Pleuropulmonary Changes Induced by Drugs in Patients with Hematologic Diseases

31

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Contents

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31.1 Introduction

Patients with hematologic diseases who are being treated with therapy drugs, or receive radiation therapy or blood transfusions may develop a host of potentially fatal infectious and noninfectious pulmonary complications [1]. The increased complexity of multimodality and high-dose treatment regimens with the intended benefit of augmented antineoplastic efficacy and prolonged disease-free survival, the use of a panel of novel drugs to treat malignant and nonmalignant hematologic conditions (e.g., azacytidine, bortezomib, cladribine, dasatinib, fludarabine, imatinib, lenalidomide, rituximab, and thalidomide), total body irradiation (TBI) and hematopietic stem cell transplantation (HSCT) have increased the incidence of severe sometimes life-threatening pulmonary complications.

As the incidence of infectious complications has decreased as a result of improved diagnostic methods

and effective prophylaxis, noninfectious, iatrogenic radiation- and drug-induced pulmonary complications have emerged as a major cause of early and late pulmonary morbidity, which may claim the lives of long-term survivors of hematologic malignancies. Toxic pneumonitis may account for 16% of all pulmonary events in this setting [2], and long-term adverse effects of treatments require prolonged follow-up in regard to the development of nonneoplastic and neoplastic conditions in heart and lung [3]. Noninfectious pulmonary complications represent a real challenge to the practitioner who needs be wary of the multitude of drug-, radiation- and procedure-induced adverse effects. Drug-induced respiratory disease in hematology patients may manifest acutely or subacutely by hypersensitivity reactions (bronchospasm, anaphylaxis), pulmonary edema, acute lung injury (ALI), an adult respiratory distress syndrome (ARDS) picture, diffuse alveolar hemorrhage, interstitial lung disease (ILD) with or without tissue eosinophilia, pleural effusion or pulmonary vasculopathy.

The diagnosis of iatrogenic disease is complex, and it is by exclusion. The diagnosis is made against [1] pulmonary involvement from the underlying benign (e.g., sickle cell disease, myelodysplastic syndrome, *polycythemia vera*) or malignant hematologic condition (e.g., acute and chronic leukemias, Hodgkin's and non-Hodgkin's lymphoma, multiple myeloma), [2] alveolar hemorrhage, [3] circulatory overload, left ventricular dysfunction and [4] an opportunistic viral, bacterial, fungal or protozoan infection with few reliable clinical or imaging discriminators to separate these entities. To complicate matters, there is often little time for establishing the diagnosis and initiating appropriate therapy before the patient's condition deteriorates irreversibly. Patients who require mechanical ventilatory support have an ominous outcome. There is almost no specific pattern of drug-induced lung involvement on pathology. Thus, the lung biopsy is mainly used to rule out diagnoses other than drugs, and patients suspected of having drug-induced lung disease may be managed conservatively using bronchoalveolar lavage (BAL), transbronchial lung biopsy (TBLB) and microbiological tests as the main diagnostic tools. Drug discontinuance followed by resolution of symptoms is a simple test that may aid in the recognition of drug-induced disease.

The diagnosis of DIRD can be straightforward in patients with a benign underlying hematologic condition who are being treated with a compatible drug as a solo agent, and drug discontinuance is followed by remission of symptoms. Drug-induced disease is more complex to diagnose in patients with a background of hematologic malignancy who received several potentially pneumotoxic drugs, each having different times for drug-induced disease to present, and/or who have received radiation therapy, blood transfusions or have a history of exposure to oxygen or corticosteroids. Such patients are likely to be severely immunocompromised under the combined influence of underlying illness, drugs used to treat their condition, corticosteroid and radiation therapy, and an opportunistic lung infection is a strong consideration [4]. Diagnosing drug-induced disease is even more complex in recipients of hematopoietic stem cell transplants, who in addition to the above complications, may develop several distinctive post-transplant manifestations, including engraftment syndrome, pulmonary edema, bronchiolitis obliterans organizing pneumonia (BOOP), diffuse alveolar hemorrhage (DAH) and late-onset noninfectious pulmonary complications including idiopathic pulmonary syndrome (IPS) [5, 6]. In rare instances, pulmonary complications develop in hematopoietic stem cell donors in the form of pulmonary infiltrates during colony-stimulating factor-(CSF)-induced stem cell mobilization [7].

The older literature is replete with cases of pulmonary toxicity induced by drugs such as busulfan, BCNU or other nitrosoureas, bleomycin, chlorambucil, cyclophosphamide, hydroxyurea or melphalan when patients with varied hematologic conditions were exposed to these drugs as a solo agent. Sometimes, the pattern of pulmonary involvement from these drugs is distinctive and can still be detected even though the drug is part of a multiagent chemotherapy or conditioning regimen. Establishing which drug in the regimen causes the lung injury is useful, for it may enable withholding the specific drug instead of all drugs in the regimen. Diagnosing drug-induced lung disease is not of pure academic interest. An important practical consequence is selective drug withdrawal while other nonpneumotoxic drugs are continued to the benefit of the patient. Although rechallenge was once considered hazardous and still is with many drugs, rechallenge and steroid-supported rechallenge can be attempted with vital drugs such as imatinib or dasatinib.

Here we review the pulmonary complications induced by drugs, blood transfusion and radiation therapy.

Drug-induced opportunistic infections, respiratory manifestations in recipients of bone marrow and stem cell transplant and iatrogenic complications of chest tubes and central venous access are covered elsewhere [8, 9].

31.2 Diagnostic Criteria for Drug-Induced Respiratory Disease

Criteria for diagnosis include the following [10]:

1. Correct identification of the drug [11]
Dose and duration of treatment with each drug taken in isolation or in a chemotherapy regimen should be reviewed. Causality is more difficult to assess when several pneumotoxic drugs were received concomitantly or in sequence. The likelihood and delay time for drug-induced disease to present vary with drug, dosage, whether the drug was coadministered with other pneumotoxic drugs and the patient. Patients of Asian descent may be at increased risk for certain drug-induced pulmonary complications. It is also necessary to compute exposure to G/GM-CSF, blood and blood components (e.g., fresh frozen plasma, whole blood-derived platelets), anesthetic agents, oxygen, parenteral nutrition and nonhematologic drugs, for all of these may effectuate lung injury [11].

2. Temporal eligibility
Respiratory signs and symptoms should follow (not predate) the onset of treatment with the suspected drug. Time to onset of the respiratory reaction varies with drug, host, schedule of administration and pattern of involvement. The shorter the latency period is, the easier the suggestion of the drug etiology. Longer delay times increase the likelihood that the drug etiology goes unrecognized. Drug-induced- bronchospasm, anaphylaxis, pulmonary edema (e.g., gemcitabine- or acaytine-induced), acute lung injury (e.g., transfusion-related acute lung injury or TRALI), acute respiratory distress syndrome (ARDS) and alveolar hemorrhage tend to develop shortly after exposure to the causal agent, with a time to onset of minutes to hours or at most a few days. Instead, it may take weeks, months or years for drug- (viz. methotrexate, azathioprine or thalidomide) induced cellular interstitial pneumonia to develop. Drug- and radiation-induced pulmonary fibrosis develops after months or years into treatment or after termination of treatment. For instance, patients who received busulfan, cyclophosphamide, nitrosoureas or radiation therapy in the past may be diagnosed with iatrogenic pulmonary fibrosis or the idiopathic pulmonary syndrome many years later [12, 13].

3. Drug singularity
Assessment of causality is problematic if patients were exposed to several pneumotoxic drugs. This creates confusion about which drug is responsible for the lung reaction, and it may at times be impossible to sort this out. In patients treated with several chemotherapy agents, drug toxicity may develop at dosages of each drug that are lower than the threshold above which drug toxicity develops when the drug is taken in isolation. Weighing the responsibility of each drug taken separately is critical regarding future management of the underlying hematologic disease. Identification of the causal drug may enable selective cessation of the culprit drug. A review on nonhematology drugs is indicated, as many drugs can injure the lung [11]

4. Whether the pulmonary reaction is appropriate for the particular drug
The pattern of involvement from some drugs can be suggestive, owing to the close temporal relationship of exposure versus onset of respiratory symptoms (e.g., the swift development of pulmonary infiltrates following treatments with anti-thymocyte globulin, gemcitabine, ATRA, cytarabine or blood transfusion (TRALI) [14]. For other drugs it is because the clinical, imaging, BAL and/or pathologic pattern of involvement is distinctive [e.g., bleomycin and bibasilar shadowing or multiple lung nodules, cyclophosphamide and severe pleuropulmonary involvement, imatinib or dasatinib and pleural effusion, methotrexate and an acute hypersensitivity pneumonitis with a granulomatous pattern of involvement, rituximab and ARDS; retinoic acid (ATRA) and diffuse alveolar hemorrhage (DAH), of BCNU/CCNU or busulfan with otherwise unexplained pulmonary fibrosis].

It is difficult to predict the pathologic background of drug-induced reactions using HRCT data alone [15], and in one study of 20 patients [16], imaging and pathology were concordant in only nine cases (45%). A confirmatory lung biopsy (open or transbronchial) can be necessary in selected cases mainly to discard etiologies other than drugs rather than to prove the drug etiology. Any attempt at deducing pathology from imaging as done in some studies [17] should be viewed with caution.

5. Exclusion of other causes

There are many diagnostic contenders to consider when pulmonary infiltrates develop in patients with hematologic disease treated with drugs. These include the pulmonary manifestations of the native benign or malignant hematologic condition (for instance, pulmonary involvement from malignant lymphoma [15] or acute leukemia [18], extramedullary hematopoiesis [19], multiple myeloma [20–22], interstitial lung disease including pulmonary alveolar proteinosis that may occur in association with untreated hematologic diseases [23]), capillary leak, tumor lysis syndrome, cardiac pulmonary edema, an opportunistic viral, bacterial, fungal or protozoan infections including *Pneumocystis jiroveci* pneumonia, a common encounter in hematology patients [24–28], and a graft-versus-host reaction [29]. All of these can produce similar patterns of involvement on imaging. The BAL and TBLB with appropriate sample staining, culture and molecular techniques should be routinely performed to help exclude an infection [2]. Heart ultrasonography and diuresis may also aid in the recognition of drug-induced vs. cardiogenic pulmonary edema.

6. Remission of signs and symptoms with removal of the drug

Signs and symptoms typically clear after drug removal. However, fulminate iatrogenic reactions to drugs (e.g., drug-induced pulmonary edema, TRALI, methotrexate pneumonitis, bleomycin lung) may progress despite removal. Similarly, pulmonary fibrosis induced by drugs or that develops as a late consequence of conditioning regimens often is an irreversible process that may not respond to drug discontinuance. Corticosteroid therapy is often given to patients with severe drug-induced lung disease to accelerate recovery. However, this is at the expense of drug causality assessment.

7. Recurrence with rechallenge

Rechallenge followed by recurrence is central to the diagnosis of any drug-induced disease [10], but seldom is performed intentionally because of risks [30]. Of note, drug-induced pleuropulmonary reactions to imatinib [31], dasatinib [32] or antithymocyte globulin [33] were shown not to relapse in all patients upon reexposure, enabling continued treatment of the underlying hematologic disease. Rechallenge is reserved for cases where the drug is vital, there is no alternative efficacious drug to treat the underlying condition, and it is given in small incremental doses of the drug and corticosteroid therapy.

8. Tests may support the diagnosis of DILD

BAL is instrumental in ruling out an infection and may show an increased percentage of lymphocytes, eosinophils or neutrophils depending on which drug caused the reaction (for a review, see [14]).

Studies of peripheral or BAL lymphocyte activation or migration following in vitro challenge with the suspected drug have produced inconsistent results, and overall, evidence for the usefulness of this test is low, and there is a lack of consensus about the appropriateness of these tests inasmuch as in a recent series, there was no correlation of lymphocyte stimulation with the clinical result effect of rechallenge with the drug [34].

KL-6 has been found to be elevated in some patients with drug-induced fibrosis. However, this marker remained normal in cases of pulmonary toxicity from rituximab, methotrexate and radiation therapy. Similarly, time-related changes in plasma or BAL TGF-ß1 and IL1 in patients receiving chemotherapy and/or radiation therapy yielded inconsistent results, and there is no consensus regarding their measurements in routine.

Areas of drug-, radiation- and talc-induced reactions can be tracer-avid on FDG-PET scans [35].

31.3 Patterns of Reactions to Drugs and Radiation

31.3.1 Interstitial-Infiltrative Lung Diseases (ILD)

ILD is a group of conditions characterized by pulmonary infiltrates, restrictive physiology, impaired gas exchange, shifts in BAL cells percentages (lymphocytes, eosinophils or neutrophils) and pathologic evidence of parenchymal inflammation. Fever, a nonproductive cough and dyspnea are common presenting symptoms. Diagnosis of drug-induced ILD is supported by BAL, a negative workup for lung infection and reversal of the symptom following drug removal. Tissue sampling is not always required. Severity of ILD ranges from mild transient pulmonary infiltrates and the asymptomatic state to diffuse shadowing or dense consolidation with the gas exchange features of ALI or ARDS [36]. Histological findings are dominated by interstitial inflammation with or without tissue eosinophilia or a granulomatous pattern

of involvement, organizing pneumonia, pulmonary edema, diffuse alveolar damage (DAD) or alveolar hemorrhage. The lung architecture is retained [37].

31.3.1.1 Cellular or Nonspecific Interstitial Pneumonia

Drug-induced cellular interstitial pneumonia, also known as alveolitis or hypersensitivity pneumonitis, is a common pattern of pulmonary reaction to drugs [11]. Drugs causing cellular interstitial pneumonia in hematology include azacytidine, azathioprine, chlorambucil, 2-chlorodeoxyadenosine (cladribine), cyclophosphamide, cytarabine, dasatinib, floxuridine, fludarabine, GM-CSF, gemtuzumab, hydroxurea, imatinib, interferon alpha and beta, lenalidomide, methotrexate, procarbazine, rituximab, thalidomide, vinca alkaloids and chest radiation therapy [11]. Time to onset is a few days to several years into treatment and is unpredictable as serial pulmonary function is not capable of predicting development of this complication. Onset of the disease may be insidious over a few days or weeks, with moderate fever followed by the development of cough and breathlessness. Methotrexate lung is known to accelerate, causing rapidly progressive respiratory failure. Radiographic studies indicate bilateral, usually symmetrical interstitial or alveolar ground-glass opacities, mosaic attenuation or consolidation. The infiltrates may predominate in the lung bases and mid-lung zones, or they can be diffuse. Radiographic attenuation can be a discrete haze, ground-glass, inter- or intralobular septal thickening, a crazy-paving, mosaic appearance or dense bilateral consolidation with air bronchograms [38–42]. A miliary pattern, pleural effusions and mediastinal lymph node enlargement are occasional features of methotrexate lung [36, 43]. Imaging features may not enable the separation of ILD due to drugs from infectious pneumonia or from the manifestations of the underlying hematologic condition [26, 44, 45]. Pulmonary function indicates restrictive physiology and impaired gas exchange [36]. Physiology tends to correlate with the extent of involvement on imaging [46] except in azathioprine pneumonitis and bleomycin lung [47, 48]. Fiberoptic bronchoscopy and BAL are indicated to rule out an infection. The BAL usually shows a lymphocyte predominance [49]. The contribution of lymphocyte typing is unclear, because increases in both CD4+ or CD8+ subsets have been observed depending on time from onset of pneumonitis and whether the patient has received corticosteroid therapy [50]. A low ratio of CD4+ to CD8+ lymphocytes is suggestive for the drug etiology, but this is not a specific finding. Other BAL patterns include neutrophilia or a pattern of lymphocytosis and neutrophilia or eosinophilia. BAL samples should be processed with special stains, cultures and molecular techniques for the detection of bacteria, fungi and protozoa and viruses, including the recently recognized metapneumovirus and H1N1 [51]. A lung biopsy may be required in selected cases, since drug-induced lung disease may be a mimic of *Pneumocystis* pneumonia [52] and other opportunistic infections [53]. The TBLB approach can document interstitial pneumonia although sample size may be an issue. Histopathological features include interstitial inflammation, edema and a cellular interstitial infiltrate. Less common findings include granulomas during treatments with methotrexate [43], interferon [54] or lenalidomide [55], organizing pneumonia with rituximab or thalidomide, and interstitial fibrosis [43]. Alveolar edema or hemorrhage may be found as a manifestation of severe ILD [43, 56].

Management includes drug removal and supportive care. This may suffice in benign cases [57]. Corticosteroids are indicated in severe cases once an infection has been reasonably ruled out. Oral prednisolone or i.v. methylprednisolone daily for a few days is indicated depending on severity, followed by a tapering dosage of oral corticosteroid therapy. Mega-doses of methylprednisolone of 1 g/day are given to patients in some countries, with no documented benefit compared to a standard dose regimen. Fatalities have been reported in patients with severe disease, particularly if corticosteroids were not given in time and in patients rechallenged with the drug [30]. Lung fibrosis following recognition and treatment of this problem is seldom seen. Although rechallenge with the drug may not be followed with relapse [32, 58], this should be discussed on an individual basis. Patients and caregivers should be instructed to avoid unjustified reexposure to the drug or to a congener.

31.3.1.2 Eosinophilic Pneumonia

The association of pulmonary infiltrates with blood and/or tissue eosinophilia defines eosinophilic pneumonia. This is an uncommon pattern of lung response

to drugs used in hematology, contrasting with non-steroidal antiinflammatory drugs and minocycline. Causal hematology drugs include bleomycin, chlorambucil, cladribine, cotrimoxazole, fludarabine, GM-CSF, interferon, inhaled or parenteral pentamidine, procarbazine and radiocontrast media. More common causal agents include nonsteroidal antiinflammatory drugs or minocycline [11]. Adverse reactions to methotrexate or blood transfusion can be accompanied by mild peripheral eosinophilia, but the BAL and pathologic features are not those of eosinophilic pneumonia. Onset of the condition is unpredictable. Acute eosinophilic pneumonia may produce acute respiratory failure. Unusual PIE cases present with rash and internal involvement, and this has been aptly coined DRESS for drug-rash and eosinophilia with systemic symptoms. A few DRESS cases were described with the use of azathioprine, bortezomib, hydroxyurea and imatinib [59]. On imaging, PIE is in the form of the photographic negative of pulmonary edema, or it is disseminated with faint shadowing, discreet ground-glass, Kerley "B" lines, or dense and diffuse infiltrates. An increase in blood, BAL and/or lung tissue eosinophils is diagnostic. The lung biopsy rarely is required and shows an interstitial infiltrate of eosinophils admixed with mononuclear cells. Drug discontinuance is indicated. Corticosteroids are reserved for severe cases. Outcome is good.

31.3.1.3 Interstitial Lung Disease with a Granulomatous Component

Granulomatosis has been reported in a few patients after treatment of non-Hodgkin's disease in the form of reticulo-nodular infiltrates and/or medisatinal lymphadenopathy [60, 61]. Most cases of drug-induced granulomatosis with or without extrathoracic organ involvement and hypercalcemia are related to treatments with interferon alpha or beta. Methotrexate and lenalidomide can also produce a granulomatous pulmonary reaction (see below under interferon and methotrexate).

31.3.1.4 Organizing Pneumonia

Organizing pneumonia (OP/BOOP) is a distinctive pattern of lung response to a few drugs and to hematopoietic stem cell transplantation as well, which is best defined by the pathologic finding of alveolar and ductal buds of connective tissue or fibrosis. Strictly speaking, organizing pneumonia is best diagnosed when a large sample of lung tissue is available for review to make sure BOOP is not an incidental finding among other more distinctive pathologic features. Claimed cases of BOOP without pathologic evidence are equivocal. This is not trivial, for pulmonary aspergillosis and BOOP can be indistinguishable on imaging [53]. Causal drugs used to treat hematologic conditions include bleomycin, busulfan (mostly the acute busulfan lung), cyclophosphamide, interferon, lenalidomide, rituximab, thalidomide and chemotherapy [11, 62]. At any rate, the diagnosis of drug-induced BOOP is against the background of BOOP, which can occur as a late noninfectious pulmonary complication in hematopoietic stem cell transplant recipients [5]. BOOP can manifest with chest pain, dyspnea and areas of consolidation or without respiratory failure [63], or it is discovered incidentally on imaging [64]. Nodular organizing pneumonia is a distinctive pattern of bleomycin pulmonary toxicity and is in the form of round-shaped areas of consolidation that may localize in lung bases and simulate metastatic lung disease [65]. A lung biopsy may be required to exclude this possibility [66], although clinical reasoning and observation coupled to 18F-dideoxyglucose PET scanning may suffice [67]. There is no BAL pattern that is characteristic of this condition. The percentage of lymphocytes and/or of neutrophils or eosinophils can be increased. If a lung biopsy is contemplated, the video-assisted approach is preferred as a larger sample lends greater support to the diagnosis. Histology reveals interstitial inflammation, superimposed on the dominant background of alveolar and ductal fibrosis [68]. Some patients present with overlapping features of organizing and eosinophilic pneumonia [66]. Drug discontinuation with corticosteroid therapy in severe cases is followed by improvement.

31.3.1.5 Diffuse Alveolar Damage and the Chemotherapy Lung

The treatment of hematologic malignancies with chemotherapy agents, particularly alkylating agents but not exclusively so, may induce a pattern of lung derangements termed the "chemotherapy lung," a wide-ranging term [14, 69]. Patients treated for leukemia,

particularly patients with high blast counts during remission induction [70], Hodgkin's disease or non-Hodgkin's lymphoma and recipients of bone marrow or stem cell transplant are at risk. The entity refers to non-hemodynamic, noninfectious and nonneoplastic pulmonary complications, which develop in a variable proportion of patients (<1–60% in some phase I or II studies) following administration of single-agent (e.g., BCNU or other nitrosoureas, bleomycin, bortezomib, busulfan, chlorambucil, cyclophosphamide, docetaxel, gemcitabine, melphalan, methotrexate, procarbazine, vinblastine) or multi-agent chemotherapy, particularly when drugs were used at elevated dosages or there is an association of several lung-toxic drugs with or without radiation therapy in the treatment schedule [71–73]. Substitution of one agent in a chemotherapy regimen can markedly alter the safety profile. For instance, in patients with de novo-treated Hodgkin's disease, the substitution of gemcitabine with dacarbazine in the ABVD regimen [doxorubicin, bleomycin, vinblastin, gemcitabine instead of dacarbazine (ABVG)] resulted in an unacceptable 42% incidence rate of pulmonary toxicity [74]. Likewise, in a phase I/II dose-escalation study in 27 patients with advanced-stage Hodgkin's disease, the substitution of gemcitabine for etoposide in the escalated BEACOPP regimen (bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone and gemcitabine instead of etoposide) resulted in pulmonary toxicity in 29.6% of the patients [75]. Crucially, the disease needs be separated from an infection, mainly pneumonia due to *Pneumocystis jiroveci* or viral agents [76], acute heart failure and an acute transfusion reaction [77, 78]. If investigation of the sputum, BAL, blood and other fluids is unrevealing, especially on two consecutive evaluations for an infection, the diagnosis of chemotherapy lung is entertained further. It is challenging to assess the specific responsibility of each drug in the regimen to the syndrome if patients have received several pneumotoxic agents concomitantly or in sequence. Assessing causality is important though, for identification of the causal drug may allow selective drug discontinuation rather than withdrawal of all drugs in the chemotherapy regimen. It may be possible to discern methotrexate or bleomycin pulmonary toxicity when it occurs in patients receiving a multi-agent chemotherapy regimen. For instance, non-Hodgkin's lymphoma patients who received m-BACOD or m-ACOD regimens developed a picture similar to methotrexate lung, whereas no pulmonary infiltrates were observed in patients receiving the CHOP regimen, which does not include methotrexate [79]. Similarly, the different incidence of pulmonary events in two arms of a therapeutic regimen that differed by only one drug (for instance with or without bleomycin, BCNU, CSF, gemcitabine, or radiation therapy) or by the dosage of one particular drug (e.g., low vs. high BCNU) enabled deducing which drug was exactly causing the reaction [80]. The likelihood of developing chemotherapy lung is increased when radiation therapy to the chest, TBI, oxygen, and possibly CSFs are given concomitantly. The term 'chemotherapy lung' is not ideal, because non-chemotherapy agents such as ATRA, IL-2 and imatinib, oxygen, transfusion of blood or proteins including IVIG, infusion of stem cells, radiation therapy and nonchemo agents can also cause the syndrome [11].

In addition to the intrinsic risk attendant to specific drugs, with busulfan carrying an extra risk compared to other chemotherapeutic agents [81], other factors include advanced age, current smoking, drug dosage and intensity of the conditioning regimen [myeloablative vs. nonmyeloablative, multi-agent combination chemotherapy, abrupt corticosteroid withdrawal, the type of stem cell transplantation (allogeneic vs. autologous, T-cell depleted) and a background of graft-vs.-host reaction in transplant recipients].

Time to onset of the chemotherapy lung is variable from shortly after the first administration of low doses of the drug [70, 82] to months into treatment or after termination of treatment. Usual doses of oral corticosteroids may not prevent the condition from developing. Depending on patient and time of diagnosis, the chemotherapy lung may have overlapping features with, and be difficult to distinguish clinically and on imaging from acute pulmonary edema, diffuse alveolar hemorrhage, accelerated pulmonary fibrosis or dense interstitial pneumonias. The main histopathological feature of chemotherapy lung is diffuse alveolar damage (DAD) with, characteristically, hyaline membranes and fibrin deposits lining the alveolar border, dysplasia of type II cells, free alveolar fibrin, cells and debris in alveolar spaces, and various stages of interstitial edema and alveolar inflammation and organization [83–85]. Reactive type II pneumocytes are sometimes present in BAL mounts [86]. The term idiopathic pneumonia syndrome (IPS) or delayed pulmonary toxicity syndrome (PTS) is used in recipients of stem cell transplant [5] to denote late lung changes that may result

from previously inflicted insult collectively induced by chemotherapeutic agents, conditioning regimens and total body irradiation [87, 88].

The clinical imaging expression of chemo- or chemo-radiotherapy lung is wide ranging [38–40, 89]. At one end of the spectrum, patients present with isolated dyspnea and a progressive decrease in the diffusing capacity as the only manifestation of toxicity [90]. Others present with bilateral interstitial and/or alveolar shadowing, which abates after discontinuation of the drugs and/or corticosteroid therapy [91]. Yet other patients with severe presentation progress to respiratory failure and respiratory death despite drug discontinuation [92]. The HRCT discloses scattered ground-glass haze, inter- and/or intralobular septal thickening or areas of condensation [40]. If patients are able to withstand the test, pulmonary function is restrictive, and hypoxemia is present. The diffusing capacity is decreased, and typically the decrease predates the onset of symptoms or the development of radiographic abnormalities. The changes are progressive or can be reactivated with further treatment with the causal drug, notably bleomycin or rituximab, and careful follow-up is needed before any further administration of the drug is contemplated [73, 90]. The BAL indicates an increase in neutrophils, or neutrophils and activated lymphocytes [93].

A lung biopsy is reserved for patients with an atypical presentation or those who do not improve on empiric antibiotic and steroid treatment [94]. Judicious use of lung biopsy may help to diagnose an infection and tailor treatment accordingly [2, 85]. However, the critical condition of these patients often precludes this option, as the procedure is associated with increased mortality when it is done in patients with significant respiratory impairment. In the setting of chemotherapy, the respective benefit of a minimally invasive approach with drug removal, empiric treatment with antibiotics and corticosteroids [95] as opposed to the more invasive approach remains unclear [96]. A fraction of patients respond favorably to drug discontinuation and corticosteroid drugs, especially if the condition is recognized early. For instance, in a series of 65 patients with hematologic malignancies who received a carmustine-based conditioning regimen prior to bone marrow transplantation, 17 (26%) developed pulmonary infiltrates thought to be drug-induced. Of these, 15 responded to corticosteroids [97]. One patient died of pneumonitis [97]. Corticosteroids should be tapered carefully to avoid catastrophic respiratory failure [98, 99]. Despite occasional success with immunosuppressive drugs [100], the response to treatment and the prognosis of this condition when it is advanced, when corticosteroids fail or when ventilatory support is required are disappointing. Chemotherapy-induced lung toxicity may also negatively impact on the management of the underlying hematologic disease, as a change in therapy may be required toward less efficacious or more toxic drugs.

In patients who recover from chemotherapy lung, mild reduction of vital capacity and/or the diffusing capacity may persist in the long term [101], and the likelihood of permanent physiologic impairment is greater in smokers [102]. Patients who receive alkylating agents for Hodgkin's disease or non-Hodgkin's lymphoma should be discouraged from smoking, as persistent smoking greatly increases the likelihood of developing lung cancer later in life [103, 104].

The high incidence, severity and unpredictability of pulmonary complications from chemotherapy raise the question of whether early detection is meaningful using pulmonary function tests or imaging. Deterioration of indices of pulmonary function is common in patients exposed to chemotherapeutic agents [105, 106], including conditioning regimens for hematopoietic stem cell transplantation [107]. Changes cannot be predicted on an individual basis and occur more in patients who receive TBI in addition to drugs. Corticosteroids may mitigate or reverse these changes [107]. In the majority of patients, though, these subclinical changes do not predict the development of overt disease. In contrast, exposure to methotrexate does not alter lung functions [108]. Some investigators believe it is prudent to discontinue chemotherapy once the diffusing capacity has decreased to <50% of pretherapy values, while others do not rely on this measurement since it is their belief that the diffusing capacity does not equate to and may not predict toxicity, and there is the risk of unnecessarily withdrawing an effective chemotherapy [109]. An abrupt fall in the monthly measurement of the diffusing capacity may indicate impending toxicity. When radiation therapy is planned after administration of chemotherapeutic agents, it is advisable to wait for any chemotherapy-induced decrease in the diffusing capacity to stabilize or show a trend toward improvement, before the patient undergoes radiation therapy [90]. Although changes on imaging are common in patients receiving bleomycin or rituximab, it is impractical to

rely on imaging to detect changes consistent with pulmonary toxicity of chemotherapeutic agents. Patients on chemotherapy may develop new opacities on CT although they never develop symptomatic disease [110]. There is no current agreement as to how patients on chemotherapy should be followed to reliably and cost-effectively detect meaningful therapy-induced pulmonary complications. However, many treating physicians have a chest radiograph, PFT and diffusing capacity measured serially during treatment, particularly if patients are being treated with bleomycin.

31.3.1.6 Cell Lysis Pneumopathy

A subset of patients with acute leukemia and high blast counts may develop acute pulmonary complications during induction of remission in the form of diffuse pulmonary infiltrates and an ARDS picture with or without alveolar hemorrhage [111, 112]. This was coined cell lysis pneumonopathy [111] because the pathology indicates blasts in pulmonary capillaries and cell remnants or debris on a background of diffuse alveolar damage. [113]. In a recent study, pulmonary failure developed acutely (within 2 weeks of the initiation of chemotherapy) in 8% of 1,541 patients during remission induction. Male sex, acute promyelocytic leukemia, poor performance status, lung infiltrates at diagnosis and increased creatinine were risk factors for the development of this syndrome. Seventy-three percent of the patient died [70].

31.3.1.7 Drug-Induced and Iatrogenic Pulmonary Fibrosis

The condition mostly develops in hematology patients treated with BCNU, bleomycin, busulfan, chlorambucil, cyclophosphamide, melphalan and/or radiation therapy/TBI. Less often, drug-induced fibrosis complicates treatments with gemcitabine, mercaptopurine, methotrexate and rituximab [11]. Drug-induced fibrosis may develop during treatment with drugs or it is diagnosed after termination of treatment. Imaging prior to onset of treatment with the drug helps confirm the time course of lung changes with respect to exposure to the drug or drugs, and enables separation from fibrosis of other causes. Early disease is in the form of

linear or streaky opacities and loss of volume. Honeycombing is a late and inconsistent finding. For those patients who are still on the causal drug, drug removal may not be followed by improvement, and the response to steroids is often not gratifying. On histology, there is interstitial fibrosis, and the lung structure may not be retained. A reactive epithelium is suggestive of but not specific to exposure to alkylating agents and/or radiation therapy. In children or adults who have received cyclophosphamide for the treatment of hematologic malignancy, pleural and subpleural fibrosis can develop in addition to the more classic changes of pulmonary fibrosis [114]. This results in encasing of the lung, anteroposterior narrowing of the chest and severe restrictive physiology causing respiratory failure. It is unfortunate when the syndrome develops in a child, while the basic disease is cured. A few patients who received chlorambucil or methotrexate develop accelerated pulmonary fibrosis in the form of acute interstitial pneumonia [115, 116]. The outcome of pulmonary fibrosis is poor, despite drug withdrawal and institution of high-dose corticosteroids. Lung transplantation has been an option in a few patients.

31.3.1.8 Drug-Induced Pulmonary Edema

Noncardiac pulmonary edema (NCPE) shows a classic pattern of response to several chemotherapeutic agents used to treat hematologic conditions. NCPE is due to the loss of integrity of the endothelial barrier and consequent fluid leakage. NCPE is characterized by the rapid or sudden onset of dyspnea, hypoxemia and alveolar infiltrates, with no evidence of left ventricular dysfunction or iatrogenic circulatory overload [although drugs used to treat malignancies may cause deterioration of cardiac function and cardiogenic pulmonary edema [117–121]. There is often close temporal association of exposure to the drug, onset of dyspnea and the development of pulmonary infiltrates. Chemotherapeutic agents associated with NCPE include ATG, cytosine arabinoside, all-transretinoic acid (ATRA), amphotericin-B, arsenic trioxide (As_2O_3), bleomycin, blood and blood components, carmustine, CSF, cyclophosphamide, deferoxamine, docetaxel, doxorubicine, fludarabine, gemcitabine, interleu-kin-2, methotrexate, mitomycin, radiocontrast agents, rituximab, vinorelbine and vinblastine

and several multiagent chemotherapy regimens [11, 122]. Most patients present with NCPE as an isolated finding, but in a few, weight gain, lower extremity or more diffuse edema and pleural and/or pericardial effusions suggest capillary leak [122, 123]. Pathology indicates bland pulmonary edema, with proteinaceous fluid filling most alveolar spaces and sometimes diffuse alveolar damage with little or no inflammation [37]. Severe cases can be fatal, but in most the infiltrates resolve with supportive care and corticosteroid therapy.

31.3.1.9 Diffuse Alveolar Hemorrhage

DAH is a unusual pattern of response to drugs in hematology patients [124]. This condition is on the background of DAH as a manifestation of the underlying disease with or without thrombocytopenia. Alemtuzumab, anticoagulants, ATRA, cytosine arabinoside and CSFs can produce this condition [11]. DAH can also occur with induction of remission in leukemia [125] and as a complication of hematopoietic stem cell transplantation [5, 29, 126, 127]. DAH is characterized by dyspnea, recent anemia, bilateral infiltrates and hypoxemia. The diagnosis is by BAL, which shows increased blood staining in sequential aliquots. DAH can be fatal [127].

31.3.2 Pulmonary Nodules

Single or multiple nodules with the features of BOOP or circumscribed fibrosis on pathology may develop in children and in adults following treatments with aracytine, bleomycin, bleomycin *and* cyclophosphamide, and vinblastine [66, 67, 128–130]. Nodules can pose a difficult challenge in a patient with a history of malignancy, particularly when they assume a round shape. A critical review of other etiologies is necessary [131]. Close follow-up including imaging and 18F-dideoxyglucose PET scan is indicated. A lung biopsy may be required to confidently exclude malignancy. A patient with chronic lymphatic leukemia developed multiple shaggy lung nodules during treatment with fludarabine [132]. The nodules corresponded to sterile aggregates of mononuclear cells on pathology. They disappeared after drug withdrawal and corticosteroid therapy.

Hematopoietic stem cell recipients may develop multiple pulmonary nodules in the context of fever a few months after infusion. Histological studies indicate sterile necrotic aggregates of leukocytes and a disrupted endothelium. The lesions have been coined pulmonary cytolytic thrombi [133].

Careful exclusion of malignancy and an infection is required in all cases, for infection due to *Pneumocystis jiroveci*, *Aspergillus* sp. and other fungi, HSP, *Rhodococcus*, *Mucor*, *Cryptococcus, Fusarium* and tuberculosis can manifest with lung nodules.

31.3.3 Acute Chest Pain

White et al. reported on 12 episodes of severe chest pain during infusions of bleomycin, suggesting the diagnosis of acute cardiac or pulmonary events [134]. Incidence of the syndrome was 2.8% of the patients being treated with the drug. Electrocardiographic changes suggestive of pericarditis were found in two cases and radiographic evidence of a small pleural effusion in one. The syndrome was self-limited or relieved with analgesics, and improvement was seen when the infusions were stopped. Further courses of bleomycin did not lead to recurrent episodes. There were no long-term sequelae. Substernal pain or pressure also was described during treatments with high-dose etoposide [135, 136] and methotrexate [137]. The lupus syndrome induced by drugs (for instance interferon) may manifest with acute chest pain [138]. Infusions of 5-fluorouracil or etoposide can produce acute coronary spasm and consequent chest pain [136]. Chest pain is a recognized adverse event in stem cell donors during mobilization [139].

31.3.4 Bronchospasm

Wheezing and bronchospasm are common symptoms in patients receiving antineoplastic drugs including monoclonal antibody therapy such as alemtuzumab or rituximab [140, 141]. Wheezing may be part of the "infusion reaction," a constellation of symptoms including dyspnea, cough, facial flushing, skin rash or urticaria, pruritus, chest tightness and malaise. There

is relapse upon rechallenge, except if pretreatment is given or the dose is reduced.

Bronchospasm has been reported with the use of amphotericin B, l-asparaginase, amphotericin B, campath-1H, etoposide, GM-CSF, methotrexate, procarbazine, vinca alkaloids and corticosteroid drugs [11]. The excipients and solvents dimethylsulfoxide [142] and cremophor [143] have also been implicated. There is a close temporal relation of drug administration and wheezing, and in most patients symptoms are mild to moderate. Patients with bronchospasm could be successfully rechallenged using slower doses or infusion rate, or following premedication with antihistamines and corticosteroids.

Some patients develop anaphylaxis, a life-threatening reaction with upper airway obstruction, severe bronchospasm, abdominal cramps and shock [144]. Drugs including antibiotics, anesthetic agents, oxaliplatin and blood can cause this condition [145, 146].

31.3.5 Pleural Involvement

Pleural effusion can be present on imaging in patients with pulmonary reactions to methotrexate, procarbazine or ATRA, especially if the reaction is severe [11, 147]. Bleomycin, cyclophosphamide, IL-2, IVIG, methotrexate, ATRA and radiation therapy can produce lone exudative pleural effusions [11, 148]. Pleural thickening and retraction is a form of late cyclophosphamide toxicity [114, 149]. Pneumothorax can complicate fibrosis induced by BCNU, cyclophosphamide or bleomycin [150]. Radiation-induced pleural changes are mentioned below.

31.3.6 Late Changes

Mild drug-induced reduction of vital capacity and/or diffusing capacity may persist for a few months in patients treated for hematologic malignancies. The likelihood of permanent physiological impairment is greater in smokers [102]. Follow-up of patients is required, especially in those who received a stem cell transplant, to monitor progressive changes (although their incidence is lower than it used to be [151]) and to

detect post-treatment lymphoproliferative disease and other malignancies.

31.3.7 Drug-Induced Lymphoma and Second Cancers

As basic disease-related mortality has decreased with time in patients with Hodgkin's disease and non-Hodgkin's lymphoma once remission is obtained, therapy-related mortality increases with time and is becoming the most prevalent cause of late deaths [152]. Although a downward trend in mortality has been noted in more recent years (1980–1995) compared to the prior treatment era (1962–1980), second cancers and cardiovascular complications still account for 20% and 14% of late deaths, respectively [152]. The risk of second or higher-order lung cancer in Hodgkin's disease and non-Hodgkin's lymphoma is increased [153], and it correlates with the dose of radiation delivered to the lung, amount of chemotherapeutic agents received and whether the patient is a smoker. In one study, the relative risk of lung cancer in patients who received ≥9.6 Gy was 9.6 compared to <1 Gy. Patients who had smoked >10 pack-years after the diagnosis of Hodgkin's disease had a further sixfold increase in risk, compared with patients who smoked <1 pack-year. A positive interaction on a multiplicative scale was observed between the carcinogenic effects of smoking and radiation [103]. Studies have found a positive interaction between treatment with MOPP (mechlorethamine, vincristine, procarbazine and prednisone), the number of cycles and the risk of lung cancer [154]. Radiation therapy added to the risk [155]. In another study, treatment with MOPP was associated with a greater risk of lung cancer, compared to chlorambucil, vinblastine, procarbazine and prednisone [156]. Since tobacco use appears to synergize the risks from treatments and increase lung cancer risk more than 15- to 20-fold, physicians treating these patients need to be wary of the risk and should make a special effort to dissuade patients with Hodgkin's disease from smoking after receiving chemotherapy and radiotherapy. Smoking cessation is a vital part of long-term management of such patients.

Incidence of pleural mesothelioma increases post-radiation therapy in malignant lymphoma survivors [157]

31.4 Drugs Causing Pleuropulmonary Toxicity in Hematology

31.4.1 Amphotericin B

Not uncommonly, infusions of amphotericin B produce wheezing and bronchospasm [11, 158]. Rarely, amphotericin evokes an anaphylactic reaction with or without upper airway obstruction [159]. Not all manifestations will return upon rechallenge, and there are guidelines to reexpose patients to the drug [160].

Wright et al. described 14 patients who developed pulmonary infiltrates and acute respiratory failure shortly after infusion of amphotericin B and granulocytes [161]. Lung biopsy and autopsy studies disclosed DAH and pulmonary edema. Other studies failed to confirm an association. The possibility of a TRALI syndrome induced by coadministered granulocytes is a possibility. No further case has appeared in the literature.

Infusion of liposomal amphotericin B or amphotericin in 20% intralipid can produce dyspnea, chest tightness, pulmonary infiltrates and pulmonary edema [162]. Histopathological studies in a fatal case evidenced fat embolism with lipid material in pulmonary capillaries [163].

31.4.2 Anti-thymocyte Globulin

Transient pulmonary infiltrates thought to represent mild pulmonary edema or, less often, an ARDS picture have been described following anti-thymocyte globulin (ATG) infusion [164]. Rechallenge was followed by recurrence of pulmonary infiltrates [164]. In one recent report, steroid-supported rechallenge was not followed by relapse [33].

31.4.3 All-trans-Retinoic Acid (ATRA) and Arsenic Trioxide As_2O_3

All-*trans*-retinoic acid or ATRA, the active metabolite of vitamin A, and arsenic trioxide (As_2O_3) have emerged as important agents to induce remission in newly diagnosed or relapsed acute promyelocytic leukemia [165], where these agents accelerate the differentiation and maturation of normal promyelocytic cells, which quenched the life-threatening hemorrhagic complications of the disease at its onset. The administration of ATRA during induction of remission is often followed in a few days by a sharp increase in the number of circulating myeloid cells and neutrophils. This is temporally associated in some patients with the development of fever, weight gain, pleuritic chest pain, pleural or pericardial effusion, lower extremity edema, dyspnea, pulmonary infiltrates, pulmonary edema, alveolar hemorrhage, or an ARDS picture [166–169]. This aggregate of symptoms developed an average of 8 days after initiation of treatment and is grouped under the eponym "retinoic acid- or ATRA syndrome" [166]. Similar manifestations are observed in patients who receive As_2O_3 in up to 31% in one study [170], causing respiratory death [171]. The condition is also referred to as ATRA or retinoic acid syndrome. Onset of ATRA syndrome can be heralded by an increase in circulating neutrophils. Patients with neutrophil counts above 10,000/μL are considered at risk of developing the syndrome, while the condition is considered unusual in leukopenic patients [166]. ATRA syndrome is thought to result from the sequestration of activated neutrophils in pulmonary capillaries, leading to acute lung injury and vascular leakage. Radiographic studies indicate ill-defined infiltrates, ground-glass opacities, lung nodules that may progress to diffuse alveolar shadows, and pleural effusions [172]. Blasts and promyelocytes containing Auer rods were evidenced in the BAL in one case [173]. Postmortem studies indicate maturing and mature myeloid cells within the pulmonary interstitium [166]. Capillaritis and diffuse alveolar hemorrhage have been reported once [174]. Patients improve on drug removal and high-dose corticosteroids [166]. Prophylactic corticosteroids have decreased both the severity and incidence of ATRA syndrome down to about 8% [175]. Mortality from ATRA syndrome is about 8% or 1% of all patients treated with these agents. In most cases, ATRA therapy can be reinstituted once the syndrome has resolved [176], although at 75% of the initial dosage [177]. ATRA may also cause venous thromboembolism and infarction in several end organs, including the lung [178]. As_2O_3 may also cause adverse cardiac effects [179].

31.4.4 Azacytidine

The DNA hypomethylating agent azacitidine was approved for treatment of myelodysplastic syndrome. A few cases report the association of treatments with the drug and episodes of ILD, BOOP, or reversible ARDS [180–182]

31.4.5 Bis-Chlororethyl Nitrosourea Carmustine

The bis-chlororethyl nitrosourea (BCNU, carmustine) drug derives from the vesicant chemical warfare mustard. BCNU is an alkylating agent introduced in 1963 in the treatment of malignant brain tumors because of its low molecular weight. Currently, BCNU is used for the treatment of high-risk breast carcinoma and as a conditioning regimen for bone marrow and stem cell transplantation along with busulfan or cyclophosphamide and total body irradiation (TBI). BCNU and TBI are thought to play a crucial role in the pathogenesis of chemotherapy lung and idiopathic pulmonary syndrome (see above). The lower incidence of idiopathic pulmonary complications with nonmyeloablative as opposed to myeloablative preconditioning regimens supports the causal role of the intensity of the conditioning regimen in its development. The pulmonary complications of BCNU when the drug was used as a solo agent have been described in children and in adults, and BCNU has caused pulmonary toxicity more often than the other nitrosoureas CCNU (lomustine), DCNU (chlorozotocin), methyl-CCNU, streptozotocine, fotemustine, and estramustine. Carmustine lung damage is dose-related, and the incidence is between 1% and 10%. BCNU pulmonary toxicity is one form of chemotherapy lung, and it resembles clinically, pathologically and on imaging the pneumonitis induced by bleomycin, busulfan, chlorambucil, cyclophosphamide, melphalan, and vinblastine. A total dose of 1,000–1,200 mg/m^2 of BCNU is considered the threshold above which the incidence of pulmonary toxicity increases steeply when the drug is used as a single agent [183]. Incidence of BCNU toxicity increases about tenfold when cyclophospamide or irradiation is given concomitantly. Up to two thirds of patients treated with high-dose chemotherapy and BCNU develop clinical and physiological evidence of pulmonary toxicity [184]. An attempt to reduce pulmonary toxicity in a modified CBV regimen using CCNU instead of BCNU followed by autologous hematopoietic cell transplantation in 16 patients with relapsed or refractory Hodgkin's disease or non-Hodgkin's lymphoma was associated with a 63% incidence of interstitial pneumonitis, and 6 of 16 affected patients died of interstitial pneumonitis [185].

Early disease presents subacutely, a form of BCNU lung toxicity that is more amenable to corticosteroid therapy, thereby having an improved prognosis [107, 184]. Late BCNU toxicity is characterized by pulmonary fibrosis [186] and progressive respiratory failure [187]. The histopathological appearances of BCNU pneumonitis are similar to those from other alkylating agents with interstitial edema, diffuse alveolar damage, a reactive epithelium, and interstitial fibrosis [188–190]. Less common features include pleural fibrosis [189], vascular thrombosis, venoocclusive disease, or pulmonary alveolar proteinosis [187]. Long-term follow-up indicates that a fraction of patients with hematologic malignancies may die late from nitrosourea-related respiratory failure [191].

31.4.6 Bleomycin

In the 1960s, bleomycin was one of the first drugs recognized as a cause of lung disease [192]. Bleomycin pulmonary toxicity (BPT) is common [193, 194] and there are recent reports in patients who received the drug with other antineoplastic agents for the treatment of malignant lymphoma [195, 196] or solid tumors [197, 198]. Many therapy-related pneumonitis cases that occur in patients receiving chemotherapy regimens containing bleomycin (e.g., ABVD, BACOD) are reported as BPT [196].

Onset of BPT is not as acute as that of methotrexate lung. BPT can be severe, but this form of toxicity may be less debilitating than busulfan, nitrosoura, or myleran lung. The characteristics of BPT may be discernible even though bleomycin is given along with other chemotherapeutic agents [193]. Even though early reports warned of the possibility of BPT after low cumulative dosages of the drug [199], for many

years it was believed that bleomycin caused pulmonary toxicity only above 500 mg. In fact, although the incidence of BPT is dose-dependent [193], BPT can occur with as little as 20 or 34 mg bleomycin [200, 201]. Renal failure places patients at higher risk of developing BPT [79, 202], owing to decreased clearance of the drug. Slow as opposed to rapid i.v. infusion and intramuscular administration of bleomycin lessen the risk of BPT. Previous use of bleomycin should be considered in those patients requiring retreatment, as there is cumulative toxicity. In some but not all studies, advancing age was a risk factor for BPT. Concomitant or recent irradiation [203, 204], treatments with cyclophosphamide [205], and exposure to high concentrations of oxygen add to the risk and may trigger the onset of BPT [206]. Although not everyone will agree [207], it is prudent to request that anesthetists use the lowest possible fractional concentration of oxygen when patients with a history of exposure to bleomycin undergo any surgical procedure. In some but not all studies, a history of BPT negatively impacts overall survival of patients with malignant lymphoma [196, 208].

Incidence of BPT was once estimated to be 2–3% [209, 210], but recent figures are around 10–15% [196, 197, 202]. Recently, a 11.5% incidence of BPT was reported when bleomycin was administered with vincristine and cisplatin every 10 days [197]. Mortality is about 10%, and overall mortality was 2.3% in a study of 194 patients treated for germ cell tumors with this agent [202]. Mortality is higher in older patients, in those with renal failure [202], and in those with severe BPT, where mortality can be as high as 60% [209].

Clinically, BPT presents acutely or subacutely with dyspnea, and sometimes chest pain [134, 194, 210]. Some chest discomfort may be present at some point before BPT is suspected, representing early BPT that went unrecognized [210]. Crackles on auscultation may precede the radiographic changes of BPT. Imaging studies indicate the predominant involvement of the lung bases as opposed to the apices, costophrenic angles, and subpleural regions, and there is often generalized loss of lung volume [193, 211]. A retrospective review of chest films may show the gradual development of these changes, and it is easy to miss the actual onset of BPT. On HRCT in mild cases, a diffuse ill-defined ground-glass pattern or haze is present. Later, patients develop discrete subpleural crescent-like opacities, streaky opacities along the

bronchovascular bundles, alveolar infiltrates, alveolar densities, consolidation, or the clinical-radiographic picture of ARDS [48, 194, 212, 213]. Changes on imaging correlate poorly with impairment of the diffusing capacity [48]. Some patients present with masses on imaging that may about the pleura [48, 214]. Pleural thickening or an effusion is an unusual finding. Several of the above mild HRCT findings are common (up to 80%) in asymptomatic patients during treatments with bleomycin [193]. However, they do not necessarily indicate toxicity, and drug discontinuance is not always required. In one study, such changes occurred in 15 out of 18 patients [215], none of which developed clinically recognizable disease. Thus, serial HRCT may not be a practical test to ensure early detection of BPT, which is best monitored using history, clinical examination, pulmonary function, and the chest radiograph.

On pulmonary function tests a restrictive defect, hypoxemia, and a reduction in the diffusing capacity are present. A low diffusing capacity does not equate toxicity and may predate onset of overt toxicity by weeks. The BAL pattern is neutrophilic [216]. Pathologic features of BPT resemble those seen with the other alkylating agents such as busulfan, chlorambucil, cyclophosphamide, melphalan, and nitrosoureas. Tissue eosinophilia is uncommon and has been reported in patients with the diffuse [198, 217] and nodular (BOOP) [66] form of the disease. The development of parenchymal lung nodules in patients receiving bleomycin is almost unique to this compound, and it can be problematical [218], raising the possibility of parenchymal involvement from the underlying hematologic malignancy [66]. The area's BPT can be tracer-avid on PET scan [35, 219]. Previous imaging, time course of disease markers, earlier PET scan, and response to chemotherapy will dictate whether watchful waiting is indicated or a lung biopsy is necessary so separate these entities. Nodular BPT corresponds to the histological pattern of BOOP with or without eosinophilia in the tissue. Nodular BPT may shrink or clear in a few weeks.

Overall, the prognosis of BPT is less dismal than with the other alkylating agents. A sizable fraction of patients with BPT have reversible disease [194], even though there was evidence for fibrosis on pathology [220]. Corticosteroids are the mainstay of treatment, and, although no controlled study is available, there is clinical evidence for benefit of this form of treatment

in mild or moderate BPT. Corticosteroid therapy can be without an effect in severe BPT [197]. It is considered that if patients survive the initial episode of BPT, they are likely to recover gradually [194]. Early or abrupt withdrawal of corticosteroids is discouraged, as this may lead to a severe relapse of BPT [209], and a slow taper is recommended. Some patients develop irreversible bleomycin-induced pulmonary fibrosis [221] with, ultimately, honeycomb lung and clubbing, and die from the condition [209].

The question of whether serial pulmonary function testing is useful in identifying patients who will develop BPT was assessed in 59 men with non-seminomatous testicular carcinoma (the findings probably apply to hematology patients as well) [110]. Patients received a three-course regimen consisting of vinblastine, bleomycin, and platinum. The average bleomycin dose was 555.5 units. Pulmonary physiology was serially evaluated prior to each treatment course. The diffusing capacity fell significant by 11.8% with bleomycin treatment. However, the diffusing capacity failed to predict which patients would develop clinical toxicity. The reduction in the total lung capacity had a better correlation with clinical toxicity [110]. Despite the inability of the diffusing capacity to detect patients who will develop clinical toxicity [110, 222], serial measurement of lung volumes and of diffusing capacity are still routinely performed in this population also for medical-legal reasons [223]. The diffusing capacity decreases in up to 75% of the patients treated with bleomycin, and in only a few will clinical toxicity develop [223]. Any asymptomatic impairment of the DLCO is likely to improve slowly upon termination of treatment. The lung of patients exposed to bleomycin in the remote past should be considered vulnerable, as suggested by occasional reports of unexpected ARDS after minor insults years after termination of treatment with this agent [224].

31.4.7 Blood and Blood Products: Transfusion-Related Acute Lung Injury

TRALI is a potentially devastating complication defined by hypoxemic respiratory failure within 6 h of transfusion, once other causes are excluded. To some extent, TRALI is avoidable and can be prevented. By definition, acute lung injury is defined by a PaO_2/FIO_2 ratio <300, hence the term TRALI. However, some severe TRALI cases would deserve the eponym TR-ARDS, for the PaO_2/FIO_2 ratio in those cases is <200. TRALI is a noncardiogenic pulmonary edema that is temporally and mechanistically related to transfusion of blood and/or blood components. TRALI occurs within 6 h of transfusion. TRALI results from the sequestration of primed and activated neutrophils in the pulmonary circulation, thereby causing endothelial injury and consequent fluid leakage. TRALI is more common in ICU patients [225], and the condition adversely affects outcome. TRALI has a 10% attendant mortality and is the leading cause for transfusion-related deaths [78, 225–231]. Although all blood components have been implicated in TRALI, those that contain a significant amount of plasma, namely fresh frozen plasma and whole blood-derived platelet concentrates, are exposed to a higher risk, compared to red blood cells or whole blood [230, 232]. Plasma-rich components carry a greater risk of containing a substantial quantity of antibody from a donor, which in the majority of cases is the cause of TRALI. Whole blood, immunoglobulins, stem cells, or, rarely, autologous blood have also been implicated [230, 232].

TRALI results from the transfusion of an anti-HLA I, -HLA AII, or human neutrophil alloantigen (HNA-3a-(5b)) antibody from one donor in the pool into patients whose leukocytes express the corresponding cognate antigens [230]. Such antibodies are found in 60–85% of cases. The case for a relationship is more compelling if concordance between the antigen specificity of the leukocyte antibodies in the donor plasma and the corresponding antigen on the cells of the affected recipient is demonstrated [233]. This is found in about 50% of cases. The antibody-antigen interaction causes complement-mediated activation and sequestration of neutrophils in the pulmonary circulation and intravascular cholesterol crystal formation [234], endothelial damage, vascular leakage, and consequent pulmonary edema [230, 234, 235]. Antibodies are more prevalent in women with a history of pregnancies, and the antibody titer increases with the number of pregnancies. Antibody prevalence is lowest in men and in nulliparous women. Although this antibody-antigen hypothesis is attractive, there are antibody negative TRALI cases, TRALI can occur in neutropenic patients, and there is one cause of TRALI

following auto-transfusion. Understanding and recognizing TRALI are important. The responsible donor, generally a multiparous woman with high titers of antibody, should be identified. Laboratory investigations should be undertaken in donors to identify the antibody and in the recipient to determine whether his leukocytes bear the cognate antigen. Then the TRALI case can be classified into immune or nonimmune TRALI, the blood bank should be notified to quarantine other components from the same donation until the diagnosis is confirmed, and the implicated donor is identified. The implicated donor should be deferred from further blood donation or their blood diverted to prepare plasma-poor products, not whole blood, FFP, or platelets [232].

TRALI is poorly known [236], and it is underreported [237]. Incidence of TRALI is about 1 in 5,000 transfusions in the US (between 0.08% and 0.16% of all blood transfusions) and is less in Europe. Incidence is higher in ICU patients and in patients with a history of recent bypass surgery, recent infection, in patients with hematologic diseases, and in those who received CSF. This is consistent with a two-hit hypothesis for TRALI, whereby pulmonary endothelial cells are first activated, and PMN are primed and sequester in the pulmonary circulation. Then, transfusion of a biologic response modifier such as anti-granulocyte antibody or biologically active lipids activates adherent neutrophils resulting in endothelial damage vascular leakage and TRALI [238].

By definition, the symptoms of TRALI develop within 6 h of the transfusion in the form of abrupt respiratory failure with rigors, dyspnea, tachypnea, cyanosis, hypotension, leukopenia, mild eosinophilia "whiteout" of the lungs [239], and evidence for fluid leakage [240]. Severe cases are heralded by a protein-rich exudate at the mouth or in ventilator tubings [241]. Sudden intraoperative hypoxemia during blood transfusion or infusion of FFP should raise the suspicion of TRALI [242, 243]. Transient hypoxemia following blood transfusion in patients on the respirator may correspond to TRALI [238]. The main competing diagnoses include transfusion-associated circulatory overload or TACO (both conditions can coexist), transfusion-related sepsis, anaphylaxis, and hemolytic reactions [244]. Imaging studies and measurement of BNP levels may aid in separating TACO from TRALI [245], and an important distinction for diuretics is

contraindicated in TRALI [230]. Once TRALI is suspected, laboratory investigation should be undertaken on the remains of transfused products, in the recipient, and in donors whose blood or component were given within 6 h prior to the development of TRALI for the presence of antibodies [226]. Retrospective investigation can evidence an antibody in one donor in the pool in up 89% of cases [246], and a cognate antigen-antibody correlation was identified in 14 of 16 TRALI cases in one study [247].

Underrecognition and underreporting of TRALI may have detrimental consequences. A lookback investigation following a fatal case of TRALI indicated that administration of blood from the implicated donor had produced 15 previous adverse reactions in 14 patients, of which eight were severe [226]. Only two were reported to the regional blood collection facility, and the donor was not deferred from blood donation [226]. Other less common mechanisms for TRALI include antileukocyte antibody in the recipient that react with donor's leukocytes [248] and shelf aging of blood products, leading to accumulation of lipid-derived biologic response modifiers.

Management of TRALI is supportive and includes judicious fluid management, oxygen, and mechanical ventilation in severe cases. Approximately three quarters of patients with TRALI need ventilatory support. The effect of corticosteroid drugs is controversial. Diuretics should be used with caution as TRALI often is associated with fluid leakage, and diuretic therapy may aggravate hemodynamic instability [249]. Diuretics are reserved for cases with documented fluid overload and/or left ventricular failure [244, 249]. Most TRALI cases will recover within 96 h.

Prevention of TRALI relies on parsimonious use of blood transfusion, particularly of plasma rich blood components and in the ICU. Other measures include blood washing to remove biologically active substances, the use of solvent-detergent plasma, improved donor selection, male predominant or male only policy, which is associated with a reduction in the incidence of TRALI, and minimization of shelf life of blood products. Awareness, proper recognition, and reporting of TRALI are essential. Screening blood donors or testing donors with a history of pregnancy or transfusion is a logical and cost-effective TRALI prevention strategy. However, this may not meet with

success, as not all blood components with antibodies will produce TRALI in the clinic.

31.4.8 Bortezomib

Treatments with the proteasome inhibitor bortezomib have been associated with the development of pulmonary infiltrates [250–253]. The incidence is 3% in Japan and is less in the West. The highest recorded incidence was 31% [254]. Corticosteroid therapy may prevent the development of bortezomid-associated pulmonary infiltrates. The condition needs be separated from the pulmonary manifestations of multiple myeloma, which include plasma cell infiltrates and crystal-storing histiocytosis, and from an infection [20, 22].

31.4.9 Busulfan (Myleran)

Most cases of busulfan lung were described in the 1960s and 1970s [255], when the drug was used as a single-agent for the treatment of chronic myelogenous leukemia [256]. Nowadays, busulfan is mainly used in conditioning prior to hematopoietic stem cell transplantation, where busulfan pulmonary toxicity is enhanced by drug dosage as seen in recipients of autologous stem cell transplant [257] and by concomitant irradiation [257]. Time to onset of busulfan lung is from a few weeks to 10 years. Administration of other chemotherapy agents increases the risk of developing the condition. Busulfan lung is notable for hugely reactive alveolar cells in the lung and in other epithelia [258], pulmonary fibrosis [259], and, less commonly, a pattern of organizing pneumonia [260], or pulmonary alveolar proteinosis [261]. Long-term exposure to busulfan may produce a brownish discoloration of the skin simulating Addison's disease [256]. Although the incidence of busulfan lung is relatively high, with figures up to 6%, the disease is difficult to predict as pulmonary function of unaffected patients may remain unchanged during treatment [262]. Although reports of pure busulfan lung have decreased in the past years, busulfan pulmonary toxicity continues to afflict patients with hematologic malignancies or breast carcinoma who receive chemotherapy regimens including this drug, although the lung illness in these cases is not coined busulfan lung any longer [257].

31.4.10 Chlorambucil

Chlorambucil is prescribed primarily for the treatment of chronic lymphatic leukemia and low-grade lymphomas. The clinical imaging presentation and pathologic features of chlorambucil pulmonary toxicity are not dissimilar to those described in other alkylating agent-induced pulmonary toxicity [263–265]. Notably, there are atypical changes in alveolar lining cells. A handful of cases of seemingly cellular interstitial lung disease have been reported, with recovery following drug discontinuance and corticosteroid therapy [265]. One recent case report of focal BOOP is thought to reflect chlorambucil pulmonary toxicity [266].

31.4.11 Colony-Stimulating Factors

Colony-stimulating factors (G & GM-CSF) stimulate the production of neutrophils from committed hematopoietic progenitor cells. These agents are used to restore neutrophil counts in patients who are receiving myeloablative chemotherapy or have aplastic anemia, and to mobilize progenitor cells in stem cell donors. A few case reports described pulmonary infiltrates in patients receiving G-CSF monotherapy [7, 267, 268]. Most cases described pulmonary infiltrates or ARDS in patients who were being treated with chemotherapeutic agents (bleomycin, busulfan, methotrexate, or TBI) in conjunction with G- or GM-CSF [208, 269]. In a series of 36 patients with non-Hodgkin's lymphoma receiving a BACOP regimen, 12 received recombinant G-CSF. Out of these 12, four developed respiratory complications (3 died), as opposed to 1 of 24 unexposed patients [270]. Other reports reported fatal respiratory distress in patients receiving CSF for hematologic malignancies [271] or nonneoplastic conditions [271].

Experimental evidence indicates that G-CSF leads to sequestration of activated neutrophils in lung [272] and enhances the damage from bleomycin [273].

However, a randomized study in patients with germ cell tumors failed to demonstrate an increase in incidence of BPT in patients who were exposed G-CSF compared to bleomycin controls [274]. In several patients, but not in all, pulmonary infiltrates developed concomitant with CSF-induced peak in circulating neutrophils [275]. A few cases were described in patients who had persistently low neutrophil counts.

Clinical severity ranged from transient subclinical hypoxemia [276] to diffuse pulmonary infiltrates or an ARDS picture [276]. Lymphocytosis was found in the BAL in one case [277]. CSF-associated infiltrates cleared in a few days or they persisted for weeks. Mortality is about 20%, and prognosis is improved on corticosteroid therapy [275]. Rechallenge may not lead to relapse of the pulmonary infiltrates [275].

CSF-induced mobilization in donors can also induce pulmonary complications. These range from a subclinical drop in PaO$_2$ with a widened A-a oxygen gradient [278] to pulmonary infiltrates, ARDS, or capillary leak and pleuropericardial effusion [7, 268, 278, 279].

31.4.12 Corticosteroids

Long-term corticosteroid therapy leads to mediastinal lipomatosis, a radiographic curiosity in most patients and a cause for cough or mediastinal hemorrhage in a few [280, 281].

Corticosteroids may induce respiratory muscle weakness, with consequent restrictive lung dysfunction [282].

Allergy and anaphylaxis are rare [283–285].

Corticosteroids exert a broad range of immunosuppressive activities [286], and patients on corticosteroids long-term run the risk of developing opportunistic pulmonary infections, including *Pneumocystis jiroveci* pneumonia [8].

31.4.13 Cyclophosphamide

Like busulfan and nitrosoureas, cyclophosphamide is an alkylating agent used in the treatment of various forms of leukemias and lymphomas and as a conditioning agent prior to stem cell transplantation. Cyclophosphamide may produce early or late pleuropulmonary toxicity [114].

Early cyclophosphamide pulmonary toxicity resembles that of other alkylating agents, is associated with BAL lymphocytosis [287], and is reversible upon removal of the drug, except in patients who develop early ARDS [288]. The prognosis of early cyclophosphamide pulmonary toxicity exceeds that for the nitrosoureas and busulfan, and if diagnosed early, this form of cyclophosphamide pulmonary toxicity is largely reversible upon removal of the drug and institution of corticosteroid therapy. It is important to rule out an infection [289], especially *Pneumocystis jiroveci* pneumonia, which is difficult to differentiate from, and can coexist with cyclophosphamide pneumonitis [290].

Late cyclophosphamide pulmonary toxicity mostly follows chronic oral exposure [114, 291], occurring with up to 13 years of treatment [292]. Chronic cyclophosphamide pneumonitis takes the form of progressive pulmonary fibrosis with respiratory failure, and sometimes digital clubbing is present [293]. The peculiar feature in a subset of patients with late cyclophosphamide toxicity is a pattern of pleuropulmonary fibroelastosis that involves the upper and lateral aspects of the pleura, which is thickened, in addition to more conventional changes of pulmonary fibrosis of the underlying lung [114, 149, 294, 295]. Progressive narrowing of the anteroposterior aspect of the thorax may develop in children, contributing the restrictive physiology, which is progressive with time [149, 296]. Pneumothorax may complicate this form of late cyclophosphamide pleuropulmonary toxicity, and it is difficult to treat as the underlying fibrotic lung reexpands poorly. Chronic cyclophosphamide pneumonitis is irreversible, even with drug withdrawal and institution of corticosteroid therapy [114].

31.4.14 Cytosine-Arabinoside (Ara-C)

Treatments with high-dose Ara-C can be complicated by transient pulmonary infiltrates or pulmonary edema [297–299]. The condition develops in close temporal association with administration of the drug [299, 300]. In a series of 181 autopsies of patients with leukemia, unexplained massive proteinaceous pulmonary edema correlated with recent administration of Ara-C [297]. Pathology discloses bland alveolar flooding by proteinaceous material, suggesting acute fluid leakage [301]. Little or no inflammation is present. Less severe

cases show diffuse alveolar damage [85]. Several case histories are consistent with a beneficial effect of corticosteroid therapy in aracytine-induced pulmonary edema.

Recently, acute pulmonary edema and bilateral pleural effusion were diagnosed in a patient who received methotrexate 1,000 mg/m² daily and cytarabine 3,000 mg/m² twice a day on day 2 and 3 and G-CSF [302]. A patient who received 10 mg/m² mitoxantrone daily for 6 days and 3 g/m² IV ARA-C developed histologically documented BOOP. Chagnon et al. described transient centrilobular nodules in six patients with acute myelogenous leukemia and treatment-induced neutropenia [303]. These abnormalities of uncertain background and significance were thought to represent drug toxicity.

31.4.15 Dasatinib

Dasatanib is a multitargeted inhibitor of bcr-abl and SRC family tyrosine kinases that is approved for rescue therapy in patients with imatinib-resistant chronic myelogenous leukemia, and it is also used when imatinib induces adverse effects. The drug is known to cause pleural effusions in 10–35% of patients who receive it [304, 305]. The effusion was an exudate in 78% of the assessable cases [306]. Dasatinib may also cause lung injury in the form of pulmonary infiltrates [32]. In 40 patients on dasatinib, 6 had a lymphocyte predominant pleural exudates, and 7 had parenchymal ground-glass or alveolar opacities or septal thickening [32]. Lymphocytes represented up to 92% of the cells in the BAL, and lymphocytes were confirmed in pleural tissue in one case. Upon dasatinib discontinuance (with corticosteroid therapy in one patient), manifestations of the disease abated or resolved in all nine cases. Interestingly, no relapse occurred in three of four rechallenged patients [32], enabling resumption of treatment with this often vital drug. Lymphocyte-rich effusions (bilateral in one case) were also reported in two patients [304]. Chylous fluid was present in one patient. The authors suggested that the effusions were the result of PDGFR inhibition [304].

Dasatinib 100 mg once daily instead of the classic 70 mg twice daily retains efficacy and reduces toxicity with reduced incidence of pleural effusions from 16% to 7% [307]. With the better delineation of dasatinib-induced pleuropulmonary toxicity, noninvasive diagnosis and management should enable cost containment of this adverse effect [308].

31.4.16 Deferoxamine

Deferoxamine is used to treat iron overload in transfusion-dependent thalassemia. When given in high dosages or over more than 24 h, deferoxamine may cause diffuse alveolar damage or pulmonary edema [309]. IgE-coated mast cells were evidenced in lung tissue [310]. Rarely, deferoxamine triggers an anaphylactic reaction [311]. No recent case has been published.

31.4.17 Etoposide

The podophylotoxin derivative etoposide (VP16-213) is part of conditioning regimens for stem cell transplantation, and the drug is used in the management of refractory Hodgkin's lymphoma. Pulmonary reactions are of the hypersensitivity type, with suggestive chronology, facial flushing, wheezing, and hypotension [141]. Prudent rechallenge with the drug can be attempted and was successful in up to three quarters of cases [135]. Very few patients with presumed etoposide pneumonitis have been described. The histopathological features may include diffuse alveolar damage, alveolar hemorrhage, and type II cells reactive changes [312].

31.4.18 Fludarabine

Fludarabine monophosphate, the 2-fluoro, 5′ phosphate derivative of 9-beta-D-arabinofuranosyl adenine (ara-A), is a purine analogue used in the treatment of a variety of hematologic malignancies, including chronic lymphatic leukemia, other low-grade non-Hodgkin's lymphoma resistant to alkylating agents, and acute leukemias. Acute interstitial pneumonitis due to fludarabine was first described in 1987 [313]. The disease improved on high-dose steroids, recurred with steroid withdrawal, and abated with further steroid therapy [313]. Fludarabine pneumonitis can occur as early as

7 days into treatment, with an incidence rate of 1–8.6% [314]. Patients with a background of chronic lymphatic leukemia and preexisting interstitial pulmonary opacities may be at higher risk of developing pulmonary toxicity [315, 316]. On pathology, cellular interstitial pneumonia, eosinophilic pneumonia, granulomas, BOOP, and DAD with reactive type II cell changes have been described [316, 317]. Fludarabine pneumonitis can occasion severe symptoms and can be fatal [318]. In most cases, symptoms abate with drug removal and corticosteroid therapy. Rechallenging the patient leads to recurrence of manifestations of the disease [316, 318].

31.4.19 Gemcitabine

Gemcitabine (2,2-difluorodeoxycytidine) is a deoxycytidine analog with structural similarities to cytosine arabinoside. The drug is to treat several hematologic and nonhematologic malignancies, including malignant lymphoma and lung cancer. The first description of gemcitabine pulmonary toxicity was in 1997 in the form of noncardiac pulmonary edema, ARDS, and alveolar hemorrhage in three patients, and corticosteroid therapy was effective in reversing symptoms [92]. Thirty-one reports of gemcitabine pulmonary toxicity were available in the literature in 2006, and there were 147 other unpublished reports gathered in the RADAR project [319].

The incidence of gemcitabine pulmonary toxicity is 0.02–3% [122, 320, 321]. Gemcitabine pulmonary toxicity may develop after one or several courses with the drug, with a mean time to onset of 48 days (range 1–529 days). Drugs that cause pulmonary injury such as bleomycin or docetaxel may synergize gemcitabine pulmonary toxicity [319]. The incidence of gemcitabine pulmonary toxicity was 22% when the drug was added to bleomycin, doxorubicine, and vinblastine in a phase I/II trial in end-stage Hodgkin's disease [75]. Combining gemcitabine and docetaxel induced a 37% incidence rate of pneumonitis [322]. In yet another study where gemcitabine was added to doxorubicin, bleomycin and vinblastine for the treatment of de novo Hodgkin disease, the incidence of pulmonary toxicity was 41.7% [74]. In a recent study, gemcitabine given with the anti-CD30 antibody VGN-30 was associated in a 31% rate of pulmonary toxicity [323]. Whether and to what extent pulmonary toxicity in these studies

is due to gemcitabine or to the coadministered drugs is unclear. Gemcitabine potentiates the adverse effects of radiation therapy [324].

Gemcitabine pulmonary toxicity manifests with cough, dyspnea, and fever in the context of diffuse bilateral ground-glass or denser shadowing with or without pleural effusion. Features consistent with capillary leak such as weight gain and lower extremity or generalized edema can be present [122]. On HRCT, the appearances of gemcitabine pulmonary toxicity include inter- and intralobular thickening, ground-glass opacities, and pleural effusions. Histopathological appearances include alveolar edema, hyaline membranes, diffuse alveolar damage, and accelerated lung fibrosis, whereas alveolar hemorrhage, interstitial pneumonia, and reactive type II cells are less common features [92, 325–327]. Corticosteroids were used with benefit in several cases. Mortality is about 20% [328]. Rechallenge with the drug produces relapse of symptoms [329] and may occasion fatal respiratory failure [92].

Gemcitabine pulmonary toxicity may also manifest in the form of the hemolytic and uremic syndrome (HUS). Presenting features include systemic hypertension, anemia, thrombocytopenia, hematuria, renal failure, and circulating schizocytes. The incidence is up to 2.2%, and 35 cases were reviewed [330]. Subclinical HUS has been described, and monitoring of hemoglobin, creatinine, and circulating schizocytes is advised in patients who have received the drug.

31.4.20 Hydroxyurea

Eleven cases of hydroxyurea-induced pneumonitis were reviewed in 2003 [331]. The pulmonary reaction developed after 3–12 weeks on the drug in the form of fever and bilateral reticular or nodular infiltrates, and a small pleural effusion was present in five cases. Rechallenge with the drug was followed by recurrence. Outcome is good [331].

31.4.21 Interferon

Interferon (IFN) alpha and beta are a therapeutic option in patients with chronic myelogenous

leukemia, myeloma, and myelofibrosis, in addition to their established use for the treatment of chronic hepatitis C virus infection and multiple sclerosis. Interferon gamma has been used experimentally as a salvage therapy of corticosteroid-resistant pulmonary toxicity syndrome following BCNU-based chemotherapy and met with limited success in the treatment of pulmonary fibrosis. The respiratory complications from IFN (mostly alpha 2b [332]) may be dose-dependent and occur more commonly following the use of pegylated IFN, and may develop regardless of the underlying disease for which IFN is given. However, most reports are in patients with hepatitis C virus infection [333]. The most distinctive adverse effect of IFN alpha and beta is a picture indistinguishable from naturally occurring sarcoidosis. After a few months into treatment, patients develop *de novo* sarcoidosis or there is reactivation of previously diagnosed quiescent sarcoidosis. The lung, liver, heart, central nervous system, and skin can be involved [333], and hypercalcemia has been reported [334]. On imaging, IFN-induced sarcoidosis-like disease is in the form of hilar or mediastinal lymphadenopathy, ground-glass shadowing, micronodular infiltrates, or thickening along the bronchovascular bundles [335]. Increased lymphocytes, generally of the CD8+ phenotype, are present in the BAL [335, 336], and this is at variance with the findings in naturally occurring sarcoidosis. Eighty-five percent of patients stabilize or improve, 15% develop chronic stable disease, and a third require corticosteroid treatment [333].

Interferons can induce other forms of ILD. Interferon therapy may induce volume loss with a disproportionate decrease of diffusing capacity for CO and no discernible pulmonary opacities [337, 338], cellular interstitial pneumonia, ARDS [339], desquamative interstitial pneumonia [340], pulmonary fibrosis [340], eosinophilic pneumonia [341], and BOOP [342]. The latter condition may manifest with diffuse infiltrates [343, 344] or a mass [64]. Most cases of IFN-induced interstitial lung disease respond to diminution of drug dosage, drug removal, and corticosteroid therapy [336]. A recent review of 25 published cases showed onset of the disease after 23 days to 10 months into treatment [332]. There was one fatality [332].

Other adverse effects of IFN include lone dyspnea, chronic cough [345], exacerbation of asthma [346], pleural effusion [347], pulmonary hypertension [348], and drug-induced lupus [349].

31.4.22 Imatinib

Imatinib is a protein kinase inhibitor that downregulates the Bcr-Abl protein kinase generated by the Philadelphia chromosome in chronic myelogenous leukemia. Pneumonitis [17, 350], fluid retention, and pleural effusion [351] have been reported during treatments of chronic myelogenous leukemia with the drug. A series of 27 interstitial pneumonitis cases (with a preponderance of males) was published in 2006 [17]. Onset of the disease was after a median of 49 days into treatment with no evidence that drug dosage was playing a role. Clinical presentation included dyspnea and hypoxemia. Histopathological findings included interstitial inflammation, fibrosis, organizing pneumonia, and eosinophilic pneumonia, and a reactive epithelium [17]. Drug lymphocyte stimulation test was negative in all nine patients so tested [17]. The drug was withdrawn in all patients, and most patients received corticosteroid therapy to alleviate symptoms. The condition resolved in seven patients and improved in 16. In the 11 patients who were rechallenged, the disease relapsed in only 4, an important consideration regarding the management of the native hematologic malignancy. One patient was successfully rechallenged while receiving 60 mg of prednisolone [352]. At least seven cases of imatinib-induced pneumonitis with or without fluid retention and pleural effusion have been reported in the interim of the above report [17]. One case of eosinophilic pneumonia ascribed to this agent is available [353], and pulmonary alveolar proteinosis developed in another patient [354].

31.4.23 Lenalidomide

Three cases of lenalidomide-induced pneumonitis have been reported in patients with multiple myeloma. Lymphocytes were increased in the BAL two cases. Pathology disclosed interstitial pneumonia and granulomas and BOOP in one case each [55, 355–358].

31.4.24 Melphalan

Meplhalan produces epithelial changes in the lung that resemble those of other alkylating agents [359]. There are

not many well-documented cases of melphalan-induced pneumonitis [360–362]. The condition typifies the chemotherapy lung. In early cases, the disease is acute and reverses with drug withdrawal and corticosteroid therapy [361]. Later cases present with the features of late chemotherapy lung, i.e., lung fibrosis and reactive type II cell changes [363]. Corticosteroids are indicated and have reversed late melphalan toxicity [362].

31.4.25 Methotrexate

Methotrexate lung can complicate treatments of various neoplastic and nonneoplastic conditions (mainly rheumatoid arthritis nowadays) in 0.86–6.9% of patients on the drug [364]. Risk factors in rheumatoid arthritis include prior ILD, advanced age, diabetes mellitus, and low serum albumin. A previous episode of methotrexate pneumonitis is the strongest risk factor for relapse, should the patient be reexposed to the drug. The first report of methotrexate pneumonitis dates back 41 years [365]. Acute pulmonary disease developed in seven children in clinical remission from their hematologic malignancy. The disease was life threatening in six. Open lung biopsy showed interstitial pneumonitis with granuloma formation. Cessation of the drug and corticosteroid therapy were effective with a return to normal in 10–40 days. Methotrexate could be continued in some patients.

In 2000, 123 cases of methotrexate lung in hematology and rheumatology patients were summarized [43]. Methotrexate pneumonitis can develop after treatment of leukemia, solid tumors, rheumatoid arthritis, psoriasis, primary biliary cirrhosis, asthma, or molar or ectopic pregnancy [36]. The majority of patients (62%) are women. Methotrexate pneumonitis develops after doses of the drug ranging from 2.5 to 1,400 mg/week. Duration of treatment was from single exposure to 5 years, although half of the patients developed the disease within the first 32 weeks of treatment [366]. The development of methotrexate pneumonitis is unpredictable. There is no correlation between dose and time to onset, or clinical severity. Fatal methotrexate pneumonitis can occur with the low-dosage regimen of methotrexate used in the treatment of rheumatoid arthritis. All routes of administration including the oral, parenteral, and intrathecal ones expose the patient to the risk. The majority of patients are on the drug at the time of pneumonitis, with rare cases of delayed onset of the condition [367]. Methotrexate lung is annunciated by the insidious onset of a dry cough for days or a few weeks, contrasted with unchanged chest radiograph. Then, the disease accelerates with cough in 81% of the patients, fever in 76%, shortness of breath in 82%, dense ILD on imaging, and hypoxemia. Mild peripheral eosinophilia is present in about 40% of patients [368]. Radiographic studies indicate diffuse symmetrical interstitial lung shadowing, and in severe cases dense bilateral alveolar opacities with air bronchograms and volume loss [369]. HRCT discloses dense, patchy, widespread, or diffuse septal lines, geographic ground-glass or alveolar densities [370]. Pulmonary physiology is restrictive, with a low diffusing capacity and significant hypoxemia. Unusual patterns of methotrexate pulmonary toxicity include a subacute presentation, eosinophilic pneumonia, pulmonary fibrosis, and acute chest pain. The BAL is best done in the ICU where provision is made to correct the hypoxemia that almost invariably occurs with the procedure. The BAL discloses increased cellularity with a percentage of lymphocytes averaging 58% vs. 10% in normals [371]. Interindividual differences in lymphocyte counts and/or CD4+ or CD8+ subtype percentages are likely to be the result of when into the disease the BAL is performed and whether corticosteroids have been given [50]. Rare cases show eosinophilia in the BAL.

The condition must be separated from an opportunistic infection, mainly *Pneumocystis pneumonia*, which methotrexate pneumonitis can resemble mainly when a granulomatous pattern of reaction is present, with no reliable clinical or radiological discriminators. The arsenal of tools to diagnose *Pneumocystis jiroveci* in BAL specimens should be used, for *Pneumocystis* is not detected in all cases on direct stains of BAL fluid, and sputum examination may be unrewarding. A lung biopsy may be needed to separate these entities. Methotrexate lung must also be separated from other opportunistic infections due to *Cytomegalovirus*, *Cryptococcus*, *Herpes zoster* and *Nocardia*, which have been described as a complication of chronic treatments with methotrexate [8], especially but not exclusively so when blood CD4+ cells are <150/µL or cumulated doses of methotrexate are above 700 mg.

Histological findings in methotrexate lung include interstitial inflammation, fibrosis, granuloma formation, and increased tissue eosinophils in 71%, 59%,

35%, and 18% of the cases, respectively [43]. Granulomas in methotrexate pneumonitis are typically small and ill-defined, with sterile necrosis being an unusual feature [43]. In patients with predominantly granulomatous methotrexate lung, the disease is patchy with intervening areas of normal lung tissue or tissue showing mild cellular inflammation [43]. Type II cell hyperplasia is an occasional feature in methotrexate lung. Alveolar edema, diffuse alveolar damage, hyaline membranes, and DAH are unusual findings that denote severe cases. Rare appearances include a DIP pattern, a sarcoid-like reaction, and acute interstitial pneumonia [43, 115]. Although the differential diagnosis of methotrexate lung is complex, the clinical-pathologic pattern of an acute granulomatous pneumonitis with no evidence of infection and mild blood eosinophilia is distinctive compared to any other chemotherapeutic agent [43].

Methotrexate pneumonitis responds to drug discontinuation. Corticosteroid therapy is indicated in severe cases. A few cases responded to corticosteroid therapy even though treatment with methotrexate was continued [43]. Dose and duration of corticosteroid treatment have not been determined precisely and are guided by clinical, physiologic, and radiographic response. It is estimated that 85% of patients with methotrexate pneumonitis recover. Mortality is 15%, mainly from progressive respiratory failure [372]. Pulmonary fibrosis following the diagnosis of this condition is unusual [43]. Rechallenge with methotrexate will not lead to recurrence in all patients. However, the disease relapses in up to two thirds of the patients, so tested with a 50% mortality rate in those patients who relapse [30].

Pulmonary function has been prospectively evaluated in patients on methotrexate long-term, in an attempt to detect methotrexate lung at an earlier stage than when the condition is diagnosed clinically [364]. As opposed to alkylating agents, nearly all studies found no deterioration of lung function or imaging that would enable early detection of methotrexate lung [108]

31.4.26 Procarbazine

Procarbazine is one drug in the MOPP regimen. The drug was mostly used to treat Hodgkin's disease and other malignant lymphomas. Eight cases of procarbazine pulmonary toxicity have been described [373]. Typically, procarbazine lung manifests acutely with fever, cough, and dyspnea. Pulmonary infiltrates may be discreet. Pleural effusion [374] and mild peripheral eosinophilia [375] were present in one case each. Procarbazine pulmonary toxicity can be fatal [376, 377]. Symptoms decline upon drug discontinuance and corticosteroid therapy. There is no recent case in the literature.

31.4.27 Rituximab

Rituximab is a chimeric monoclonal antibody directed against the CD20-receptor on B cells. The drug is mainly used to treat malignant lymphomas of B cell lineage, post-transplantation lymphoproliferative disorders, bullous pemphigoid, and rheumatoid arthritis. Incidence of pulmonary toxicity is 0.03–8% [378]. Most patients were receiving rituximab in association with CHOP, CEOP, or CVP and had increased incidence of pulmonary toxicity compared to the pre-rituximab era [379]. Bitzan et al. reviewed 30 cases of rituximab-associated lung disease. Seventy-one percent of the patients received concomitant chemotherapy. Time to onset from the last rituximab dose was 14 days. Eleven of 31 patients required mechanical ventilatory support, and nine died (29%). High-dose glucocorticoid therapy did not improve survival or prevent the development of severe lung disease or death [380]. Forty-five cases of rituximab-associated pulmonary injury were reviewed [381]. The most common presentation in 37 of the 45 cases was in the form of acute or subacute BOOP and respiratory failure within 2 weeks after the fourth course of treatment, resolving (in most cases with corticosteroid therapy. A CD4 + -predominant lymphocytosis (up to 90% of all cells) was found in the BAL. Five patients developed early acute pneumonitis, DAD, or ARDS within a few hours after the first infusion of the drug, a pattern consistent with acute cell lysis pneumopathy or cytokine release. Two of these five patients died. Three patients developed macronodules of organizing pneumonia, a form of toxicity that responded successfully to corticosteroid therapy. Mortality was 18%. Pulmonary infiltrates relapsed in about 2/3 of the patients rechallenged with the drug. Two cases of DAH have from this agent have also been reported [11].

31.4.28 Thalidomide

Thalidomide was approved in 2006 for the treatment of multiple myeloma, myelodysplastic syndrome, and graft-vs.-host disease. The first cases of thalidomide-associated pneumonitis was from Spain [382, 383] in the form of ILD, which improved with drug removal and corticosteroid therapy. Two cases had excess lymphocytes in the BAL [384, 385], and eosinophilia was present in another case [386]. One case of BOOP has been reported [387]. Rechallenge with the drug was followed by relapse [384]. A patient was switched to lenalidomide after an episode of thelidomide pulmonary toxicity and did not experience relapse of the interstitial pneumonia [356]. Other adverse effects of thalidomide include pulmonary hypertension [388] and venous thromboembolism [389, 390]. The risk of thromboembolic events is higher when thalidomide is given in association with darpoietin-alpha [390].

31.4.29 Vinca Alkaloids

Treatments with vinca alcaloids (vinblastine, vinorelbine) alone or in combination with mitomycin C in lung cancer patients can be complicated by wheezing, bronchospasm, abrupt dyspnea, or pulmonary infiltrates that correspond to pulmonary edema or diffuse alveolar damage on pathology [391]. Ventilatory support is required is some patients. Incidence of acute shortness of breath and pulmonary infiltrates is 4–6%. On PFTs, there is deterioration of gas exchange and of the diffusing capacity. In several patients, rechallenge with the drug was followed by recurrence of symptoms. Approximately 60 percent of the patients experienced residual chronic respiratory impairment, in the form of restrictive lung function impairment with or without hypoxemia, and residual pulmonary opacities that only respond incompletely to corticosteroid therapy [391].

31.5 Adverse Effects of Radiation Therapy to the Chest

For those patients who receive in-field radiation therapy to the chest, the clinical imaging picture of radiation pneumonitis includes classic radiation pneumonitis, which typically develops 1–2 months after the onset of treatment in the form of a discrete haze, ill-defined patchy opacities, or an area of condensation predominantly in the radiation field. Radiation metrics (area, beam trajectory, fractionation, mean lung dose, and volume of the lung that receives >20 Gy) are used to monitor the risk of radiation pneumonia. A lymphocyte-predominant BAL accompanies these changes, and, interestingly, the lymphocytic reaction also involves the contralateral lung. These changes usually reverse within 6 months, or slowly progress towards a demarcated area of fibrosis and distortion, with volume loss and later bronchiectasis [392, 393]. Late complications of this form of radiation scar are unusual, and include pneumothorax or colonization by *Aspergillus* sp. Although patients with early radiation pneumonitis usually respond well to the administration of corticosteroids, these drugs are not required in all cases, and the dosage and duration of treatment are guided by the severity of symptoms. In rare instances, infiltrates of radiation pneumonitis extend outside the radiation field to involve the lung diffusely or both lungs bilaterally. This is associated with significant clinical symptoms, and, in some patients, respiratory failure or an ARDS picture develops [394]. Most patients respond satisfactorily to the administration of corticosteroids. Acute diffuse radiation/chemoradiation pneumonitis may develop in stem cell transplant recipients following the administration of a conditioning regimen followed by TBI. Whether or not TBI is given and the amount of radiation (>12 Gy) influence the likelihood of developing diffuse pulmonary toxicity, a detrimental prognostic indicator [392].

Most chronic complications from radiation therapy that are now seen are the result of methods, indications, and equipment used in the past [13]. Radiation therapy is not given any longer to patients who achieve complete response after ABVD, and extended field radiation therapy has been supplanted by newer conformal techniques, which spare more of the normal lung. Due to the anatomical complexity and intricateness of multiple organs in the chest, there are a multitude of early or late complications that may cause severe impairment [13]. Depending on the radiation dose and beam, long-term progressive changes following chest radiation therapy may injure the lung, airways, pleura, heart valves, myocardium, pericardium, coronary arteries, mediastinum, lymphatics, esophagus, and cranial nerves, imparting

varied clinical and imaging expressions to late radiation-induced injury [13, 395, 396]. A restrictive lung dysfunction can be found in up to a third of patients who received radiation therapy in childhood or adolescence [397]. A fraction of patients (about 3%) develop progressive restrictive lung dysfunction, impacting the quality of life. Paramediastinal sharply demarcated opacities of fibrosis and architectural distortion are present in the previously irradiated area. These changes are greater in patients previously exposed to bleomycin [204]. Fibrosis localizes in the bilateral apices, and paramediastinal and parahilar areas following mantle irradiation. However, these changes are not found in every patient, and the presence and severity of the fibrosis are influenced by the area and size of the radiation fields, particularly with regard to the volume of the irradiated lung, and on whether or not in-field coverage of the hilum or lung was required. The "amount" of chemotherapy, and particularly the dose of bleomycin or other alkylating agents, also may influence the expression of radiation-induced changes in the lung [204]. In severe cases, a distinctive, Y-shaped pattern of fibrotic changes is present on frontal chest films. Severe restriction or encasing of mediastinal structures may ensue. Pleural effusion and chylothorax [13, 398] and the "dropped head syndrome" may be present [13]. Lymphoma survivors must also be evaluated and monitored using auscultation, cardiac ultrasonography, and cardiac stress regarding the frequent development of valvular incompetence/regurgitation, coronary disease, atrioventricular block, or other late cardiac complications of radiation therapy (e.g., heart failure, pericardial thickening/effusion, and pulmonary vein compression), phrenic nerve, or left vocal cord palsy [13, 397, 399, 400].

Patients must also be explored regarding esophageal dysmotility and cranial nerve dysfunction, which may cause chronic aspiration and inflict further lung damage. Late patients also need to be followed up carefully, because second and higher order cancers may occur years after irradiation, including lung cancer, which accounts for one fifth of all lung cancers in lymphoma survivors. Of note, late fibrotic changes in the chest when present may hamper optimal management of lung cancer. Since radiation and antineoplastic drugs synergize the effect of smoking, smoking cessation is an essential step in long-term management and follow-up of patients with a history of cured hematologic malignancy.

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