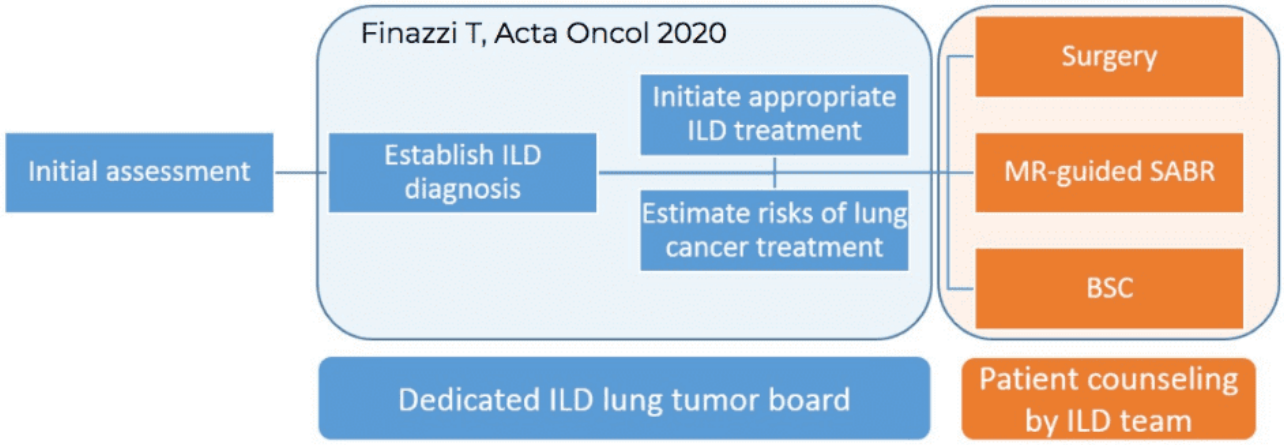
Cancerworld

Interstitial Lung Disease (ILD) as adverse event

Adriana Albini / 7 June 2022



Interstitial lung disease (ILD) is a collective term used to describe a heterogeneous group of over 200 different non-infectious diseases affecting the lung parenchyma, that are characterised by nonspecific clinical, radiological, and pathological patterns. Identifiable causes of ILD include infections (bacterial, mycotic and viral – including SARS-CoV-2), environmental triggers, pneumotoxic drugs, occupational exposures, radiation therapy, and systemic diseases. In cancer patients, cancer treatment-induced ILD is primarily associated with cytotoxic chemotherapy, targeted agents such as CDK4/6 inhibitors, radiation and immunotherapy. With the development of immunotherapies, novel antibody drug conjugates (ADCs) and other targeted agents, it has become a focus of attention, but it is a long-standing issue related to radiation and drugs such as Busulfan and Bleomycin.

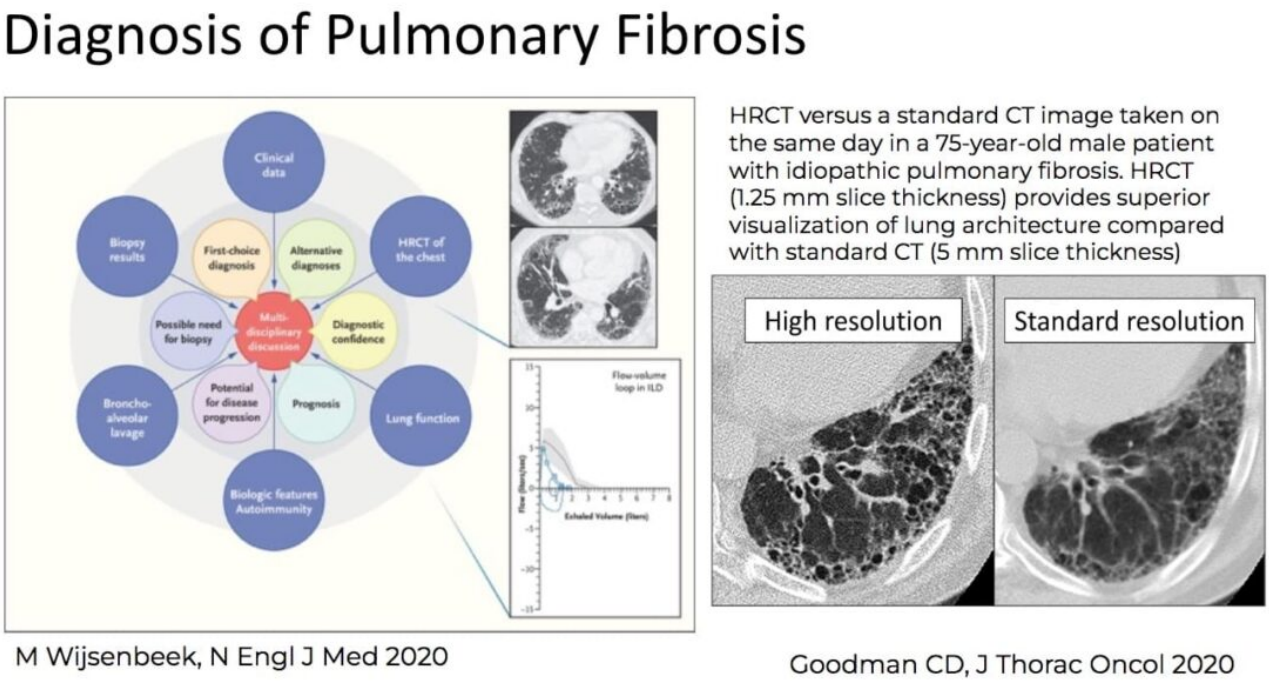
SPCC has gathered a group of experts to become the core faculty of a project on ILD as an adverse event in cancer treatment. The initiative took off with a closed remote meeting of the task force on 25 April, to prepare a series of educational online events on the topic. The meeting was chaired by the coordinators of the project, Matti Aapro, medical oncologist based in Genolier, Switzerland, and President of SPCC, and Hope S. Rugo, professor of medicine and director of breast oncology and clinical trials education at the University of California, San Francisco Comprehensive Cancer Center. Five speakers each gave a ten-minute presentation on ILD focusing on their areas of

expertise, followed by Q&A and a general discussion on the project.

ILD and Radiation Oncology

Suresh Senan is a thoracic radiation oncologist at the Amsterdam University Medical Centers, NL.

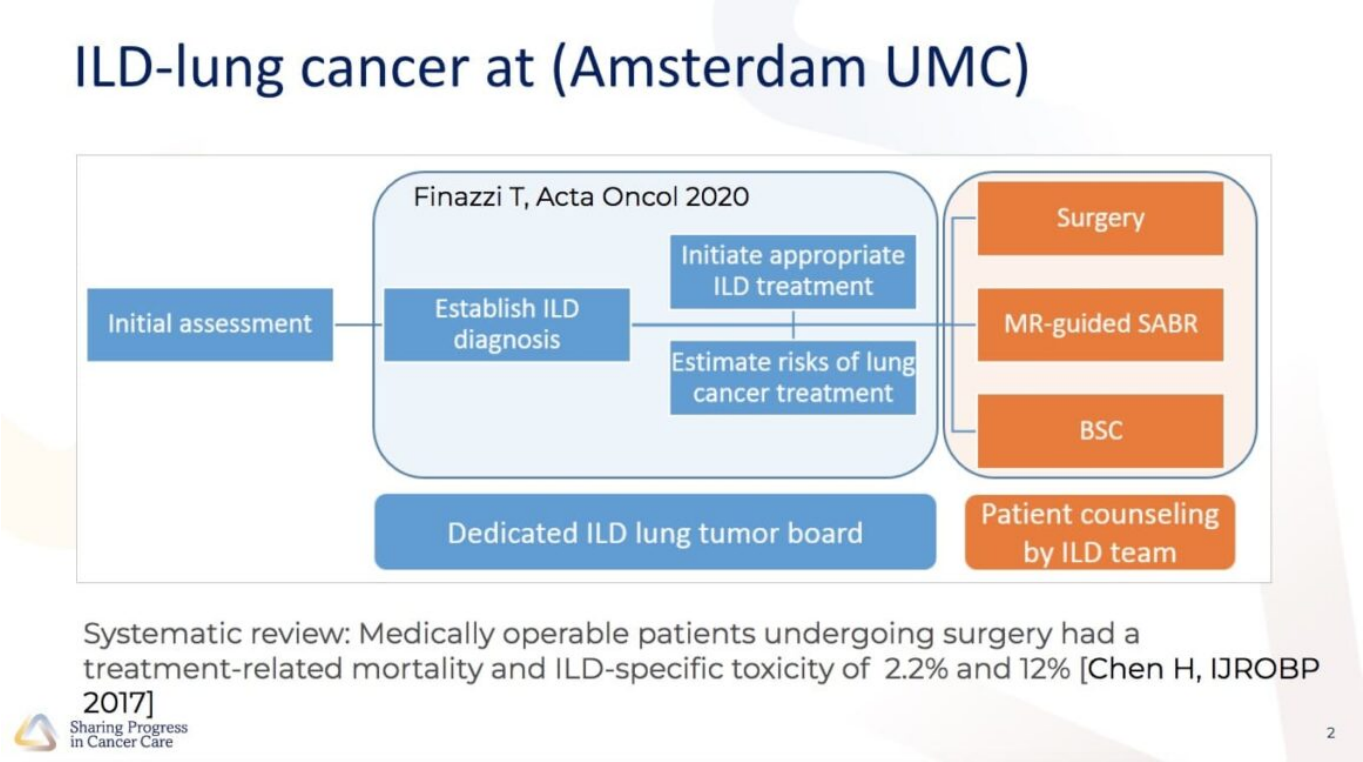
Thoracic radiotherapy is frequently used for treating common tumours, including lung, oesophageal and breast cancers. **Radiation-induced lung injury (RILI)** is a common radiological finding in such patients, although symptomatic RILI occurs less frequently now due to improved delivery techniques. Radiotherapy can be broadly divided into large field and small field delivery. Large field delivery is employed for stage III lung cancer, oesophageal and breast cancer, and some palliative treatments. Stereotactic ablative radiotherapy (SABR), on the other hand, involves the use of small field, high-dose delivery, and is widely used in early-stage lung cancer and for thoracic oligometastases.



Lung alveolar tissue is sensitive to ionizing radiation damage, which induces an acute cascade of damage-associated molecular patterns, pro-inflammatory cytokines, and chemokines released by dying and/or senescent epithelial cells, endothelial cells, and activated immune cells. RILI then evolves into a subacute phase that can last for several months, during which release of pro-inflammatory cytokines triggers extensive lung tissue remodelling. The late phase of RILI is characterised by irreversible changes in lung architecture, changes that can progress for several years.

Radiation in patients with ILD issues is encountered in Stage I Non-Small Cell Lung Cancer (NSCLC), where SABR is now the standard of care for patients who have medically inoperable disease. In ILD patients with a stage III NSCLC, toxicity becomes a serious problem, particularly following concurrent/sequential radiotherapy. Patients with stage III NSCLC undergo adjuvant immunotherapy as a standard of care, and the development of interstitial changes arising from either RILI, immunotherapy or a combination thereof can pose a diagnostic dilemma. A flare of pre-existing ILD has also been reported after palliative radiotherapy (Okumura M, Radioth Oncol 2021) and following surgery (Ozawa Y, Am J Radiol 2021).

Following SABR, radiographic changes manifest in most patients within 6 months, as diffuse consolidation, patchy consolidation, and, more rarely, diffuse or patchy ground glass opacities. Fibrotic changes may occasionally be difficult to distinguish from tumour recurrence. Late evolving RILI changes in lung parenchyma can pose a diagnostic dilemma, especially when patients undergo adjuvant immunotherapy, or subsequent immunotherapy when the disease has progressed. Some radiologic features of immunotherapy related pneumonitis, such as ground glass opacities or an organising pneumonia-like appearance are also observed in patients with RILI.
A systematic review of SABR outcomes in patients with ILD and medically inoperable early-stage lung cancer reported fatal toxicities in 15.6% of patients, and exacerbation of ILD in 25% (Chen H, *Int J Radiat Oncol Biol Phys* 2017). There is a recognised link between ILD itself and the development of lung cancer, even when checking for other risk factors. Pre-existing fibrotic ILDs are the subtypes most associated with enhanced risk of high-grade RILI. The reference standard for diagnosing ILD is assessment at a multidisciplinary discussion between pulmonologists, radiologists, and pathologists experienced in the diagnosis of ILD. The multi-disciplinary team considers the appropriate diagnosis, the need for biopsy, the differential diagnosis, and determine the prognosis, which then allows for the relevant antifibrotic treatment. However, many times patients come to the clinic without the correct diagnosis, without, for example, HRCTs (high-resolution computed tomography), bringing just standard imaging CTs with 5mm thickness, so a consultation is needed to make the best decision possible at short notice.



The term **interstitial lung abnormalities (ILAs)** refers to CT findings in patients that are potentially compatible with ILD, with nondependent changes affecting >5% of any lung zone, but without clinical suspicion of the disease. ILAs are a common feature on lung CT scans in individuals over the age of 50, with a higher incidence in smokers.

At the Amsterdam University Medical Centers, where Prof. Senan is based, a dedicated ILD-Lung Cancer MDT was established about five years ago. The board establishes an ILD diagnosis and estimates the risks of lung cancer treatment-related toxicity, which is then discussed with the patient. The patient returns to the standard tumour board, where a decision is made as to whether he/she should undergo surgery, no treatment at all or MR-guided SABR. Awareness of RILI has led to surgery being considered more often for early-stage NSCLC. When patients are candidates for

SABR, the preferred treatment in Amsterdam is MRI-guided gated radiotherapy, which allows treatment delivery using only small radiation fields. Other techniques to limit radiation field-sizes are available at many specialist centres worldwide.

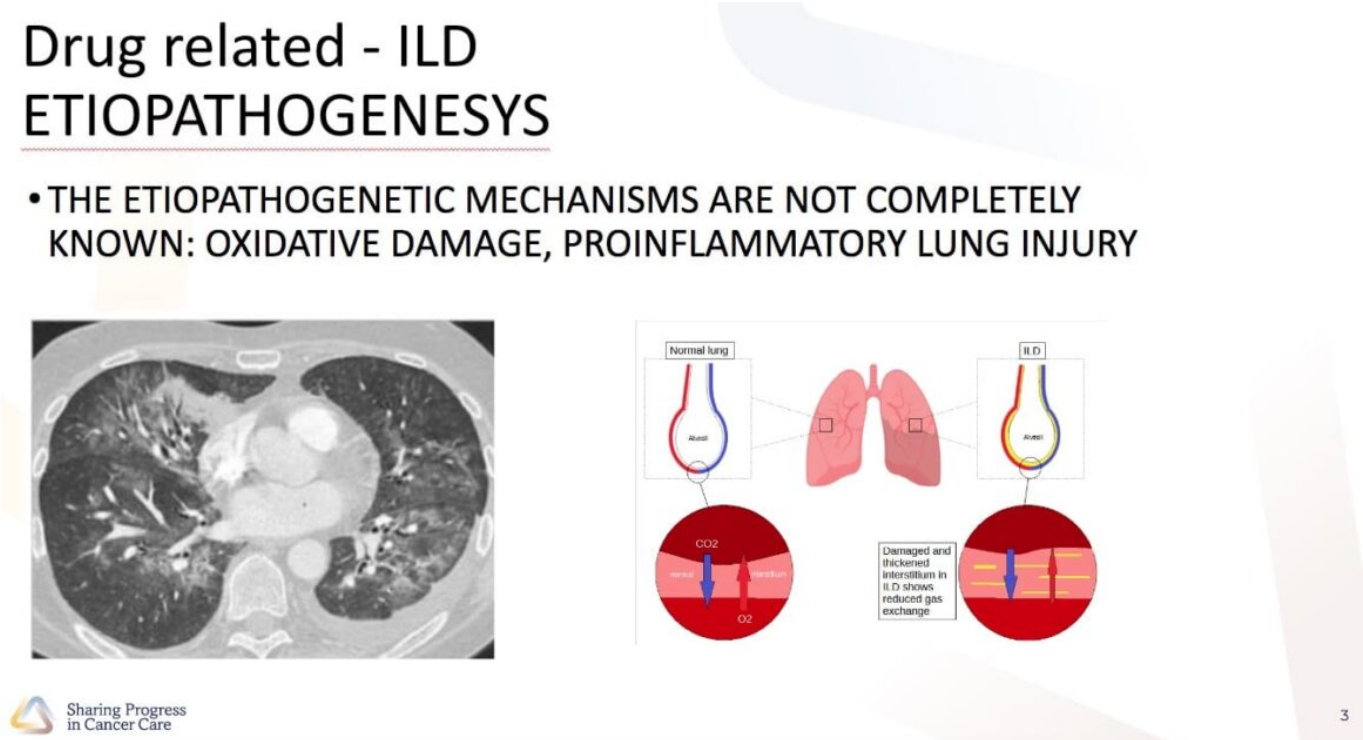
The challenges most often encountered are: that patients may present with unrecognized ILDs; the lack of extensive data on the safety of combining radiotherapy with anti-fibrotic agents (such as Pirfenidone or Nintedanib); and use of prognostic ILD-GAP scores (Gender, Age, and Physiology), for instance, to decide when the therapeutic ratio of radiotherapy is acceptable in an ILD patient.

ILD and cancer drugs

Sara Cherri is MD in the oncological department of Fondazione Poliambulanza Hospital, Brescia, IT.

Suspicion for ILD usually arises with new or worsening clinically respiratory symptoms and suggestive radiological findings. However, no clinical or radiological finding is pathognomonic for ILD, which makes it a diagnosis of exclusion.

Symptoms (dyspnea, cough, hypoxemia, low grade fever), clinical history (including medications, prior radiation), chest imaging, and clinical laboratory findings help to exclude alternative diagnoses. A prompt diagnosis with early intervention is crucial because the potential complications of ILD can lead to respiratory failure.



Many different types of cancer drugs used in clinical practice can cause lung damage: chemotherapy, targeted therapy, ADCs, and immunotherapy, but incidence varies widely and is poorly documented in most settings. In most cases, the mechanisms that lead to ILD are unknown. ILD may be triggered by the mechanism of action of the cancer drug itself, although the frequency varies widely among drugs belonging to the same family. This is the case of the ALK inhibitors drugs.
For some cancer drugs, the risk of lung toxicity was known since publication of the initial pivotal study. For new drugs, this toxicity should be reported, when observed, to the pharmaceutical agency.

Several radiological patterns are used to describe ILD, unfortunately they often cannot differentiate between the multitude of potential conditions, including infection, immunological disease, idiopathic ILD or even progression of the disease. However, radiologic evaluation can help to grade the severity and guide the therapeutic management.

According to the European Respiratory Society, the most common radiological patterns are: acute interstitial pneumonia (AIP), cryptogenic organising pneumonia (COP), nonspecific interstitial pneumonia (NSIP) and hypersensitivity pneumonia (HP). It is important to note that it might not always be possible to identify a case with a specific pattern and overlapping patterns are also possible.

With chemotherapy, pulmonary toxicity may be dose dependent (Bleomycin); it can be observed several years after administration (cyclophosphamide); the clinical presentation is mostly non-specific, and we do not have a protocol of prevention, but a careful clinical evaluation of patients who develop respiratory symptoms, and radiological monitoring in fragile subjects can help prevention.

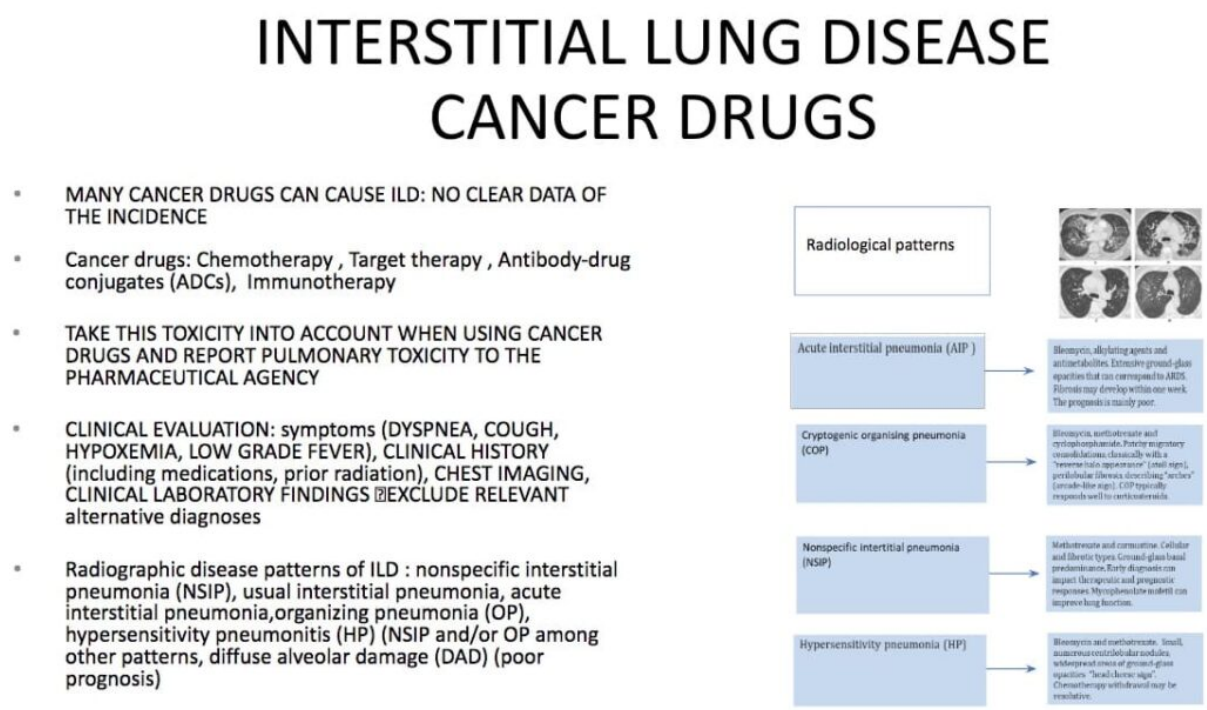
Bleomicyn was the first chemotherapy drug associated with ILD. The first data about lung damage was reported in the pivotal study of 1960. The aetiopathogenesis is still not entirely known, but we know the mechanism involves oxidative damage and deficiency of bleomycin hydrolase. The incidence can vary considerably: from 5% to 16% depending on the chemotherapeutic regimen used, and it can be fatal in 1-3% of cases. Risk factors to consider are a cumulative dose of Bleomycin, reduction in glomerular filtration rate, renal failure, and age. It is important to underline that the risk increases in combined treatments. For example, if we use Gemcitabine alone the risk is 1-4%, but this can go up to 20% when given in combination with taxanes.

Antibody-drug conjugates (ADCs) are complex molecules composed of a monoclonal antibody linked to a biologically active cytotoxic drug. One of these drugs, Trastuzumab deruxtecan (T-DXd), was recently approved for the treatment of metastatic HER2+ breast cancer. ILD is a known complication of T-DXd, with incidences up to 15.8%. Although the initial mortality rate was 2.7%, recognition with early intervention markedly reduced the risk of serious ILD. In the recent phase III Destiny Breast03 trial, the rate of ILD dropped to just over 10%, with no deaths reported. The issue of pulmonary toxicity will be of critical importance in the near future, in which the rapidly increasing therapeutic scenario sees these drugs as the main leading actors in the target treatment across tumour types and also in the curative settings.

Immunotherapy treatment has become the standard of care in the treatment of several neoplastic diseases. Since the first immunotherapy studies, interstitial pulmonary toxicity has been highlighted as a rare but serious side effect to be taken into consideration. The toxicity profile of immunotherapy drugs differs from that of cytotoxic drugs, and is characterized by specific toxicity, known as immune-related adverse events. A single-centre retrospective study conducted by Okada and colleagues among 102 patients treated for lung cancer diagnosed with ILD concluded that ECOG PS (Performance Status according to Eastern Cooperative Oncology Group) ≥ 2 and a history of smoking acted as risk factors for ILD.

Diagnosis of ILD should be based on the following criteria: the treatment history with cancer drugs, clinical, laboratory, and radiological findings suggestive of ILD, exclusion of other possible causes and improvement of clinical manifestations after drug discontinuation. Patients need to be educated to rapidly report respiratory symptoms such as cough, dyspnoea, and fever. Once the diagnosis is made, we must grade the toxicity and treat the patient accordingly. We can use the ASCO guidelines, which employ clinical criteria along with radiological pattern in order to grade the severity. For grade 1 we can continue the treatment, monitoring the patient, for grade 2,3 and 4 we

must suspend the treatment (for grade 2 we can restart it if there is a resolution of symptoms, for grade 3 and 4 the treatment must be stopped permanently). Therapy consists in corticosteroids or anti-inflammatory drugs in patients with a steroid refractory disease. In the case of fibrosis, we must consider anti fibrotic drugs.



It is important to increase the awareness of this drug toxicity because it can be fatal, especially in fragile patients.

ILD and Trastuzumab-like agents

Véronique Diéras is Senior Medical Oncologist, Breast Cancer Group, Department of Medical Oncology, Centre Eugène Marquis, Rennes, France

There has been a major improvement in the outcome of HER2+ breast cancers since the introduction of Trastuzumab and anti-HER2therapies. Trastuzumab emtansine (T-DM1), was the first antibody-drug conjugate (ADC) targeting HER2 approved, first in metastatic then early setting.

What are the possible mechanisms of Anti-HER2 ADC-induced lung toxic effects?

a. ERB2-dependent uptake of the ADC. And we know that in the epithelial cells of the lung we may have low expression of ERB-2.
b. ERB2-independent uptake of the ADC in intra-alveolar immune cells.
c. Bystander killing by the free payload released from targeted cancer cells.
d. Deconjugated payload circulating in the bloodstream. (Tarantino P at al. *JAMA Oncology* 2021)

A Japanese study carried out on monkeys, points to the second hypothesis, the ERB2-independent uptake of the ADC, as the most likely, because the free payload is not toxic in the monkeys when it is injected (Kumagai K. et al. *Cancer Science* 2020).

It must be stressed yet again how important it is to have clear patient education about symptoms, and to work in multidisciplinary teams. When we suspect ADC-related ILD, first we should

discontinue the ADC and then perform an exploration of the history and physical examination of the patient: laboratory tests, HRCT, pulmonologist consultation, bronchoscopy, and so on. We also need a differential diagnosis to exclude other causes. If ADC-related ILD is confirmed, then there are different treatment options according to the grade of ILD (Conte P et al 2022).

Looking at the rate of ILD or pneumonitis reported in trials with anti-HER2 ADCs, in 3290 patients treated with Trastuzumab emtansine, the ILD incidence was very low (0.5), although there were some fatal cases. But the incidence increased in the early breast cancer setting when T-DM1 was given with radiotherapy, and even more with Atezolizumab. The highest incidence observed was with Trastuzumab deruxtecan in HER 2+ mutant lung cancer. With Trastuzumab duocarmazine some cases of fatal ILD were also reported (Tarantino P et al 2021).

Charles Powell and co-investigators performed an analysis to look at the characteristics of ILD in patients included in phase 1 and 2 programmes with Trastuzumab deruxtecan (T-DXd) (Powell CA, AACR 2021). During treatment, 38 of the 245 patients in the trial experienced an ILD event that was adjudicated as drug related. The global incidence of ILD in phase 1 and 2 programs was 15.5, most were grade 1 or 2 events. However, there were six cases of grade 5 deaths related to ILD, and some grade 3 and 4. An important point is that when the adjudication committee looked at this cohort of patients, they frequently identified ILD onset earlier than the investigators, with a median difference of 52 days. This stresses the importance not just to educate the patient but also the physician. The median time of the first ILD event was 5.6 months and the risk of ILD decreased after 12 months.

Looking at other tumour types, beside breast cancer, there are many studies in colorectal, lung and gastric cancer. In 2019, the ILD monitoring and management guidelines were updated, and as a result, the incidence, as well as the severity of the ILD, was clearly much lower.

The ILD in phase 1 and 2 programmes demonstrated that effective early detection and optimal management are critical in preventing high grade ILD. They also indicated that the risk of ILD may decrease over time, which suggests no cumulative toxicity. Incidence seemed higher in Japanese vs non-Japanese patients, and in patients with moderate to severe renal impairment at baseline vs no impairment. The limitations of these studies were the small sample size and extensive prior treatment that may be a risk factor for this toxicity. However, the overall clinical data support the positive benefit-risk profile of T-DXd. The incidence of ILD in DESTINY-Breast03: T-DXd vs T-DM1 trial, had decreased, it was only 10.5%, no grade 5 toxicity, and low incidence of grade 3 toxicity (1.9%).

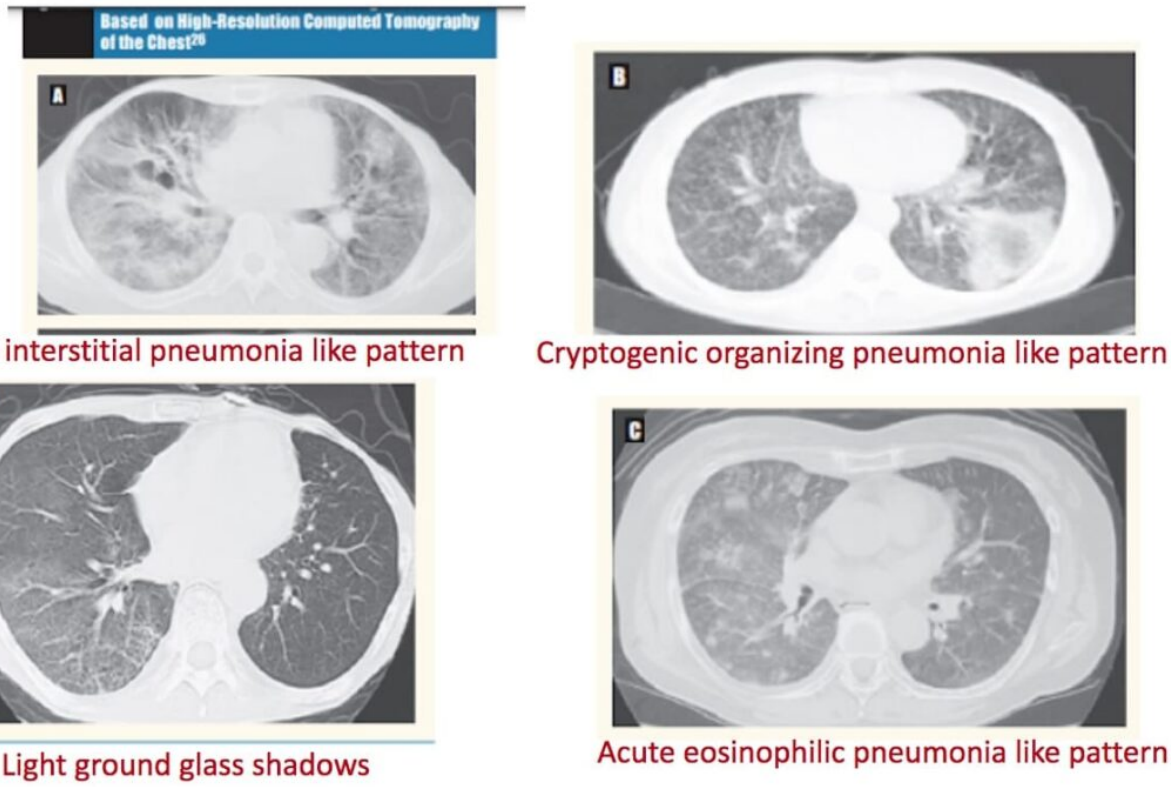
In conclusion, for the future directions for Trasuzumab-like agents, we need correct and early diagnosis with adequate education of physicians and patients, a multidisciplinary team, intensive monitoring protocols for ADC-related ILD. Diagnosis may be improved. There are some trials looking at imaging: the EORTC Image ILD trial; biomarkers in serum (KL-6) or in exhaled breath; multiparametric devices (PRO, vital signs, respiratory functions, etc.). As for the treatment, the optimal corticoid schedule needs to be better determined with a trial comparing longer vs shorter duration of the corticosteroids. Perhaps some premedication with corticosteroids could be considered. In some cases, some corticosteroid-refractory ILD could be treated with Infliximab? Or immunoglobin? There are ongoing trials.

Clearly, we need a better understanding of the pathogenesis, such as the role of pulmonary alveolar macrophages and the impact of pharmacogenomics as we know for instance about irinotecan. And we need to develop specific guidelines (Conte P 2022). It is very important to have a safe extension of the use of anti-HER2 ADCs in breast cancer and across different tumour types.

ILD and TKIs and mTOR inhibitors

Alfredo Addeo, Consultant Medical Oncologist, University Hospital of Geneva, Switzerland, focussed on DI-ILD (drug-induced interstitial lung disease), in particular from Tyrosine Kinase Inhibitor (TKI) and mammalian Target of Rapamycin (mTOR). As already mentioned by the previous speakers, ILD is very difficult to diagnose and is often under-diagnosed. It is also not clear how it should be followed up and treated. The ESMO Open paper gives general guidance mainly based on common sense, as data is not largely available, we do not really know the mechanisms of drug-induced ILD. An ILD diagnosis cannot normally be made by just one person. It requires a whole team of experts, to diagnose and manage patients who already have ILD or have developed it from drugs. This creates a major dilemma, when treatments that are otherwise working need to be stopped because of toxicity, particularly in lung cancer where not many treatment options are available.

The data about TKIs mostly comes from relatively old papers. Looking at lung cancer drugs, there is not much difference in ILD or DI-ILD between them in terms of incidence. The difference is in how accurate we can be in reporting these events. The diagnosis is pretty much an exclusion diagnosis. Patients with lung cancer already have respiratory symptoms, therefore detecting IDL or DI-ILD at the very beginning is challenging. Patients who are on Osimertinib already have metastatic cancer, and patients with this mutation have an overall survival rate of 3 years. Once we have used this drug, the second line is pretty much standard chemotherapy treatment, and we are in no man's land for the third line, we do not exactly know what to do. With a patient who is responding well to the drug but has developed ILD, we can hold the drug, but this will lead to a flare up of their cancer at some point. It is tricky to manage, but thankfully relatively rare, an incidence of about 1%.
DI-ILD can show different radiological presentations, it is very hard to diagnose, especially if you are not a radiologist, and that is why we need to have an expert to help us.



Some of the DI-ILDs we are seeing for TKI may be influenced or triggered by exposure to immunotherapy at some point in the pathway. A patient might be put on immunotherapy at the beginning and show no positive response. He/she then might be exposed to a TKI and experience a high rate of lung toxicity. Mortality is also very high. So, the combination of the two treatments is

likely to increase the risk of developing severe ILD.

mTOR for breast cancer has been used a while. Pneumonitis is a possible toxicity, and we hope to detect it early, not when it is already in grade 3 or 4. But it is not that simple. Grade 1 could be asymptomatic. Again, the treatment is empirical. We imagine that there is an immune-related event and therefore using steroids or an immunosuppressive drug can be of help.

The ESMO Open paper came out in April this year, and is the most recent publication on the subject. The recommendations are based on expert opinions, as there is not a lot of data available. The advice is to try and detect ILD as soon as possible. But the conundrum is: what shall we do once we've detected it? If the patient is on an effective drug, we can start them on steroids and then hold the drug. But then would you restart the drug? The likelihood of ILD reoccurring is very high.

We don't have many lines of treatment for patients with incurable cancer. Management for grade 2-3 is very similar: hold the drug, give steroids as immunosuppressants, then escalate to more sophisticated immunosuppressive drugs or antibiotics. It is a very blurred area. We do not know exactly what we should be doing, and we are more guided by expert opinion than real evidence.

In conclusion: DI-ILD related to TKIs or mTOR is an adverse effect of particular importance. It is rare, but proper diagnosis and management are essential to avoid fatal events. We want to manage ILD because we want to avoid a toxic death, but unfortunately with lung cancer we have limited resources, we do not have a valid alternative, especially with patients with epidermal growth factor receptor (EGFR) mutation. It is important to share awareness and develop expertise, so we can detect ILD early and try to avoid progression.

The radiologist approach to the diagnosis

Cornelia Schaefer-Prokop is a chest radiologist at Radboud University Nijmegen, NL; and Meander MC Amersfoort, NL.

Drug-induced ILD is a challenging diagnosis not only for physicians but also for the radiologist because there is a major overlap of imaging findings seen in infection (including opportunistic ones), oedema, underlying malignant disease, radiation induced pneumonitis, exacerbation of pre-existing interstitial lung disease and drug induced pneumonitis.

Radiologists should be part of an interdisciplinary team; because of this overlap it can be very difficult to define the diagnosis on the ground of imaging alone. Unfortunately, clinical symptoms such as fever, cough, and dyspnoea are nonspecific. In a number of cases, the diagnosis of DI-ILD will be made, if withdrawal of drug exposure with and without accompanying immunosuppressive therapy improves clinical symptoms and imaging findings.

It might be necessary to exclude an infection (via bronchoscopy and BAL). Only rarely, the diagnosis is made by invasive biopsy. There are no validated circulating biomarkers for the diagnosis or prognosis of DI-ILD. Prognosis is highly variable between drugs and patient populations. There is a helpful, freely available website which lists all potential effects of a large variety of drugs (not only oncologic drugs) which is regularly updated (pneumotox.com). The website does not demonstrate radiological images but lists potential patterns.

In terms of CT acquisition technique, it is recommended to obtain thin section (1mm) volumetric CT in full inspiration, reconstructed with a sharpening lung filter. Intravenous contrast administration is not necessary for evaluation of interstitial parenchymal findings. CT should be obtained early in the clinical course; it allows for early detection of pulmonary changes still at a reversible stage or help

to identify findings of alternative diagnosis that can explain the symptoms of the patient (Johkoh et al).

Lung response patterns

The patterns we see in DI-ILD are the same as we see in idiopathic or other ILDs and include a broad variety of imaging findings. Consequently, the terminology used for description is the same (Johkoh et al.). Different radiological patterns of ILD can occur with the same causative agent. None of the radiological findings are pathognomonic of DI-ILD, however, there is a preference for non-specific interstitial pneumonia (=NSIP), organising pneumonia (=OP), hypersensitivity pneumonitis (HP) and diffuse alveolar damage (DAD). Other types such as alveolar proteinosis, alveolar haemorrhage, desquamative interstitial pneumonia (DIP), lymphocytic interstitial pneumonia (LIP) or eosinophilic pneumonia are seen much less frequently, especially in the context of oncologic drugs (Skeoch et al.).

- *Nonspecific interstitial pneumonia (NSIP*) can vary from pure ground glass (frequently described as pneumonitis) to the combination of ground glass with reticulation, interlobular septal thickening and bronchiectasis. Bronchiectasis can be temporary and regress after appropriate treatment or can persist and then be a sign of architectural distortion and fibrosis. The distribution is usually bilateral, symmetric and predominantly subpleural and basal but can be also patchy and peribronchovascular. For example, a NSIP patterns has been reported in patients undergoing gefitinib or erlotinib treatment.
- *Organising pneumonia (OP)* s characterised by sharply defined solitary or multiple consolidations in a peripheral distribution or along the central bronchovascular structures. In addition to consolidations there can be sharply defined ground glass. Frequently there are smoothly dilated bronchi within the opacifications. Linear opacities, perilobular opacities and lobular sparing are other terms that help the radiologist to make the diagnosis of organising pneumonia. Opacifications can spontaneously migrate without therapeutic intervention. For example, radiologic OP pattern may occur in patients treated with immune-checkpoint inhibitors, EGFR – TKI, mTOR inhibitors and ALK inhibitors.
- *Hypersensitivity pneumonitis (HP)* pattern is characterised by small poorly defined centrilobular ground glass opacities that may confluence to diffuse ground glass. It is mostly associated with lobular air trapping caused by bronchiolitis. For example, radiologic HP pattern may occur after gefitnib or erlotinib treatment, mTOR inhibitors and immune-checkpoint inhibitors.
- *Diffuse alveolar damage (DAD)* is clinically the most serious reaction and associated with high mortality, though CT patterns is not consistently found to be a predictor of mortality. It is characterised by diffuse ground glass with reticulation, it can be combined with widespread consolidations, and there is radiological and clinical overlap with ARDS. This pattern has been reported in patients treated with EGFR-TKIs, ALK inhibitors and immune-checkpoint inhibitors.

What information is important for the radiologist?

There has to be a **temporal association** between new CT findings and drug exposure; important information is to know since when, how much and in which combination drugs have been prescribed.

There are a number of **synergistic effects** that increase the risk for developing DI-ILD such as pre-existing lung disease (e.g., COPD, ILD), a history of smoking, accompanying liver or renal insufficiency, increasing age and – importantly – the combination of therapies such as combined immunotherapies, the combination of immune- and chemotherapy or the combination of systemic and radiation therapy. The presence of pre-existing ILD – even if subtle – represents an important

additional risk factor. Therefore, it is important to know whether the patient is suffering from an underlying systemic disease, such as rheumatoid arthritis, collagen vascular diseases or vasculitis,

Radiologists would like to know about the presence of radiation therapy. Important information is when and in which anatomic location it was administered, what the time delay is between the end of the radiation therapy and the time point of CT acquisition.

Most important Differential diagnosis

Obviously, immunosuppression due to therapy or underlying malignancy (e.g., leukaemia, lymphoma) often increases the risk for pulmonary infection. Depending on the affected cell line and other factors the risk for specific organisms differs. If these conditions are taken into account, it is sometimes possible to estimate whether the patient is more likely to develop a bacterial, viral or fungal infection.

In patients with predominant ground glass, differential diagnosis includes infections caused by virus or atypical germs such as Mycoplasma or Pneumocystis Jirovecii. In these patients, imaging is helpful to rule out bacterial pneumonia, which is characterized by bronchocentric nodular or confluent, mostly asymmetric consolidations and not by ground glass.

Pulmonary oedema is not uncommon in patients undergoing oncologic therapy. Especially patients with renal insufficiency may develop pulmonary oedema, characterized by ground glass (in a ventro-dorsal gradient if patient is lying in bed), smoothly thickened interlobular septa (Kerley lines), thickened bronchovascular interstitium (bronchial cuffing) and pleural effusion.

With respect to differentiate DI-ILD from underlying malignancy, multifocal lepidic adenocarcinoma represents the most challenging differential diagnosis in patients who develop predominantly ground glass, or any type of adenocarcinoma in patients who develop an organizing pneumonia pattern.

DI-ILD under traditional and targeting chemotherapy

Bleomycin induced ILD is an example of the classic “chemotherapeutic lung disease: very widespread ground glass and consolidations associated with widening of the bronchi and reticulation. Under increased obstructive pulmonary dysfunction, the patient may develop mediastinal emphysema, spreading into the chest wall. Similar patterns can be seen in acute exacerbation of pre-existing ILD and in other cytotoxic drugs. Pulmonary toxicity of some of the older chemotherapy agents can be dose dependant (e.g., bleomycin, carmustin) or be seen several years after completion of therapy (e.g., cyclophosphamide busulfan and carmustin).

Also, with targeting agents there is a certain preference for patterns such as organising pneumonia, DAD, and NSIP. The most frequent finding includes multiple or confluent areas of ground glass with a preference for the periphery and the basal lung regions. Bronchiectasis and reticulation may be associated but not in all cases. An increased incidence for all grade and high-grade pneumonitis has been described for combination therapy for EGFR inhibitors and PD-L1 inhibitors.

In patients treated with Osimertinib transient asymptomatic pulmonary opacities (TAPOS) can be seen. They are described to be associated with a longer progression-free survival. Findings on CT include focal areas of ground glass or consolidations with a halo of ground glass around, which vanishes without treatment over time.

Pneumonitis in checkpoint inhibitors

We know that under immune-checkpoint-inhibitor therapy adverse systemic, non-pulmonary reactions occur such as colitis, hypophysitis, hepatitis, pancreatitis. thyreoditis and others. Pulmonary toxicity is seen more often (3.6 vs 1.3%) and more severe (incidence of grade 3-4 pneumonitis 1.1 versus 0.4%) with PD-1 inhibitors as compared to PD-L1 inhibitors (Khunger et al). Interestingly higher rates of pneumonitis were seen in treatment-naïve patients (4.3 versus 2.8%). According to a metanalysis no clear relationship was seen between the occurrence of pneumonitis and treatment duration or dose level (Khunger et al.). Intensity of reactions vary widely from a fulminant clinical course with diffuse ground glass, consolidations, and volume loss on CT (also described as acute interstitial pneumonia = AIP), others have a milder course with NSIP pattern or only subtle low density ground glass.

NSCLC has higher incidence rates for all grade and high-grade pneumonitis followed by renal cell carcinoma and melanoma. It occurs more often in combination therapy than in monotherapy. It occurs mostly within 0 and 27 months, in 40 % of the cases within the first two months. Knowing the delay when the ILD occurs in relation to the beginning of treatment can be helpful for the differential diagnosis.

Approximately one third of patients are able to restart immune checkpoint inhibitor therapy after successful treatment of a pneumonitis, others will develop the same pattern of DI-ILD after restart of therapy or switch of medication. Which factors influence the recurrence of adverse reactions is unknown. The term pneumonitis flare refers to the fact that ground glass opacifications typical for pneumonitis may reoccur after successful treatment with corticosteroids without restarting immunotherapy. Even more than one episode of pneumonitis flare can occur which challenges the differential diagnosis with e.g., an atypical infection (Nishino et al.).

Sarcoid-like granulomatosis with pulmonary (FDG avid) consolidations mostly located in the upper lobes and/or symmetric mediastinal and hilar lymphadenopathy is another important adverse reaction seen in patients under immunotherapy. Mostly but not exclusively it is described for patients with melanoma treated with ipilimumab. Lymphadenopathy and pulmonary opacifications may resolve spontaneously but nevertheless are very difficult to differentiate from primary tumour or metastases. Biopsy might be indicated in those patients.

In **conclusion**, drug related ILD requires an interdisciplinary approach that includes imaging findings, a detailed clinical history, and possibly BAL findings. The most frequent patterns are OP, DAD, HP and NSIP. Parenchymal findings can be migrating, progressive and recurrent. An understanding of the radiological findings associated with pulmonary complications can facilitate surveillance for drug toxicities and can prevent misinterpretation of drug effects as disease progression or infection.

Final Discussion

After all the speakers had given their presentations, it was time to brainstorm about the various types of messages that should be recorded for the public at large.

The thought is to develop **three educational webinars** – all of which CME accredited – each focussing on a specific topic. The structure would be for three experts to give a 15-minute lecture each, followed by a 25-minute discussion and Q&A. There will also be **five podcasts** focussing on one topic, 7-10 minutes long, with one expert. All of the above will be accessible free of charge on the OncoCorner platform.

The podcast presentations will be similar to the ones that were given at this meeting, but shorter, maximum 10 minutes. Dr Rugo started with some suggestions about the structure and contents of the future webinars. The goal could be to make some kind of timeline of what we think people need to know, for instance the different causes of ILD, the time frame and the appropriate management. That could be done by separating the different subjects, as it was done here, but we would lose a global overview, so it would be best to start with one webinar dedicated to that global view.

Dr Aapro informed us that there will be an **educational meeting in the first quarter of 2023**, a virtual event that will examine all the issues. It will follow the usual structure of this type of meetings: two hours in the afternoon, two days in a row, usually on Thursdays and Fridays. Dr Rugo suggested the idea of attaching a talk to a relevant symposium, a link to a webinar that has been recorded. But in terms of the webinars, Rugo stressed the importance of starting with a broad overview, where there could be a lot of interaction between the speakers, to then focus on specific topics for the next two, such as: T-DXd, antibody drug conjugates, or small molecules and radiation for the second one, and also have some discussion between experts and case-based discussions. Dr Senan reiterated the importance of an interdisciplinary approach so that the tumour board be made aware of ILD pre-existing or potential problems that could influence the diagnosis and choice of medication. A compromise needs to be found for the practical management and subsequent therapy. In radiation oncology in early-stage lung cancer often clinicians do not recognise ILD, and treatment which could have a high curate becomes toxic. For example, if you are a breast cancer doctor, you would probably want to know about radiation-induced damage, mostly in patients with pre-existing ILD. And when you come across it, who should you consult, who should give advice to the tumour specific experts to tailor the treatment? So, one of the speakers could be an expert in ILD who explains the different scenarios that we might encounter, where advice is needed before we make tumour specific therapy related decisions. Dr Aapro agreed on the need to really understand what the potential risk is for something like ILD, which is quite rare, but does exist, has existed, and has been neglected in favour of other issues.