxel has been connected to edematous states after subsequent cycles, pulmonary edema is rare. In two studies, 20% and 62% of patients treated with docetaxel suffered from fluid retention which was typically peripheral, with pleural effusions reported less often. Notably, docetaxel appears to cause a capillary protein leakage independent of the presence or absence to interstitial lung disease (39). Animal studies of taxanes (paclitaxel and docetaxel) have shown increased albumin extravasation (40). Such toxicity is seen more often in patients receiving a total dose of 500 mg/m^2 (39). It has also been described in patients treated with docetaxel and thalidomide (35). Although diuretic treatments should not be used to resolve the edematous symptoms, steroids are indicated for the possible prevention or delay of the onset of symptoms if given before and after the administration of docetaxel (41). The usefulness of corticosteroids in combination therapies of docetaxel with radiotherapy or gemcitabine is uncertain and death may still ensue (30, 34, 37).

Non-cardiogenic pulmonary edema, or ALI, which may be precipitated by chemotherapeutic drugs is characterized by the presence of severe hypoxemia, bilateral alveolar infiltrates on chest radiographs and no evidence of left atrial hypertension/congestive heart failure (42). Exclusion of any infectious, metabolic, or cancer-related causes and a response to corticosteroids may further support such a diagnosis.

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 (43) and usually involves myelosuppression which is dose-limiting (44). Higher incidences of neutropenia can be seen more commonly in combination therapy rather than in first-line therapy (45).

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 (43, 46).

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 (47, 48). 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% (47, 49). Most of these cases could be managed by withdrawing gemcitabine and concomitant administration of diuretics and corticosteroids. More rare side-effects are interstitial lung fibrosis, pleural effusion, alveolar hemorrhage and various airway diseases with bronchospasm (24).

Acute interstitial pneumonitis related to this agent has been suggested to be a cytokine-mediated hypersensitivity reaction, due to its improvement after the administration of steroids (48). The response to corticosteroids in gemcitabine-associated interstitial lung disease (ILD) is inconsistent (27, 37, 48).

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% (46). An extreme elevation of the erythrocyte sedimentation rate (ESR) (>100 mm/h) at the time of diagnosis may be used as a guide for ARDS development, according to one study (50).

Although in general serious toxicity is not common with gemcitabine, it has been observed to cause some fatalities (47, 51). 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 (52). Recently, another study investigated the effects of gemcitabine on pulmonary function tests (PFTs) in patients with non-thoracic malignancies in a prospective setting. It showed that a subset (24%) of patients developed a clinically silent, reversible decrease in DLCO. Other lung function indices, such as forced vital capacity (FVC) and forced expiratory volume in one second, remained unaffected (53).

To reiterate, combination chemotherapy with docetaxel and gemcitabine is associated with a higher incidence of interstitial pneumonitis (36, 54). Additionally, diffuse alveolar damage or ARDS has been seen in those receiving docetaxel combined with gemcitabine (37, 54).

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 and advanced forms of Kaposi's sarcoma. Paclitaxel, used in the treatment of thoracic-based tumors such as breast and lung cancer is not known to cause significant pulmonary toxicity. However, symptoms occurring within the first five minutes after the first dose of drug therapy, characterized by dyspnea, chest tightness, bronchospasm, urticaria and hypotension, have been seen in up to 30% of patients in early trials which were attributed to a probable type I hypersensitivity reaction (55). These symptoms may be attributed to IgE antibody formation to paclitaxel or to its vehicle, or may be mediated by the release of histamine and other vasoactive substances. Premedication subsequently reduced the occurrence of such reactions to 1% (56). Pretreatment with an antihistamine, a corticosteroid and a histamine 2 blocker (H2-receptor antagonists) mainly prevents this reaction (57).

ILD in the form of nonspecific or hypersensitivity pneumonitis has been described in a number of case reports and clinical studies (58-63). On the other hand, multi-therapeutic studies found the incidence of pneumonitis to be very low (1%), even with radiation therapy (64). The symptoms and radiological findings of pulmonary infiltrates eventually resolved within 24-96 hours after steroid administration (64). 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 (65). On the whole, the incidence of interstitial pneumonitis is much higher if paclitaxel is given concurrently with radiation (47% of patients) (66), or with other agents that may potentially cause lung toxicity, including gemcitabine (33% of patients) (67, 68). 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 (58, 63).

Other rarer side-effects are DAD and lung fibrosis. DAD has been documented in two patients treated with paclitaxel and gemcitabine (69), and lung fibrosis has been seen in one patient treated with paclitaxel and carboplatin (70).

A delayed-type hypersensitivity reaction involving immunological and non-immunological mechanisms has been proposed as a possible pathophysiological mechanism (62) 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 (62). Protracted lymphocytopenia can be seen for up to three months, which may invite opportunistic infections to arise accounting for the pulmonary infiltrates (66).

With regard to PFTs, paclitaxel may impair FVC and DLCO, which may decrease (71). No relationship has been established between changes in PFTs and the incidence of acute or late pulmonary toxicity.

Irinotecan. Irinotecan is an antineoplastic agent of the topoisomerase I inhibitor class. Irinotecan is usually used in the treatment of colorectal cancer and is known to cause pneumonitis, whether alone or in combination with other drugs or radiotherapy (72-74). However, severe pulmonary events are infrequent. In clinical studies evaluating the weekly dosage schedule, NCI-CTC (National Cancer Institute-Common Toxicity Criteria, version 3.0) dyspnea grade 3 or 4 was reported in 4% of patients. Over half of the patients with dyspnea had lung metastases, which made it difficult to clarify if irinotecan was the culprit. However, in those who had been exposed to 5-fluorouracil (5-FU), pulmonary toxicity was reported in >20% of the patients given irinotecan (75, 76).

Interstitial pneumonitis, which responded to steroids, has been described in a few case reports (72, 77). A low incidence of pneumonitis at 1.8% was found in the early Japanese trials although fatalities have been described. It is rather difficult to assess clearly the exact contribution of irinotecan to these symptoms as the patients had lung tumors or other pulmonary comorbidities (78, 79). It is clear that the incidence of pneumonitis is higher if irinotecan is combined with paclitaxel (12.5% of patients) (65) or with radiotherapy (56% of patients) (73). Combination chemotherapy with cisplatin and irinotecan and concurrent radiotherapy have been correlated to increased levels of pulmonary fibrosis (80, 81).

Multimodality Therapy in Lung Cancer and Pulmonary Toxicity

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 (NCI-CTC Grade 3) pneumonitis, in 47% of the patients, in concurrent administration with radiotherapy (23).

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 (62). 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 (80). Serious pneumonitis (NCI-CTC 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 (82).

Pemetrexed, a new multitarget antifolate, is currently used in malignant pleura mesothelioma and in first and second-line treatment of NSCLC (83). When this agent is combined with platinum based chemotherapy and radiation, it may be associated with fatal pneumonitis (84).

Targeted Therapies and Pulmonary Toxicity

Several studies of the last decade have indicated the pivotal role of angiogenesis and EGFR activation in tumor growth and metastatic dissemination (85). 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) (namely gefinitib and erlotinib) have been used as salvage treatment in refractory NSCLC (83, 86, 87). VEGF-TKIs (namely sorafenib and sunitinib) (88) and monoclonal antibodies against the VEGF receptor VEGFR (bevacizumab) (89) are combined with chemotherapy in standard first-line treatment or in phase II and III first- and second-line clinical trials in NSCLC.

Treatment with gefinitib and erlotinib has been correlated with interstitial pneumonitis in 1% and 0.8% of treated patients (90, 91). Symptoms such as dyspnea, cough and low-grade fever, start from day five up to nine months after starting therapy (92). 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 (5, 93). However, further research to elucidate the key cell types involved is needed.

Monoclonal antibodies are used in the treatment of various hematopoietic malignancies and solid tumors. Most recently, bevacizumab has been used in lung cancer (83) and has been correlated with serious and fatal hemoptysis (94), 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).

Supportive and Prophylactic Treatment in Lung Cancer Patients

Chemotherapy regimens are dose limited by their adverse effect on bone marrow and myelosuppression. Colony-stimulating growth factors (G-CSF) (*e.g.* filgrastim and pegfilgrastim) are of great importance in the supportive care of cancer patients. They are effective in reducing the nadir and duration of neutropenia by permitting the optimum dose intention when necessary (96). Pulmonary injury has been described with the use of marrow stem cell growth factor (97). Since in all the reports the pulmonary symptoms started during or after neutropenia recovery, it appears that the proposed mechanism of toxicity is mediated by neutrophilic invasion into the lungs with release of cytokines. Capillary-leak syndrome and ALI are the pathological patterns displayed. Since most cases have been reported as recurrent exacerbation by G-CSF of chemotherapy-related pulmonary toxicity, it is possible that the stem-cell growth factors may strengthen the lung toxicity of several chemotherapeutic agents (42, 97). Given the importance of neutrophils in the onset of toxicity, high-risk patients must be under close monitoring and should discontinue G-CSF administration as soon as the leukocyte count rises to 1,000 cells/μl (97).

Positron-emission Tomography (PET)

The increased metabolic activity of tumors sites can be demonstrated by PET scan. This novel imaging technique has proved its effectiveness in lung cancer staging and the current literature is focusing on other serviceable uses. The accumulation of cells and cytokines as well as the generation of the apoptotic mechanism after lung injury suggest alteration of the metabolic activity of the lung cells. In a small, but very interesting study by Hassaballa *et al.* (98) in lung cancer patients after radiation and chemotherapy, PET distinguished changes in the shielded normal lung tissue after treatment. Imaging with PET may provide an early

barometer of pulmonary toxicity. Further investigation is needed, but based on these early data, this novel imaging tool could prove to be useful in monitoring or even predicting high risk patients for lung toxicity.

Summary and Future Prospects

Novel antineoplastic agents have the potential to induce pulmonary toxicity. The exact incidence of lung toxicity is currently unclear. The clinical presentation of many drug-induced effects is similar; however, some are presented acutely and are severe. The most recognizable clinical pattern consists of unspecified dyspnea and as this mimics lung cancer symptoms it has to be distinguished from disease progression. The development of ILD associated with anticancer treatment strategies is considered to be a multistep process and one of the initiating factors is likely to be the apoptosis of non-neoplastic type I and II pneumocytes. The mitochondrial mediated apoptotic pathway may also be involved in the pathology of the disease. The fact that only a small fraction of cancer patients develop lung toxicity from the unselective action of radiotherapy and chemotherapy implies that genetic predisposition, autoimmune conditions, or superimposed disease may be also involved. The fundamental requirement of up-to-date oncology is for patients to be treated as individuals with a specific care plan for each one. This need will be addressed in the future by pharmacogenomics. To date, relatively few pharmacogenomic findings have made a transition from "bench to bed-side" (99), but candidate gene approaches may lead to clinical tests for toxicity avoidance and efficacy prediction.

Conflict of Interest

The authors declare no conflict of interest.

References

1 Camus P, Foucher P, Bonniaud P and Ask K: Drug-induced infiltrative lung disease. Eur Resp J *18*: 93-100, 2001.

2 Bardales RH, Xie SS, Schaefer RF and Hsu SM: Apoptosis is the major pathway responsible for the resolution of type II pneumocytes in acute lung injury. Am J Pathol *149*: 845-852, 1996.

3 Polunovsky VA, Chen B, Henke C, Snover D, Wendt C, Ingbar DH and Bitterman PB: Role of mesenchymal cell death in lung remodeling after injury. J Clin Invest *92*: 388-397, 1993.

4 Fehrenbach H: Alveolar epithelial type II cell: defender of the alveolus revisited. Respir Res *2*: 33-46, 2001.

5 Camus P, Kudoh S and Ebina M: Interstitial lung disease associated with drug therapy. Br J Cancer *91*: S18-S23, 2004.

6 Nagata S and Golstein P: The Fas death factor. Science *267*: 1449-1456, 1995.

7 Park DR, Thomsen AR, Frevert CW, Pham U, Skerrett SJ, Kiener PA and Liles WC: Fas (CD95) induces proinflammatory cytokine responses by human monocytes and monocyte-derived macrophages. J Immunol *170*: 6209-6216, 2003.

8 Hagimoto N, Kuwano K, Miyazaki H, Kunitake R, Fujita M, Kawasaki M, Kaneko Y and Hara N: Induction of apoptosis and pulmonary fibrosis in mice in response to ligation of Fas antigen. Am J respire Cell Mol Biol *17*: 272-278, 1997.

9 Hagimoto N, Kuwano K, Inosima I, Nakamura N, Fujita M, Maeyama T and Hara N: TGF-b1 as an enhancer of Fas-mediated apoptosis of lung epithelial cells. J Immunol *168*: 6470-6478, 2002.

10 Reed JC: Proapoptotic multidomain Bcl-2/Bax-family proteins: mechanisms, physiological roles, and therapeutic opportunities. Cell Death Differ *13*: 1378-1386, 2006.

11 Yoneda K: Distribution of proliferating-cell nuclear antigen and epidermal growth factor receptor in intraepithelial squamous cell lesions of human bronchus. Mod Pathol *7*: 480-486, 1994.

12 Polosa R, Prosperini G, Leir SH, Holgate ST, Lackie PM and Davies DE: Expression of c-erB receptors and ligands in human bronchial mucosa. Am J Respir Cell Mol Biol *20*: 914-923, 1999.

13 Aida S, Tamai S and Sekiguchi N: Distribution of epidermal growth factor and epidermal growth factor receptor in human lung: immunohistocemical and immunoelectron-microscopic studies. Respiration *61*: 161-166, 1994.

14 Nissen NN, Polverini PJ, Koch AE, Volin MV, Gamelli RL and Di Pietro LA: Vascular endothelial growth factor mediates angiogenic activity during proliferative phase of wound healing. Am J Pathol *152*: 1445-1452, 1998.

15 Puddicomle SM, Polosa R, Richter A, Krishna MT, Howarth PH, Holgate ST and Davies DE: Involvement of the epithelial growth factor receptor in epithelial repair in asthma. FASEB J *14*: 1362-1374, 2000.

16 Bussat S, Eddahibi S, Caste A, Fataccioli V, Gouge M, Housset B, Adnot S and Maitre B: Expression and regulation of vascular endothelial growth factor in human pulmonary epithelial cells. Am J Physiol Lung Cell Mol Physiol *279*: 371-378, 2000.

17 Trott KM, Herrmann T and Kasper M: Target cells in radiation pneumopathy. Int J Radiat Oncol Biol Phys *58*: 463-469, 2004.

18 Monson JM, Stark P, Reilly JJ, Sugarbaker DJ, Strauss GM, Swanson SJ, Decamp MM, Mentzer SJ and Baldini EH: Clinical radiation pneumonitis and radiographic changes after thoracic radiation therapy for lung carcinoma. Cancer *82*: 842-850, 1998.

19 Bradley JD, Graham MV and Winter KW: Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small cell lung carcinoma. Int J Radiat Oncol Biol *61*: 318-328, 2005.

20 Seppenwoolde Y, Lebesque JV, de Jaeger K, Belderbos JS, Boersma LJ, Schilstra C, Henning GT, Hayman JA, Martel MK and Ten Haken RK: Comparing different NTCP models that predict the incidence of radiation pneumonitis. Int J Radiat Oncol Biol Phys *55*: 724-735, 2003.

21 Chen Y, Williams J, Ding I, Hernade E, Liu W, Smudzin T, Finkelstein JN, Rubin P and Okuniff P: Radiation pneumonitis and early circulatory cytokine markers. Semin Radiat Oncol *12*: 26-33, 2002.

22 Mauri D, Pentheroudakis G, Bafaloukos D, Samantas E, Syrigos KN, Kosmidis P, Fountzilas G and Pavlidis N: Non-small cell lung cancer in the young: a retrospective analysis of diagnosis, management and outcome data. Anticancer Res *26*: 3175-3181, 2006.

23 Onishi H, Kuriyama K, Yamaguchi M, Komiyama T, Tanaka S, Araki T, Nishikawa K and Ishihara H: Concurrent two-dimensional radiotherapy and weekly docetaxel in the treatment of stage III non-small cell lung cancer: a good local response but no good survival due to radiation pneumonitis. Lung Cancer *40*: 79-84, 2003.

24 Dimopoulou I, Bamias A, Lyberopoulos P and Dimopoulos MA: Pulmonary toxicity from novel antineoplastic agents. Ann Oncol *17*: 372-379, 2006.

25 Polyzos A, Syrigos KN, Stergiou J, Panopoulos C, Potamianou A, Vamvakas L and Georgoulias V: Phase I trial of weekly docetaxel with a 4-weekly cisplatin administration in patients with advanced gastric carcinoma. Cancer Chemother Pharmacol *55(5)*: 466-470, 2005.

26 Syrigos KN, Michalaki B, Alevyzaki F, Machairas A, Mandrekas D, Kindilidis K and Karatzas G: A phase-II study of liposomal doxorubicin and docetaxel in patients with advanced pancreatic cancer. Anticancer Res *22*: 3583-3588, 2002.

27 Syrigos KN, Dannos I, Dionellis G, Bofos I, Alamara C, Dimakou E, Stratakos G and Papiris S: Biweekly administration of docetaxel and gemcitabine as first-line therapy for non-small cell lung cancer: a phase II study. Anticancer Res *25*: 3489-3494, 2005.

28 Aamdal S, Wolff I, Kaplan S *et al*: Docetaxel (Taxotere) in advanced malignant melanoma: a phase II study of the EORTC Early Clinical Trials Group. Eur J Cancer *30A*: 1061-1064, 1994.

29 Etienne B, Perol M, Nesme P, Vuillermoz S, Robinet G and Guerin JC: Acute diffuse interstitial pneumonopathy following docetaxel (Taxotere). *Apropos* of 2 cases. Rev Mal Respir *15*: 199-203, 1998.

30 Merad M, Le Cesne A, Baldeyrou P *et al*: Docetaxel and interstitial pulmonary injury. Ann Oncol *8*: 191-194, 1997.

31 Karacan O, Eyuboglu FO, Akcay S and Ozyilkan O: Acute interstitial pneumopathy associated with docetaxel hypersensitivity. Oncology *27*: 563-565, 2004.

32 Wang CS, Yang KY and Perng RP: Life-threatening hypersensitivity pneumonitis induced by docetaxel (Taxotere). Br J Cancer *85*: 1247-1250, 2001.

33 Morris MJ, Santamauro J, Shia J Schwartz L, Vander Els N, Kelly K and Scher H: Fatal respiratory failure associated with treatment of prostate cancer using docetaxel and estramustine. Urology *60*: 1111, 2002.

34 Reed WL, Mortimer JE and Picus J: Severe interstitial pneumonitis associated with docetaxel administration. Cancer *94*: 847-853, 2002.

35 Behrens RJ, Gulley JL and Dahut WL: Pulmonary toxicity during prostate cancer treatment with docetaxel and thalidomide. Am J Ther 10: 228-232, 2003.

36 Kouroussis C, Mavroudis D, Kakolyris S, Voloudaki A, Kalbakis K, Souglakis J, Agelaki S, Malas K, Bozionelou V and Georgoulias V: High incidence of pulmonary toxicity of weekly docetaxel and gemcitabine in patients with non-small cell lung cancer: results of a dose-finding study. Lung Cancer *44*: 363-368, 2004.

37 Dunsford ML, Mead GM, Bateman AC, Cook T and Tung K: Severe pulmonary toxicity in patients treated with a combination of docetaxel and gemcitabine for metastatic transitional cell carcinoma. Ann Oncol *10*: 943-947, 1999.

38 Syrigos KN, Karapanagiotou L, Charpidou A, Dilana K, Dannos I, Dionellis G, Rigopoulou A, Georgatou N and Roussos C: Biweekly administration of docetaxel and gemcitabine for elderly patients with advanced non-small cell lung cancer (NSCLC). A phase II study. J Chemother *19(4)*: 438-443, 2007.

39 Semb KA, Aamdal S and Oian P: Capillary leak syndrome appears to explain fluid retention in cancer patients who receive docetaxel treatment. J Clin Oncol 16: 3426-3432, 1998.

40 Bronstad A, Berg A and Reed RK: Effects of the taxanes paclitaxel and docetaxel on edema formation and interstitial fluid pressure. Am J Physiol Heart Circ Physiol 287: H963-968, 2004.

41 Piccart MJ, Klijn J, Paridaens R, Nooij M, Mauriac L, Coleman R, Bontenbal M, Awada A, Selleslags J, Van Vreckem A and Van Glabbeke M: Corticosteroids significantly delay the onset of docetaxel-induced fluid retention: final results of a randomised study of the European Organization for Research and Treatment of Cancer Investigational Drug Branch for Breast cancer. J Clin Oncol 15: 3149-3155, 1998

42 Briasoulis E, Froudarakis M and Milionis HJ: Chemotherapy-induced non-cardiogenic pulmonary edema related to gemcitabine plus docetaxel combination with granulocyte colony-stimulating factor support. Respiration 67: 680-683, 2000.

43 Aapro MS, Martin C and Hatty S: Gemcitabine – a safety review. Anticancer Drugs 9: 191-201, 1998.

44 Stathopoulos GP, Syrigos KN, Polyzos A, Fountzilas G, Rigatos SK, Ziras N, Potamiannou A, Tsiakopoulos I, Androulakis N, Aravantinos G, Athanasiadis A, Papakotoulas P and Georgoulias V: Front-line treatment of inoperable or metastatic pancreatic cancer with gemcitabine and capecitabine: an intergroup, multicenter, phase II study. Ann Oncol 15: 224-229, 2004.

45 Angelaki S, Syrigos KN, Christophylakis C, Boukovinas I, Varthalitis J, Pavlakou G, Athanasiadis A, Kouroussis C, Vardakis N, Maltezakis G, Milaki G and Georgoulias V: A multicenter phase II study of the combination of irinotecan and gemcitabine in previously treated patients with small cell lung cancer. Oncology 66: 192-196, 2004.

46 Roychowdhury DF, Cassidy CA, Peterson P and Arning M: A report on serious pulmonary toxicity associated with gemcitabine-based therapy. Invest New Drugs 20: 311-315, 2002.

47 Pavlakis N, Bell DR, Millward MJ and Levi JA: Fatal pulmonary toxicity resulting from treatment with gemcitabine. Cancer 80: 286-291, 1997.

48 Vander Els NJ and Miller V: Successful treatment of gemcitabine toxicity with a brief course of oral corticosteroid therapy. Chest 114: 1779-1781, 1998.

49 Marruchella A, Fiorenzano G, Merizzi A, Rossi G and Chiodera PL: Diffuse alveolar damage in a patient treated with gemcitabine. Eur Respir J 11: 504-506, 1998.

50 Davidoff S, Shah RD and Arunabh T: Gemcitabine-induced respiratory failure associated with elevated erythrocyte sedimentation rate (ESR). Respir Med 100: 760-763, 2006

51 Gupta N, Ahmed I, Steinberg H, Patel D, Nissel-Horowitz S and Mehrotra B: Gemcitabine-induced pulmonary toxicity. Case report and review of the literature. Am J Clin Oncol 25: 96-100, 2002.

52 Maas KW, van der Lee I, Bolt K, Zanen P, Lammers JW and Schramel FM: Lung function changes and pulmonary complications in patients with stage III non-small cell lung cancer treated with gemcitabine/cisplatin as part of combined modality treatment. Lung Cancer 41: 345-351, 2003.

53 Dimopoulou I, Efstathiou E, Samakovli A, Dafni U, Moulopoulos LA, Papadimitriou C, Limperopoulos P, Kastritis E, Roussos C and Dimopoulos MA: A prospective study on lung toxicity in patients treated with gemcitabine and carboplatin: clinical, radiological and functional assessment. Ann Oncol 15: 1250-1255, 2004.

54 Syrigos KN, Konstantinou M, Sepsas E, Papamichales G, Loulias A, Belenis I, Skottis I, Charpidou A and Roussos C: Biweekly administration of docetaxel and gemcitabine as adjuvant therapy for stage II and IIIA non-small cell lung cancer: a phase II study. Anticancer Res 27(4C): 2887-2892, 2007.

55 Rowinsky EK and Donehower RC: Paclitaxel (Taxol). N Engl J Med 332: 1004-1014, 1995.

56 Gonzalez ID, Saez RS, Rodilla EM et al: Hypersensitivity reactions to chemotherapy drugs. Allergiol Immunol Clin 15: 161-181, 2000.

57 Bookman MA, Kloth DD, Kover PE, Smolinsky S and Drols RF: Short-course intravenous prophylaxis for paclitaxel-related hypersensitivity reactions. Ann Oncol 8(6): 611-614, 1997.

58 Goldberg HL and Vannice SB: Pneumonitis related to treatment with paclitaxel. J Clin Oncol 13: 534-535, 1995.

59 Schweitzer VG, Juillard GJ, Bajada CL and Parker RG: Radiation recall dermatitis and pneumonitis in a patient treated with paclitaxel. Cancer 76: 1069-1072, 1995.

60 Wong P, Leung AN, Berry GJ, Atkins AK, Montoya GJ, Ruoss JS and Stockdale EF: Paclitaxel-induced hypersensitivity pneumonitis: radiographic and CT findings. AJR Am J Roentgenol 176: 718-720, 2001.

61 Taniguchi N, Shinagawa N, Kinoshita I, Nasuhara Y, Yamazaki K, Yamagushi E, Akita H and Nishimura M: A case of paclitaxel-induced pneumonitis. Nihon Kokyuki Gakkai Zasshi 42: 158-163, 2004.

62 Fujimori K, Yokoyama A, Kurita Y, Uno K and Saijo N: Paclitaxel-induced cell-mediated hypersensitivity pneumonitis. Diagnosis using leukocyte migration test, bronchoalveolar lavage and transbronchial lung biopsy. Oncology 55: 340-344, 1998.

63 Ramanathan RK, Reddy VV, Holbert JM and Belani CP: Pulmonary infiltrates following administration of paclitaxel. Chest 110: 289-292, 1996.

64 Khan A, McNally D, Tutschka PJ and Bilgrami S: Paclitaxel-induced acute bilateral pneumonitis. Ann Pharmacother 31: 1471-1474, 1997.

65 Yamada K, Ikehara M, Tanaka G, Nomura I, Oshita F and Noda K: Dose escalation study of paclitaxel in combination with fixed-dose irinotecan in patients with advanced non-small cell lung cancer (JCOG 9807). Oncology 66: 94-100, 2004.

66 Reckzeh B, Merte H, Pfluger KH, Pfab R, Wolf M and Havemann K: Severe lymphocytopenia and interstitial pneumonia in patients treated with paclitaxel and simultaneous radiotherapy for non-small cell lung cancer. J Clin Oncol 14: 1071-1076, 1996.

67 Thomas AL, Cox G, Sharma RA, Steward WP, Shields F, Jeyapalan K, Muller S and O'Byrne KJ: Gemcitabine and paclitaxel associated pneumonitis in non-small cell lung cancer: report of a phase I/II dose-escalating study. Eur J Cancer 36: 2329-2334, 2000.

68 Kosmidis PA, Kalofonos HP, Christodoulou C, Syrigos KN, Makatsoris T, Skarlos D, Bakogiannis C, Nicolaides C, Bafaloukos D, Bamias A, Samantas E, Xiros N, Boukovinas I, Fountzilas G and Dimopoulos MA: Paclitaxel and gemcitabine versus carboplatin and gemcitabine in patients with advanced non-small cell lung cancer. A phase III study of the Hellenic Cooperative Oncology Group. Annal Oncol 19(1): 115-122, 2008.

69 Kudrik FJ, Rivera MP, Molina PL, Maygarden S and Socinski Ma: Hypersensitivity pneumonitis in advanced non-small cell lung cancer patients receiving gemcitabine and paclitaxel: report of two cases and review of the literature. Clin Lung Cancer 4: 52-56, 2002.

70 Sotiriou C, van Houtte P and Klastresky J: Lung fibrosis induced by paclitaxel. Support Care Cancer *6*: 68-71, 1998.

71 Robert F, Childs HA, Spencer SA, Redden DT and Hawkins MM: Phase I/IIa study of concurrent paclitaxel and cisplatin with radiation therapy in locally advanced non-small cell lung cancer: analysis of early and late pulmonary morbidity. Semin Radiat Oncol *9(2 Suppl 1)*: 136-147, 1999.

72 Madarnas Y, Webster P, Shorter AM and Bjarnason GA: Irinotecan-associated pulmonary toxicity. Anticancer Drugs *11*: 709-713, 2000.

73 Yamada M, Kudoh S, Hirata K, Nakajima T and Yoshikawa J: Risk factors of pneumonitis following chemoradiotherapy for lung cancer. Eur J Cancer *34*: 71-75, 1998.

74 Souglakos J, Syrigos KN, Potamianou A, Polyzos A, Boukovinas I, Androulakis N, Kouroussis Ch, Vardakis N, Christophilakis Ch, Kotsakis A and Georgoulias V: Combination of irinotecan (CPT-11) plus oxaliplatin (L-OHP) as first-line treatment in locally advanced or metastatic gastric cancer: a multicentre phase II trial. Ann Oncol *15(8)*: 1204-1209, 2004.

75 Rothenberg ML, Eckardt JR, Kuhn JG *et al*: Phase II trial of irinotecan in patients with progressive or rapidly recurrent colorectal cancer. J Clin Oncol *14*: 1128-1135, 1996.

76 Pitot HC, Wender DB, O'Connell MJ *et al*: Phase II trial of irinotecan in patients with metastatic colorectal carcinoma. J Clin Oncol *15*: 2910-2919, 1997.

77 Michielin O, Udry E, Periard D *et al*: Irinotecan-induced interstitial pneumonia. Lancet Oncol *5*: 322-324, 2004.

78 Fukuoka M, Niitani H, Suzuki A *et al*: A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small cell lung cancer. J Clin Oncol *10*: 16-20, 1992.

79 Masuda N, Fukuoka M, Kusunoki Y *et al*: CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small cell lung cancer. J Clin Oncol *10*: 1225-1229, 1992.

80 Ohe Y, Yamamoto S, Suzuki K, Hojo F, Kakinuma R, Matsumoto T, Ohmatsu H and Nishiwaki Y: Risk factors of treatment-related death in chemotherapy and thoracic radiotherapy for lung cancer. Eur J Cancer *37*: 54-63, 2001.

81 Pectasides D, Samantas E, Fountzilas G, Briasoulis E, Kosmidis P, Skarlos D, Dimopoulos MA, Kalofonos HP, Economopoulos T and Syrigos KN: Combination chemotherapy with cisplatin, etoposide and irinotecan in patients with extensive small cell lung cancer: a phase II study of the Hellenic Co-operative Oncology Group. Lung Cancer *58(3)*: 355-361, 2007.

82 Hirose T, Mizutani Y, Ohmori T, Ishida H, Hosaka T, Ando K, Shirai T, Okuda K, Ohnishi T, Horichi N, Kubota H and Adachi M: The combination of cisplatin and vinorelbine with concurrent thoracic radiation therapy for locally advanced stage IIIA or IIIB non-small cell lung cancer. Cancer Chemother Pharmacol *58(3)*: 361-367, 2006.

83 Gkiozos I, Charpidou A and Syrigos KN: Developments in the treatment of non-small cell lung cancer. Anticancer Res *27(4C)*: 2823-2827, 2007.

84 Allen AM, Czerminska M, JannePA, Sugarbaker DJ, Bueno R, Harris JR, Court L and Baldini EH: Fetal pneumonitis associated with intensity modulated radiation therapy for mesothelioma. Int J Radiat Oncol Biol Phys *65*: 640-645, 2006

85 Bozec A, Fischel JL and Milano G: Epidermal growth factor receptor/angiogenesis dual targeting: preclinical experience. Curr Opin Oncol *18*: 330-334, 2006.

86 Shepherd FA, Pareira JR, Cluleanu TE, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabárbara P and Seymour L, for the National Cancer Institute of Canada Clinical Trials Group: Erlotinib in previously treated non-small cell lung cancer. N Engl J Med *353*: 123-132, 2005.

87 Manegold C: Gefitinib (Iressa™, ZD 1839) for non-small cell lung cancer (NSCLC): recent results and further strategies. Adv Exp Med Biol *532*: 247-252, 2003.

88 Grinelli C, Maione P, Del Gaizo F, Colantuoni G, Guerriero C, Ferrara C, Nicolella D, Comunale D, De Vita A and Rossi A: Sorafenib and sunitinib in the treatment of advanced non-small cell lung cancer. Oncologist *12*: 191-200, 2007.

89 Sandler A, Gray R, Perry MC, Schiller JH, Dowlati A, Lilenbaum R and Johnson DH: Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. N Engl J Med *355*: 2542-2550, 2006.

90 Evans TL: Highlights from the tenth conference on lung cancer. Oncologist *9*: 232-238, 2004.

91 Genetech Pharmaceuticals Corporation: Tarceva (erlotinib) prescribing information. San Francisco, CA, pp. 1-2, 2004.

92 Sumpter K, Harper-Wynne C and O'Brien M: Acute lung injury as an adverse event of gefitinib. Lung Cancer 43: 367-368, 2004.

93 Danson S, Backhall F, Hulse P and Ransom M: Interstitial lung disease in lung cancer: separating disease progression from treatment effects. Drug Saf *28*: 103-113, 2005.

94 Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, Langer CJ, DeVore RF, Gaudreault J, Damico LA, Holmgren E and Kabbinavar F: Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small cell lung cancer. J Clin Oncol *22*: 2184-2191, 2004.

95 Herbst RS and Sandler AB: Non-small cell lung cancer and antiongiogenetic therapy: what can be expected of bevacizumab? Oncologist *9*: 19-26, 2004.

96 Polyzos A, Tsavaris N, Kosmas C, Gogas H, Vadiaka M, Markopoulos C, Giannopoulos A, Kalahanis N, Stamatiadis D, Kouraklis G, Karatzas G, Liapis C and Syrigos KN: Docetaxel and epirubicin supported by granulocyte colony-stimulating factor first-line in advanced breast cancer. Anticancer Res *23(3C)*: 2917-2923, 2003.

97 Azoulay E, Attalah H, Harf A, Schlemmer B and Delclaux C: Granulocyte colony-stimulating factor on neutrophil-induced pulmonary toxicity: myth or reality? Chest *120*: 1695-1701, 2001.

98 Hassaballa HA, Cohen ES, Khan AJ, Ali A, Bonomi P and Rubin D: Positron-emission tomography demostrates radiation-insuded changes to non-radiated lungs in lung cancer patients treated with radiation and chemotherapy. Chest *128*: 1448-1452, 2005.

99 Walgren RA, Meucci MA and McLeod HL: Pharmacogenomic discovery approaches: will the real gene stand up? J Clin Oncol *23*: 7342-7349, 2005.