LEADING ARTICLE

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Interstitial Lung Disease in Lung Cancer

Separating Disease Progression from Treatment Effects

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Abstract

Lung cancer often develops in individuals with pre-existing pulmonary and cardiac pathology. Many of these individuals with pre-existing pathology are also at risk of occupational lung disease. New and worsening symptoms can be secondary to pre-existing pathology, progressive cancer or treatment. Pulmonary toxicity, including interstitial lung disease, following radiotherapy and conventional cytotoxic chemotherapy (e.g. cyclophosphamide, bleomycin), has been recognised for many years. Pulmonary toxicity also occurs with the newer classes of cytotoxic agents, including the deoxycytidine analogue gemcitabine. A small percentage (0.88%) of patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib have developed interstitial lung disease. This complication has been reported at a higher frequency in Japanese patients than in US patients (1.9% vs 0.34%, respectively) and in those with pre-existing pulmonary fibrosis. This review discusses the difficulties in both recognition and treatment of gefitinib-associated interstitial lung disease. Symptoms are vague, such as dyspnoea, cough and fever and can be difficult to differentiate from progressive disease, co-existing morbidity and new pulmonary pathology. Diagnosis is, therefore, by rigorous investigation to exclude all other differential diagnoses. Treatment, at present, is supportive and includes discontinuation of gefitinib, oxygen supplementation, high-dose corticosteroids and antibacterials.

Lung cancer accounts for one-third of all cancer deaths worldwide.[1] Lung cancer often develops in individuals with pre-existing pulmonary pathology and the development of interstitial lung disease (ILD) during or after therapy often poses significant diagnostic problems.

ILD is defined as 'a heterogeneous group of lung parenchyma infiltrations, which often result in similar pathophysiologic outcomes: extensive alveolar wall fibrosis, pulmonary hypertension and congestive heart failure'.[2] The development of ILD during or after therapy (e.g. radiotherapy and chemotherapy) often poses significant diagnostic problems. Clinical features of ILD include increasing dyspnoea, cough and fever, thus, diagnosis may be hampered by the presence of infection or progressive tumour, which have similar features. High-resolution computed tomography (HRCT) features of ILD include pulmonary reticular change and ground glass opacity, which are non-specific and may not readily point towards a precise aetiological factor. Methods for better diagnosis and a greater understanding of ILD pathogenesis are likely to be the key to understanding this entity.

The interstitial pulmonary toxicity that may occur following radiotherapy and cytotoxic chemotherapy for lung cancer has been recognised for many years and has been previously reviewed else-

Table I. Causes and treatment of pulmonary symptoms in lung cancer patients

Cause	Treatment options
Progressive disease	
Increase in size of tumour	Radiotherapy, chemotherapy
Increase in pleural effusion	Pleural drain, chemotherapy
Pericardial extension	Pericardial drain, chemotherapy
Superior vena cava obstruction	Stent, radiotherapy, chemotherapy, anticoagulation, corticosteroids
Lymphangitic carcinomatosis	Corticosteroids, chemotherapy
Comorbidity	
Chronic obstructive pulmonary disease	Stop smoking, optimise lung function
Congestive cardiac failure	Stop smoking, optimise cardiac function
Smoking-related interstitial lung disease	Stop smoking, optimise lung function
Occupational lung disease	Consider changing occupation, optimise lung function
Environmental lung disease	Avoid cause, optimise lung function
Chest infection	Antibacterials, corticosteroids, physiotherapy
Pulmonary embolus	Anticoagulation
Drug-related symptoms (other than chemotherapy)	Consider stopping drug, optimise lung function
Surgery	
Reduced pulmonary reserve	Chest physiotherapy, breathing exercises
Surgery-related complications (arrhythmia)	Treat complication appropriately
Radiotherapy	
Acute respiratory distress syndrome	Corticosteroids, supportive treatment[a]
Pneumonitis	Corticosteroids, supportive treatment[a]
Fibrosis	Optimise lung function
Cytotoxic chemotherapy	
Cyclophosphamide-induced interstitial lung disease	Discontinuation of treatment, supportive treatment[a]
Bleomycin-induced pneumontis	Corticosteroids, supportive treatment
Bleomycin-induced fibrosis	Optimise lung function
Gemcitabine-induced acute dyspnoea	Corticosteroids, supportive treatment
Gemcitabine-induced severe pulmonary toxicity	Discontinuation of treatment, corticosteroids, diuretics

a Including oxygen supplementation (including ventilation), physiotherapy, breathing exercises, antibacterials as needed.

where.[3,4] There has been renewed interest in the diagnosis, pathophysiology and management of ILD because of its occurrence in a small percentage of patients treated with the epidermal growth factor receptor (EGFR) inhibitor gefitinib.[5-7] This review discusses the background of treatment-related ILD, with special reference to lung cancer treatment.

1. Co-Existing Morbidity in Lung Cancer Patients

The strong association of lung cancer with smoking usually results in lung cancer patients having other pulmonary or cardiac problems.[8,9] Table I summarises the possible causes of pulmonary symptoms in lung cancer patients and the treatment options. Smoking may be a trigger for ILD and several forms of smoking-related ILD have been recognised and described, such as respiratory bronchiolitis-associated ILD, pulmonary Langerhans' cell histiocytosis, idiopathic pulmonary fibrosis and desquamative interstitial pneumonia.[10] Some lung cancer patients have lung damage from occupational or environmental agents, for example asbestos, silica or coal dust, that result in asbestosis, silicosis or pneumoconiosis.[11,12] Lung cancer patients may also develop intercurrent infections or pulmonary emboli. Drug treatment of co-existing conditions may alter pulmonary function, such as lung fibrosis associated with amiodarone use, which is used for the treatment of cardiac arrhythmias.[4] Progressive lung cancer may be insidious in nature and patients may

present with symptomatic deterioration (cough, sputum, dyspnoea or haemoptysis) with worsening radiological features (pulmonary nodules, pleural effusion or lymphangitic carcinomatosis).[13] Thus, establishing a diagnosis of ILD in such circumstances may be difficult.

2. Treatment-Related Interstitial Lung Disease

2.1 Radiotherapy

Radiotherapy can cause acute and chronic ILD, that may be categorised into acute respiratory distress syndrome, pneumonitis or fibrosis, according to clinical symptoms and time of appearance. Radiation-induced pneumonitis is an inflammatory process with two distinct mechanisms of pathophysiology. The first is classical radiation-induced pneumonitis in which radiation-induced injury to capillary endothelial and epithelial lung cells results in an acute alveolitis. The inflammatory process leads to pulmonary fibrosis and is confined to the field of radiation. The second mechanism is sporadic radiation-induced pneumonitis or an 'out-of-field' response. This is thought to be an immunologically-mediated process resulting in bilateral lymphocytic alveolitis.

Although pathological changes in lung tissue occur in the initial 24–48 hours after radiation, the changes are undetectable both clinically and radiologically. Symptoms of acute radiation pneumonitis develop 1–6 months after completion of therapy and include dyspnoea, cough, pinkish-tinged sputum and fever. Severe reactions can result in dyspnoea, pleuritic chest pain, haemoptysis, acute respiratory distress and, rarely, death.[3] The characteristic feature of classical radiation-induced pneumonitis is a diffuse infiltrate corresponding to a previous radiation treatment field. Changes detected by computed tomography (CT) consistent with this occur in up to 50% of patients receiving high-dose external-beam radiation, but most patients are asymptomatic. In general, symptomatic radiation-induced pneumonitis develops in 5–15% of lung cancer patients.[14-16] Factors that affect the risk of damage to lung tissue include the volume of lung included in the field of radiation, the total radiation dose and the size and frequency of each fraction (individual dose) of radiotherapy, individual susceptibility to radiation, previous exposure to radiation, low performance status, concomitant chemotherapy and abrupt corticosteroid withdrawal.[17] Interestingly, the risk of radiation-induced pneumonitis has been shown to vary with radiation site.[18] The incidence of pneumonitis was 70% after radiation to the lower lung field compared with 20% for other sites. Guidelines for minimising the effects of radiotherapy with or without chemotherapy, which can potentiate radiation-induced damage (see section 2.2.3), have been produced and readers are referred to these.[19,20] Some serum markers, such as KL-6, surfactant protein A and transforming growth factor-β, can be increased in radiation-induced pneumonitis and could be used to differentiate between this and other causes of ILD. They could also potentially be used to monitor the severity and prognosis of radiation-induced pneumonitis;[21-24] however, none are presently recommended for routine clinical use. Corticosteroids are commonly used for the treatment of radiation-induced pneumonitis. Prednisolone is started at a dosage of 1 mg/kg/day upon diagnosis and is continued for several weeks and then tapered slowly. Ongoing trials are investigating the protective efficacy of the free radical scavenger, amifostine, prior to radiotherapy. Preclinical studies strongly support a protective effect of amifostine in radiation-induced toxicities in rodents and monkeys,[25] and phase II clinical results have suggested that amifostine may be effective in reducing the incidence of both acute and late radiation-induced toxicities.[26] Data from large randomised trials is needed to confirm clinical benefit and the recent phase III study evaluating the use of amifostine for the prevention of radiation-related toxicity in patients with advanced non-small-cell lung cancer (NSCLC) did not detect a lower incidence of pneumonitis in those who received amifostine and radiation compared with radiation alone.[27] Other agents that have been used for treatment of radiation-induced pneumonitis include azathioprine and ciclosporin (cyclosporine), but data regarding their efficacy is limited.[28,29]

2.2 Cytotoxic Chemotherapy

The occurrence of ILD with cytotoxic chemotherapy is well recognised and a wide range

of drugs have been implicated, including bleomycin[30], busulfan,[31] carmustine,[32] chlorambucil,[33] cyclophosphamide,[34] cytarabine,[35] docetaxel,[36] fludarabine,[37] fluorouracil,[38] gemcitabine,[39] irinotecan,[40] melphalan,[41] methotrexate,[42] mitomycin,[43] paclitaxel,[44] procarbazine,[45] and vinorelbine.[46] Of these agents, the majority of data relates to the use of bleomycin, cyclophosphamide and gemcitabine. These drugs are discussed in detail in the following sections. However, most reports of ILD are anecdotal and it can be difficult to give the precise incidence with each cytotoxic agent. What is clear is that ILD acquires particular importance in malignancies in which therapy is being delivered with curative intent. Pulmonary damage from cytotoxic agents probably arises from a combination of direct toxicity and from indirect inflammatory processes. For example, pre-clinical models of bleomycin-induced pulmonary toxicity show initial endothelial damage of the lung vasculature with oedema. This is followed by influx of inflammatory cells into the lung parenchyma and then fibroblasts that lead to the development of pulmonary fibrosis.[47]

2.2.1 Bleomycin

Bleomycin is the cytotoxic agent most often associated with ILD. Bleomycin use results in lung injury in 3–5% of treated patients, with an increased risk if the cumulative dose is >450 units.[4] The diagnosis of ILD can be difficult to establish. When bleomycin-related lung toxicity occurs, patients complain of dyspnoea, cough and occasionally fever. Pulmonary function tests show deterioration and HRCT of the thorax shows mid- and lower-lung ground glass opacities.[30] Ground glass opacities are seen with parenchymal changes in the lung. Bleomycin-induced pneumonitis can progress to fibrosis. Despite bleomycin-induced pulmonary toxicity having been described for years, there are no proven effective treatments, although high-dose corticosteroids are often administered. Rodent models[48] and anecdotal evidence support the use of corticosteroids; however, the responses seen could be because the underlying indication was in fact bronchiolitis obliterans with organising pneumonia (BOOP)/cryptogenic organising pneumonia (COP) or eosinophilic pneumonia, which are known to be responsive to corticosteroids.[49] Well-established animal models of bleomycin-induced pulmonary fibrosis have been used to assess other strategies, which could be used preventatively or as treatment for bleomycin-related pulmonary toxicity. Bleomycin-related toxicity in animal models is ameliorated using amifostine,[50] dexrazoxane,[51] ciclosporin,[52] curcumin,[53] captopril,[54] caspase inhibitors[55] and matrix metalloproteinase inhibitors.[56] However, there is no randomised data on such strategies in humans. When patients survive bleomycin-induced pneumonitis, they almost always recover completely with no residual radiographic or functional abnormalities.[30] Cyclophosphamide, doxorubicin and vincristine (CAV) and bleomycin were assessed for the treatment of small-cell lung cancer in one study,[57] but bleomycin was discontinued because of pulmonary toxicity. CAV remains a standard of care for small-cell lung cancer and bleomycin remains a key drug for the treatment of testicular cancer and Hodgkin's disease but is no longer used for the treatment of lung cancer.[30]

2.2.2 Cyclophosphamide

Cyclophosphamide is used to treat a variety of malignancies, including lung cancer. There appears to be no relationship between lung toxicity, which is usually diffuse alveolar damage (figure 1), and dose or duration of therapy. The onset of toxicity can be from 2 weeks to 13 years after administration. Discontinuation of treatment is typically associated with a good prognosis.[34]

2.2.3 Gemcitabine

Gemcitabine is a deoxycytidine analogue with anti-tumour activity in lung, bladder and pancreatic cancers. The efficacy of gemcitabine is further improved in NSCLC when gemcitabine is combined with a platinum agent.[58,59] Gemcitabine is well tolerated and the dose-limiting toxicity is myelosuppression. The commonest form of gemcitabine-associated pulmonary toxicity is dyspnoea that occurs within a few hours, lasts 1–6 hours and is believed to be secondary to bronchospasm. There are no associated radiographic changes or hypoxaemia and discontinuation of gemcitabine is usually not warranted.[60]

However, numerous cases of ILD called gemcitabine-induced severe pulmonary toxicity (GISPT) have also been reported. A recent systematic review

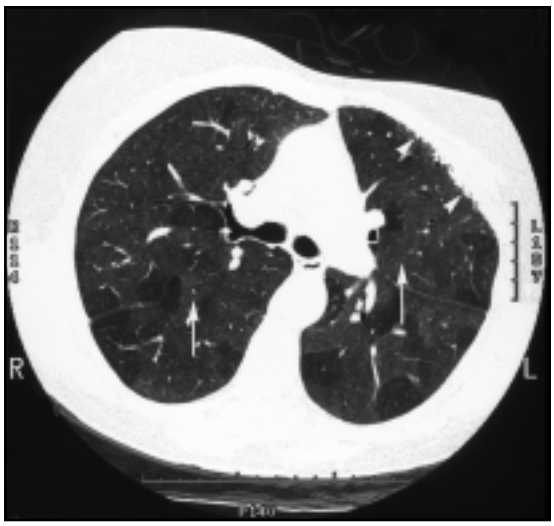

Fig. 1. Cyclophosphamide-induced interstitial lung disease, in a patient treated for recurrent breast cancer. High resolution computed tomography image at the level of the carina demonstrates bilateral ground glass opacity (arrows) in a geographical distribution secondary to a hypersensitivity reaction. Note the band of pulmonary fibrosis (arrowheads) adjacent to the left anterior chest wall that are caused by tangential beam radiotherapy to the left breast.

of reported cases of GISPT[39] found an incidence of 0–5%, with a mortality rate of 20%, in those who develop this complication. Risk factors, including previous pulmonary disease or previous thoracic irradiation, have been reported. Gemcitabine is a potent radiosensitizer, thus full-dose gemcitabine given concurrently with radiotherapy increases the risk of potentially life-threatening radiation-induced pneumonitis and oesophagitis. Subsequent studies have suggested that it is feasible to administer gemcitabine at lower doses with concurrent radiotherapy with predictable toxicity.[61] The optimum regimen for safe administration of gemcitabine with therapeutic doses of radiation has not yet been determined. The postulated pathology of GISPT is that of a cytokine-mediated inflammatory reaction, mixed exudative and fibrotic reaction, which particularly affects the alveolar capillary wall and creates an abnormal permeability of the alveolar membrane.[39] Clinical presentation is usually of a subacute clinical syndrome of dyspnoea and hypoxaemia, with signs of pulmonary oedema on examination. The main differential diagnosis is cardiogenic pulmonary oedema. The predominant radiographic pattern seen on chest radiograph is of reticulo-nodular interstitial infiltrates. An HRCT scan may show ground-glass opacities, thickened septal lines and reticular opacities (figure 2). Distribution of these lesions tends to be diffuse and bilateral but not necessarily symmetrical.[62] Treatment involves discontinuation of gemcitabine and the early initiation of supportive measures with oxygen. Corticosteroids and diuretics are also frequently used treatments, but other measures have been utilised including bronchodilators, expectorants, antibacterials and bed rest.

2.3 Gefitinib

Gefitinib has evoked a lot of interest because of its efficacy in advanced NSCLC and tolerability profile. Although potentially fatal ILD has been reported with gefitinib in a small proportion of patients, ILD does not appear to be a major adverse event with other targeted therapy, although clinical data continues to accrue and this may change. For example, two cases of interstitial pneumonitis thought to be induced by the c-kit tyrosine kinase inhibitor, imatinib, have recently been described,[63,64] and a case of trastuzumab-associated BOOP/COP has also been reported.[65] Erlotinib-related ILD has also been reported.[66]

The EGFR family regulates a complex system that plays an important role in the growth and sur-

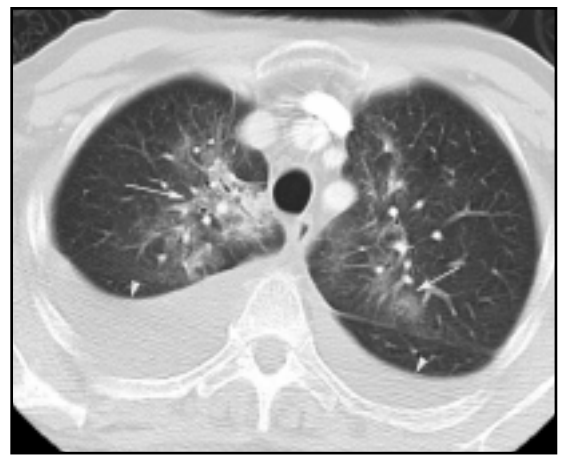

Fig. 2. Gemcitabine-induced severe pulmonary toxicity (GISPT) in a patient treated for pancreatic cancer. Transaxial computed tomography image of the upper lungs demonstrates bilateral perihilar ground glass opacity secondary to pulmonary oedema (arrows) and bilateral pleural effusions (arrowheads).

vival of many solid tumours, including NSCLC, through modulation of proliferation, angiogenesis, invasion, metastasis and apoptosis.[67] In NSCLC, EGFR overexpression has been correlated with reduced survival, greater risk of metastasis and more advanced disease by some groups,[68-70] but this remains controversial.[71]

Gefitinib is an orally-active EGFR tyrosine kinase inhibitor that blocks signal transduction pathways and has anti-tumour activity *in vivo*.[72] Phase I trials of gefitinib identified that the drug was active in advanced-stage pre-treated NSCLC.[73-76] Efficacy was also demonstrated in two randomised, double-blind, phase II, multicentre studies comparing two oral daily doses of gefitinib (250mg vs 500mg): the IDEAL (Iressa Dose Evaluation in Advanced Lung Cancer) 1 and 2 trials.[77,78] These trials, in recurrent or refractory NSCLC (post-platinum chemotherapy), reported objective response rates of 9–18% and symptom improvement rates of 40.3–43.1%, with a median time to onset of improvement of 8–10 days, with a dosage of 250 mg/day.

In July 2002, gefitinib was licensed in Japan for the treatment of patients with NSCLC previously treated with platinum-based chemotherapy.[79] In May 2003, gefitinib received accelerated approval by the US FDA as a monotherapy treatment for patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies.[80]

Based on the evidence that gefitinib monotherapy was well tolerated with a different tolerability profile and mechanism of action to conventional chemotherapy, and following on from phase I combination trials,[81,82] two large randomised phase III trials were conducted in chemotherapy-naive, stage III and IV NSCLC patients:[83,84] the INTACT (IRESSA™ [1] NSCLC Trial Assessing Combination Treatment) 1 and 2 trials. In total, 2130 patients were randomised to receive a dosage of gefitinib (250mg or 500mg daily) or placebo in combination with either gemcitabine plus cisplatin or carboplatin plus paclitaxel. Results from these studies showed no additional benefit from adding gefitinib, at either dosage, to chemotherapy. Consequently, gefinitib is only recommended for use as monotherapy at this time. A recent phase III trial has suggested that the combination of gemcitabine with gefitinib is safe, with good disease control, and should be studied further. However, the levels of toxicity when gefitinib is combined with vinorelbine is unacceptable.[85] Two trials investigating the oral EGFR tyrosine kinase inhibitor erlotinib (Tarceva™; OSI774) in combination with gemcitabine and cisplatin (the TALENT trial [Tarceva™ Lung Cancer Investigation]) and paclitaxel and carboplatin (the TRIBUTE trial [Tarceva™ Responses in Conjunction with Paclitaxel and Carboplatin]) as first-line treatment in NSCLC have recently been reported,[86,87] and the data on the incidence of ILD is awaited. In addition, two studies have demonstrated that somatic mutations of EGFR may correlate with clinical dramatic (major) responses to gefitinib therapy.[88,89] This needs to be confirmed in larger patient series but may allow EGFR inhibitors to be offered to a subset of patients in whom response is more likely.

Common adverse events associated with gefitinib treatment include diarrhoea, acneiform rash, dry skin, nausea, vomiting and anorexia.[77,78] Most toxicities are common toxicity criteria grade 1 or 2 and do not require active management with other therapies. However, case reports have been published of major, life-threatening diffuse alveolar damage/ILD associated with gefitinib, usually occurring during the first 3 months of treatment.[5-7,90] Gefitinib-related ILD is a complex disease that is described, investigated and treated in different ways by different physicians. Symptoms may include the acute onset of progressive dyspnoea, with or without cough or low-grade fever. These symptoms typically worsen rapidly and patients require hospitalisation. Inspiratory crackles may be audible on auscultation and the patient becomes increasingly hypoxic.[5] The main differential diagnoses are infectious pneumonia, radiation-induced pneumonitis and lymphangitic carcinomatosis. Pathological examination of post mortem cases has shown diffuse alveolar damage with hyaline membrane formation, epithelial desquamation, oedema, fibroblastic proliferation of the alveolar walls and neutrophilic influx into the alveolar spaces.[5]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

The mechanism of injury has not yet been fully elucidated. However, EGFR is known to be upregulated in acute lung injury,[91] which suggests that the receptor may play a part in normal repair following injury. Therefore, it is conceivable that the inhibition of EGFR may lead to a syndrome of exacerbated pulmonary injury, especially in patients with pulmonary comorbidities.[6] In a rodent model of bleomycin-induced pulmonary fibrosis, the addition of gefitinib was shown to augment the fibrosis.[92] The finding that some patients who initially took gefitinib with no signs of ILD, and then stopped therapy, subsequently developed ILD upon recommencement of the drug may indicate that immune-related mechanisms contribute to ILD.[6] Thoracic HRCT demonstrates ground glass opacities,[5,7] sometimes with interlobular septal thickening[7] (figure 3).[93] Diagnosis is made by rigorous exclusion of all other differential diagnoses of ILD as well as progressive disease and infection. This is a complex exclusion and will involve at least a thorough history, clinical examination, comparison of present and previous radiological examinations and bronchoalveolar lavage, to exclude infection and pulmonary haemorrhage, and transbronchial biopsy. Biopsy changes include diffuse alveolar damage and neutrophilic influx. Treatment of ILD in these cases may involve discontinuation of gefitinib, oxygen supplementation, high-dose corticosteroids and antibacterials.[5,7]

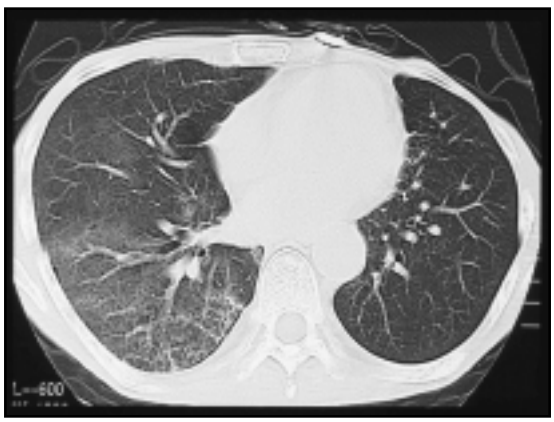

Fig. 3. Gefitinib-induced interstitial lung disease. Transaxial computed tomography image demonstrates ground glass opacity in both lungs with mild bronchiectasis but no loss of volume (reproduced from AstraZeneca,[93] with permission).

It is worth noting that ILD was not apparent in the pre-clinical toxicology studies of gefitinib.[67] Grade III/IV dyspnoea was described in up to 12.5% of patients in phase I trials, but this was not clearly drug related and could be attributed to advancing disease.[73-76] Worldwide, the incidence of ILD with gefitinib is 0.88% at a dosage of 250 mg/day[77,78,83,84,94] (table II). Approximately one-third of ILD cases are fatal.[80]

Predisposing factors to gefitinib ILD are being sought. The incidence seems to be higher in Japanese patients, with 1.9% developing ILD in Japanese postmarketing experience compared with 0.34% in the US expanded access programme.[94] In two recently published series, Hotta et al.[95] and Seto and Yamamoto[96] observed ILD rates of 6.8% and 3.2%, respectively, in Japanese patients. The reason for this discrepancy between Japan and elsewhere is unknown but may be because of ethnic, environmental or clinical practice differences. Recent data suggests a higher incidence of EGFR somatic mutations in Japanese patients and this may be a contributing factor but, at the present time, this remains highly speculative.[88] It should also be noted that the Japanese have a higher incidence of ILD compared with other Asian countries.[94] ILD may occur regardless of whether patients are chemotherapy-naive or have received prior radiotherapy or chemotherapy,[80] but others suggest that previous thoracic irradiation and poor performance status increase the chances of ILD.[6] Those with concurrent idiopathic pulmonary fibrosis whose condition worsens while receiving gefitinib have a higher mortality rate.[80,95,96] Whether smoking plays a role in gefitinib-related ILD has also not been determined and establishing a linkage may be difficult in this cohort of patients as almost all are present or ex-smokers.

At the present time, physicians are advised to remain vigilant about ILD in patients receiving gefitinib. If patients present with the worsening of respiratory symptoms, such as dyspnoea, cough and fever, gefitinib should be interrupted and the patient investigated and treated appropriately.[97] A summary of geftinib-related ILD is shown in table III.

The major aim of therapy in advanced NSCLC is usually to palliate disease-related symptoms without compromising quality-of-life. Patients who are con-

Table II. Incidence of interstitial lung disease (ILD) in phase II and III trials with gefitinib

Trial	Country	No. of patients	Gefitinib (mg)	ILD incidence	
				No. of patients	%
Fukuoka et al.[77] (IDEAL 1)	Japan	209	250	0	0
			500	2	1.9
Kris et al.[78] (IDEAL 2)	US	216	250	0	0
			500	0	0
Giaccone et al.[83] (INTACT 1)	Europe and US	1093	Chemotherapy[a] and placebo	3	0.85
			Chemotherapy[a] and 250	1	0.28
			Chemotherapy[a] and 500	3	0.84
Herbst et al.[84] (INTACT 2)	Europe and US	1037	Chemotherapy[b] and placebo	3	0.88
			Chemotherapy[b] and 250	7	2.05
			Chemotherapy[b] and 500	5	1.46
Total[c]		**2555**	Chemotherapy and placebo	6	0.85
			250 alone	0	0.00
			500 alone	2	0.94
			Chemotherapy and 250	8	1.13
			Chemotherapy and 500	8	1.13

a The chemotherapy used in the INTACT 1 trial was gemcitabine/cisplatin.

b The chemotherapy used in the INTACT 2 trial was paclitaxel/carboplatin.

c Overall incidence of ILD with 250mg of gefitinib: 0.88%.

IDEAL = Iressa Dose Evaluation in Advanced Lung Cancer; **INTACT** = IRESSA™ NSCLC Trial Assessing Combination Treatment.

sidering treatment with gefitinib tend to have a bleak prognosis and may have severe symptoms. Oral chemotherapy is generally perceived to be safer than intravenous treatments, but the recognition of gefitinib-related ILD challenges this perception. The informed decision that patients must make is that there is a 40% chance that their symptoms may improve, a 9–18% incidence of objective response but an overall risk of 0.88% of developing potentially fatal gefitinib-related ILD. They should be informed that the incidence of ILD is lower than this outside of Japan. In our experience, most choose to try gefitinib. All patients taking gefitinib must be warned to consult their prescribing doctor in the event of any new or worsening pulmonary symptoms, although in the vast majority of cases this will be because of progressive disease rather than gefitinib-related ILD.

Gefitinib is now being assessed in earlier stage disease. For example, the phase III SouthWest Oncology Group (SWOG) BR.19 trial is ongoing to compare adjuvant treatment with gefitinib for 2 years versus placebo in patients with completely resected stage Ib-IIIa NSCLC. There may also be a role for gefitinib, perhaps in combination with other non-cytotoxic agents such as the cyclo-oxygenase-2

Table III. Summary of gefitinib-related interstitial lung disease (ILD)

Incidence	0.88% at a dosage of 250 mg/day (1.9% in Japan, 0.34% in US)
Risk factors	Japanese ethnicity; pulmonary comorbidities
Symptoms	Rapid worsening of dyspnoea, cough with or without fever
Mechanism	Possibly exacerbated pulmonary injury
Investigations	Medical history: other concomitant drugs; radiotherapy Clinical: crackles on auscultation; tachypnoea; pyrexia Hypoxia on arterial blood gases High-resolution computed tomography: ground glass opacities Bronchoalveolar lavage and biopsy: diffuse alveolar damage Other tests as deemed appropriate
Treatment	Discontinuation of gefitinib Oxygen, corticosteroids, antibacterials, immunosuppression
Mortality	One third of patients developing ILD will die as a result

inhibitors, in chemoprevention.[98] The impact of ILD in these groups of patients is an entirely different issue and one that must be considered and debated more fully.

3. Conclusions

It can be difficult to make a diagnosis of drug-related ILD in lung cancer patients because of the high incidence of co-existing lung disease, infections and progressive malignancy. A high index of suspicion should be placed on new or worsening symptoms in patients receiving treatment. These symptoms should be investigated thoroughly to try to exclude all other possible causes.

Conventional chemotherapy seems to have reached an efficacy plateau in lung cancer, with different chemotherapy doublets giving comparable results in terms of both efficacy and toxicity.[99] Innovative treatments under evaluation often target areas outside of the cell nucleus, such as transduction pathways, that have become deregulated in cancer cells. Thus, these agents may offer more specific anti-tumour activity with less toxicity to normal tissues than conventional chemotherapeutic agents. The advent of novel targeted therapies provides more treatment options to patients with lung cancer, but they must be aware of the balance between possible disease/symptom stabilisation or improvement and the rare but potentially fatal drug-induced ILD.

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