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REVIEW

Pulmonary toxicities from targeted therapies: a review

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Abstract Pulmonary toxicity is rarely seen with most commonly used targeted therapies. The endothelial growth factor receptor (EGFR) small-molecule tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib can cause interstitial lung disease (ILD). BCR-ABL tyrosine kinase inhibitors imatinib and dasatinib can cause pleural effusions. Infusion-related bronchospasm is common with the monoclonal antibodies to EGFR cetuximab and panitumumab, and case reports of bronchiolitis and pulmonary fibrosis have been described. Up to one-sixth of patients taking mammalian target of rapamycin (mTOR) inhibitors get a reversible interstitial pneumonitis. Bevacizumab, the monoclonal antibody to vascular endothelial growth factor (VEGF), has been associated with hemoptysis and pulmonary embolism particularly in patients with squamous cell lung cancer. Infusion-related bronchospasms, acute respiratory distress syndrome (ARDS), and interstitial pneumonitis can be seen with the anti-lymphocyte monoclonal antibodies rituximab, ofatumumab, and alemtuzumab. While most pulmonary toxicities from these therapies are mild and resolve promptly with dose reduction or discontinuation, it is important for the clinician to recognize these potential toxicities when faced with treatment-related complications. Discerning these pulmonary adverse effects may help in making decisions on diagnostic testing and therapy, particularly for those with pulmonary and cardiovascular co-morbidities.

Keywords Pulmonary toxicity · Targeted therapy · Erlotinib · Gefitinib · mTOR inhibitors · Dasatinib · Interstitial pneumonitis · Non-specific acute interstitial lung disease

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Introduction

Targeted anti-neoplastic agents are commonly used in the treatment of various malignancies today. Therapies including monoclonal antibodies, small-molecule tyrosine kinase inhibitors (TKIs), and mammalian target of rapamycin (mTOR) inhibitors have been adopted as standard therapy in lung, breast, gastrointestinal, genitourinary, central nervous system, and hematologic cancers. Part of the benefit of these targeted agents is a toxicity profile different from that seen with conventional systemic cytotoxic chemotherapy.

The most common adverse effects of targeted agents are well recognized by hematologists and oncologists. For example, the endothelial growth factor receptor (EGFR) small molecule tyrosine kinase inhibitors gefitinib and erlotinib are known to cause diarrhea, rash, and acne [1, 2]; the BCR-ABL tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib cause nausea, neutropenia, and fluid retention [3–6]; cetuximab and panitumumab, the monoclonal antibodies to EGFR, commonly cause diarrhea, acneiform skin rash, neutropenia, and electrolyte disturbances [7, 8]; and mTOR inhibitors are implicated in a variety of metabolic side effects including hyperglycemia and dyslipidemia [9, 10].

Pulmonary toxicities are infrequent with most commonly used targeted therapies. However, early clinical trial reports and the US Food and Drug Administration (FDA) drug safety summaries of these agents have described life-threatening respiratory side effects. It is important for the oncologist to recognize these toxicities early to prevent morbidity. It is also important to integrate awareness of these toxicities into risk-benefit decision-making prior to starting therapy. This review highlights a variety of pulmonary toxicities associated with the molecularly targeted agents that have been described in the literature. They are summarized in Table 1.

Anti-epidermal growth factor receptor (EGFR) small molecule tyrosine kinase inhibitors (TKIs)

Gefitinib

Gefitinib (Iressa®, AstraZeneca, Osaka, Japan) is currently approved in Europe and Asia for the treatment of patients with EGFR mutation positive advanced non-small cell lung cancer (NSCLC) cancer. It was approved in 2002 after multiple phase II studies showed favorable responses and a low toxicity profiles in previously treated patients with advanced NSCLC [11, 12]. The Iressa Pan-Asia Study (IPASS) showed gefitinib to have superior progression-free survival compared to carboplatin plus paclitaxel in patients with advanced pulmonary adenocarcinoma who had EGFR mutations [13]. A more recent phase III trial in patients with EGFR-mutated metastatic NSCLC confirmed these findings [14].

Although the initial studies of gefitinib leading to its approval did not report significant pulmonary toxicity, multiple large studies have since highlighted its association with acute interstitial lung disease (ILD). A 2003 FDA analysis of 50,000 patients who received gefitinib reported a 1% worldwide incidence of ILD [15]. Notably, the incidence of ILD was higher in Japan (2%) than in the United States (0.3%). ILD usually develops within 3–7 weeks of initiating therapy and one third of cases are fatal. Approximately 90% of patients who develop gefitinib induced ILD have received prior radiation or chemotherapy. In a review of over 1,900 Japanese patients with NSCLC treated with gefitinib over a 4-month period 70 cases (3.5%) of ILD were reported of which 44% were fatal [16]. The higher incidence of ILD in Japanese patients correlates with the larger percentage of patients in this population with EGFR mutations and clinical responses to gefitinib [17]. Other than Japanese ethnicity, risk factors for the development of ILD include male sex, a history of smoking, and a coincidence of interstitial pneumonia (Odds ratios: 3.1, 4.79, and 2.89, respectively) [16]. In addition, 6.6% of men with a history of smoking develop ILD. Other series have suggested recent radiation therapy and chemotherapy as risk factors for ILD [18].

The mechanism for developing gefitinib-induced ILD is most likely related to a decrease in alveolar regeneration, a process normally regulated by EGFR, in a population with a high co-incidence of pulmonary disease [19, 20]. Patients typically present with acute onset of dyspnea, cough, and pyrexia. A case series of Japanese patients describes imaging with diffuse ground glass opacities and histology showing diffuse alveolar damage with hyaline membrane formation [19]. Most series describe drug discontinuation and supportive therapy with mechanical ventilation and high dose corticosteroids as the only useful interventions and up to 40% of cases are fatal. Resuming gefitinib after resolution of symptoms has been associated with recurrence of ILD [21].

Table 1 Drug and associated pulmonary toxicity

Drug	Pulmonary toxicity
Gefitinib, erlotinib	Acute interstitial lung disease
Imatinib, dasatinib	Pleural effusions, pneumonitis
Cetuximab, panitumumab	Bronchospasm, bronchiolitis, pulmonary fibrosis
Trastuzumab	Pneumonitis
Everolimus, Temsirolimus	Pneumonitis
Bevacizumab	Hemoptysis, pulmonary embolus, pulmonary hemorrhage
Sorafenib	Pneumonitis
Sunitinib	Recall pneumonitis
Rituximab	Infusion-related bronchospasm, ARDS, interstitial pneumonitis
Ofatumumab	Interstitial pneumonitis
Alemtuzumab	Dyspnea, hypoxia, pulmonary hemorrhage (post solid organ transplant)
Bortezomib	Pleural effusions, organizing pneumonia, bronchiolitis obliterans
Thalidomide/lenalidomide	Pulmonary embolism, pneumonitis, organizing pneumonia, eosinophilic pneumonia

Erlotinib

Erlotinib (Tarceva®, Genentech, Inc, South San Francisco, CA) is a human epidermal growth factor receptor-1/epidermal growth factor receptor (HER1/EGFR) TKI that is used for advanced NSCLC and pancreatic adenocarcinoma. Phase III studies have shown that compared to conventional first-line chemotherapy erlotinib has superior overall survival in the subset of patients with NSCLC who have never smoked [22, 23]. A phase III trial from the National Cancer Institute of Canada (NCIC) showed erlotinib to have a modest survival benefit when added to gemcitabine in patients with advanced pancreatic cancer [24].

The incidence of ILD observed in the TRIBUTE trial (carboplatin-paclitaxel+erlotinib/placebo) was 1% and 0.2% in the erlotinib and placebo arms respectively [22]. In the other phase III trial (cisplatin-gemcitabine+erlotinib/placebo) there were two cases of ILD in the placebo arm and one fatal case in the erlotinib arm [23]. In the NCIC CTG study in pancreatic cancer ILD was seen in 2.4% and 0.4% in the erlotinib and placebo arms respectively [24]. The rate of ILD may be higher when erlotinib is used with gemcitabine as both classes of drugs are associated with pulmonary toxicity. In the FDA approval report for erlotinib the overall incidence of ILD was 8% [2]. The various pulmonary disease entities described with erlotinib include interstitial pneumonia, pneumonitis, acute respiratory distress syndrome, pulmonary fibrosis, and alveolitis. Symptoms developed within a median of 47 days after starting erlotinib and included dyspnea, cough, and pyrexia. Risk factors for developing ILD were similar to gefitinib. Case reports describe similar imaging, histological features, and rate of mortality to gefitinib [25, 26].

Tyrosine kinase inhibitor of human epidermal growth factor receptor type-2 (HER-2)

Lapatinib (Tykerb, GlaxoSmithKline, Philadelphia, PA) is an oral small molecule HER2 tyrosine kinase inhibitor. Lapatinib has shown superior time-to-progression when added to capecitabine for refractory metastatic breast cancer [27]. Dyspnea was the only adverse pulmonary effect reported in this early trial and it occurred no more frequent than with capecitabine alone.

Monoclonal antibodies against the HER family of receptors

Cetuximab and panitumumab are monoclonal antibodies that bind directly to EGFR, whereas trastuzumab binds to the HER2 protein on breast cancer cells, which inhibits the EGFR pathway.

Cetuximab and panitumumab

Cetuximab (Erbitux®, Bristol-Myers Squibb, New York, NY) and panitumumab (Vectibix®, Amgen Inc, Thousand Oaks, CA) are monoclonal antibodies that target EGFR. Cetuximab is currently used in metastatic colorectal cancer (mCRC) and squamous cell carcinoma of the head and neck (mSCCHN). Multiple phase III studies have shown that the addition of cetuximab to conventional chemotherapy improves overall response rates and progression free-survival in KRAS wild-type patients with mCRC and overall survival in patients with mSCCHN [7, 28, 29]. Panitumumab has been shown to have an improvement in mean progression-free survival compared to best supportive care in patients with EGFR expressing mCRC (13.8 weeks versus 8.5 weeks) [8].

Adverse pulmonary events are rare with these agents. Cetuximab can cause severe hypersensitivity infusion reactions including bronchospasms in up to 3% of patients [30]. This reaction is similar to that seen with other chimeric antibodies (i.e., rituximab) and typically resolves with stopping or slowing the infusion rate. Bronchiolitis obliterans has also been reported with cetuximab [31]. Both cetuximab and panitumumab have rarely been associated with pulmonary fibrosis [31, 32].

Trastuzumab

Trastuzumab (Herceptin®, Genentech, South San Francisco, CA) is a monoclonal antibody targeting the HER2 protein. Since it was approved in 1998 it has significantly improved survival in women with HER2-positive breast cancer [33, 34]. Other than dyspnea related to cardiac toxicity, this antibody is rarely associated with adverse pulmonary events. The original trials using trastuzumab in the adjuvant setting reported a 0.6% rate of interstitial pneumonitis.

Tyrosine kinase inhibitors of BCR-ABL

Imatinib, dasatinib, and nilotinib

Imatinib mesylate (Gleevec®, Novartis, East Hanover, NJ) is an inhibitor of the tyrosine kinases (TKIs) for BCR-ABL, C-KIT, platelet-derived growth factor receptor, and ARG. Since it was approved in 2003 it has revolutionized the outlook of patients with chronic myeloid leukemia (CML) [4]. Dasatinib (Sprycel®, Bristol-Myers Squibb, New York, NY), and nilotinib (Tasigna®, Novartis, East Hanover, NJ) are newer generation TKIs that have recently shown efficacy in imatinib-resistant CML [5, 6]. Imatinib is also approved for Kit (CD117) positive gastrointestinal stromal tumors (GIST) in both the adjuvant and metastatic settings [35, 36].

Pleural effusion is the most commonly reported pulmonary adverse event with these agents. Dasatinib is most frequently associated with pleural effusions, reported in 10–35% of patients [37, 38]. One report of 138 patients found that those who were treated in the accelerated phase, with cardiovascular co-morbidities and with twice-daily dosing were at higher risk of developing pleural effusions. Most pleural effusions were exudative (78%); 19% required thoracentesis (median volume 1.5 l); and most resolved upon discontinuation of dasatinib [37]. A recent economic analysis reported a significant cost burden of managing TKI-associated pleural effusions [39].

In addition, pneumonitis has been reported with imatinib [40–42]. All cases were reversible with steroids and drug discontinuation. One case series of patients receiving dasatinib for imatinib-resistant CML reported pneumonitis 17.5% of the time [43]. Although these agents generally have a minimal toxicity profile, dasatinib should be used with caution in patients with pre-existing pulmonary and cardiovascular disease.

Mammalian target of rapamycin (mTOR) inhibitors

The mTOR pathway is dysregulated in multiple human cancers including renal cell carcinoma. Activation of this pathway causes over expression of hypoxia-inducible factor 1 (HIF-1) that promotes tumor angiogenesis, which promotes the growth of renal cell carcinoma [44]. Metabolic side effects of the mTOR inhibitors used for renal cell carcinoma, including hyperglycemia and dyslipidemia, are common. In addition, a variety of interstitial lung diseases including non-infectious pneumonitis and diffuse alveolar hemorrhage have been described [45–48].

Everolimus

Everolimus (Afinitor®, Novartis, East Hanover, New Jersey) is an oral mTOR serine-threonine kinase inhibitor that was approved in 2010 for the treatment of advanced renal cell carcinoma after disease progression on sunitinib or sorafenib [9, 10]. It is also approved for unresectable astrocytomas associated with tuberous sclerosis.

During the RECORD-1 trial most adverse events were related to metabolic disturbances, stomatitis, and rash. However, non-infectious pneumonitis was suspected in 13.5% of patients receiving everolimus [9]. Nine patients (3.3%) had grade 1 (asymptomatic), 18 (6.6%) had grade 2 (did not interfere with daily living), and 10 (3.6%) had grade 3 (interfered with daily living or oxygen indicated) pneumonitis. Half of the patients who developed grade-3 pneumonitis had radiographic evidence of pneumonitis before starting everolimus. Fifty-four percent of cases resolved during follow-up. New radiographic evidence of pneumonitis without overt symptoms was more common in the everolimus group compared to placebo (38.9% vs. 15.2%). Radiographic findings included ground glass opacities to diffuse patchy airspace disease. The onset of symptoms ranged from 24 to 257 days from initiating of therapy.

Following the RECORD-1 trial, an 11-member expert advisory panel established guidelines for the management of everolimus-associated adverse events including non-infectious pneumonitis (Table 2) [49].

Temsirolimus

Temsirolimus (Torisel®, Wyeth, Inc, New York, NY) is an intravenous mTOR inhibitor that was approved in 2007 for the treatment of advanced renal cell carcinoma [50].

Two follow up safety analyses of this phase III study have been reported [51, 52]. An increase in cough from baseline was almost twice as common in patients receiving temsirolimus. Pneumonitis was seen in 2.5% and 0.5% of patients receiving temsirolimus and interferon-alfa respectively. Radiographic evidence of pneumonitis was higher with temsirolimus (29%) versus interferon-alpha (6%). Symptoms were present only 31% of the time when pneumonitis was found on radiograph. A smaller series of 22 patients treated with temsirolimus reported that 36% developed drug-induced pneumonitis [53]. Half of these patients were asymptomatic. Dry cough and dyspnea were the most common symptoms. The development of pneu-

Table 2 Management recommendations for everolimus-induced pneumonitis [49]

Grade	Management	Dose modification
1	No specific therapy; continue everolimus	No change
2	Consider dose interruption/reduction, pulmonologist consultation, diagnostics to exclude infection, corticosteroids, if no infection	Hold until grade≤1 and restart at reduced dose; consider re-escalation; if no recovery to grade≤1
3	Interrupt everolimus, pulmonologist consultation, diagnostics to exclude infection, corticosteroids if infection ruled out	Hold until grade≤1; may restart within 2 weeks at reduced dose if clinical benefit
4	Same as grade 3	Discontinue everolimus

monitis was more common in patients with pre-existing lung disease. The authors of these reports recommend close monitoring for the development of pneumonitis and de-escalating or discontinuing therapy if necessary.

Monoclonal antibodies to vascular endothelial growth factor (VEGF)

Bevacizumab

Bevacizumab (Avastin®, Genentech, South San Francisco, CA) is a recombinant humanized monoclonal IgG1 antibody to VEGF that is currently approved for use in metastatic colorectal cancer (mCRC), NSCLC, renal cell carcinoma (RCC), and glioblastoma multiforma. Multiple phase III studies have shown bevacizumab to have modest survival benefits in mCRC, NSCLC, and RCC [54–56]. Each of these trials reported a significantly higher rate of adverse events with bevacizumab. Although hypertension, bleeding, anorexia, and proteinuria were the most commonly reported adverse events, some of these trials reported a slightly higher rate of dyspnea and thromboembolic disease [56].

Pulmonary toxicity is relatively uncommon with bevacizumab. An early phase II trial of bevacizumab in NSCLC reported a higher rate of hemoptysis compared to conventional chemotherapy (19% vs. 6%) [57]. In this trial hemoptysis was seen more frequently with squamous cell histology and in patients with tumors close to major blood vessels. Due to the high rate of hemoptysis seen in this study, patients with baseline hemoptysis and squamous histology were excluded from the phase III trial. However, this trial showed that bevacizumab was still associated with more hemoptysis (1.9% vs. 0.2%) and five patients (1.2%) died of pulmonary hemorrhage [57].

Anti-vascular endothelial growth factor (VEGF) small-molecule tyrosine kinase inhibitors

Sorafenib and sunitinib

Sorafenib (Nexavar ®, Bayer, Berkeley, CA) is a small-molecule multikinase inhibitor of VEGF and platelet-derived growth factor (PDGF). It is currently approved for hepatocellular carcinoma (HCC) and advanced RCC. Adverse pulmonary events with these agents are uncommon and are limited to case reports. Interstitial pneumonitis has been reported with sorafenib [58]. Pneumonitis was diagnosed 24 days after starting therapy and completely resolved upon discontinuation. Recall pneumonitis was reported in one case of sunitinib 3 weeks after completion of chest radiotherapy [59].

Anti-lymphocyte monoclonal antibodies

Rituximab

Rituximab (Rituxan®, Genentech, South San Francisco, CA) is a chimeric anti-CD20 monoclonal antibody that targets B-lymphocytes. It is currently used in a variety of B-cell non-Hodgkin lymphomas (NHLs), rheumatologic conditions, idiopathic thrombocytopenic purpura (ITP), and autoimmune hemolytic anemia.

Bronchospasm is a well-recognized component of the acute infusion reaction associated with rituximab [38]. Along with chills, fever, and hypotension the infusion reaction has been reported in almost 10% of patients. The reaction typically resolves shortly after stopping or decreasing the rate of infusion and is usually less severe with subsequent cycles.

A variety of other pulmonary toxicities have also been described with rituximab [60–65]. In 2003 Genentech reported a less than 0.03% rate of drug induced lung injury [61]. Interstitial pneumonitis, including one fatal case, which develops within weeks of treatment, has been described in multiple case reports of lymphoma patients. One series of over 100 lymphoma patients treated with CHOP with or without rituximab reported a trend of more interstitial pneumonitis with the antibody (7% vs. 3%; $p=0.771$) [62]. The stage of disease and presence of cardiopulmonary co-morbidities did not predict for the development of interstitial pneumonitis. Most cases completely resolved after discontinuation of therapy and with steroids. The development of interstitial pneumonitis with rituximab seems independent of chemotherapy, as it has been reported in patients treated for ITP and systemic lupus erythematosus [65, 66]. Fatal acute pulmonary fibrosis following weekly rituximab for follicular lymphoma has also been reported [60]. A review of 45 cases of rituximab-induced lung injury described acute respiratory failure and diffuse alveolar hemorrhage that developed within hours of administration [67]. Multifocal alveolar and ground glass opacities were the most common radiographic findings. Although not completely understood, it is thought that rituximab-induced lung injury is caused by lymphocytes releasing cytokines that cause direct lung injury [19].

Ofatumumab

Ofatumumab (Arzerra®, GlaxoSmithKline, Collegeville, PA) is a fully human anti-CD20 monoclonal antibody that was approved in 2009 for refractory chronic lymphocytic leukemia (CLL). It has also shown promise in other types of NHL [68]. Interim analysis of an ongoing phase II trial involving patients with refractory CLL showed an overall response rate (ORR) of up to 58% [69]. Although experience with ofatumumab is

Table 3 Pulmonary toxicities and associated targeted agents

Toxicity	Targeted agents
Pleural effusion	Imatinib, gefitinib, bortezomib
Non-specific acute interstitial lung disease	Gefitinib, erlotinib, ofatumumab
Pneumonitis	Gefitinib, erlotinib, imatinib, dasatinib, trastuzumab, everolimus, temsirolimus, sorafenib, sunitinib, rituximab, ofatumumab, thalidomide, lenalidomide
Pulmonary fibrosis	Erlotinib, cetuximab, panitumumab, rituximab
Bronchospasm	Cetuximab, rituximab
Bronchiolitis	Cetuximab, bortezomib
Dyspnea	Lapatinib, bevacizumab
Hemoptysis	Bevacizumab
Pulmonary embolism	Bevacizumab, thalidomide, lenalidomide
Diffuse alveolar hemorrhage	Rituximab, alemtuzumab
Organizing pneumonia	Bortezomib, thalidomid, lenalidomide
Eosinophilic pneumonia	Thalidomide, lenalidomide

limited, an early phase I/II study of 33 patients reported one case of fatal interstitial lung disease and one case of pneumonia [70].

Alemtuzumab

Alemtuzumab (Campath®, Genzyme, Cambridge, MA) is a humanized anti-CD52 antibody that is approved for refractory CLL. Phase II studies have reported overall response rates up to 40% in patients with p53 mutations [71, 72]. Although the majority of adverse events are infectious, these studies report infusion-related pulmonary symptoms of dyspnea and hypoxia in up to 28% of patients. Diffuse alveolar hemorrhage has been reported with alemtuzumab in the post-renal transplant setting [73].

Other agents

Bortezomib

Bortezomib (Velcade®, Millennium Pharmaceuticals) is an inhibitor of the 26-S proteasome. It is currently approved as frontline therapy for multiple myeloma and refractory therapy for mantle cell lymphoma [74, 75]. In a series of 13 Japanese patients treated with bortezomib for multiple myeloma, four reported acute pulmonary toxicity [76]. Two patients died and radiographs showed parenchymal disease with pleural effusions. One autopsy was done and confirmed acute and organizing pneumonia. A more recent case report describes a rapidly progressive bronchiolitis obliterans organizing pneumonia that resulted in respiratory failure. This patient responded rapidly to high dose glucocorticoids [77].

Thalidomide and lenalidomide

Thalidomide and lenalidomide (Thalomid® and Revlimid® respectively, Celgene Corporation, Summit, NJ) share a complex mechanism of action that includes suppression of tumor necrosis factor alpha, down-regulator of cell surface adhesion, and anti-angiogenesis. Both are currently approved for newly diagnosed multiple myeloma in combination with dexamethasone [78, 79] and lenalidomide is also approved for myelodysplastic syndrome (MDS) with 5q deletion [80]. The most common pulmonary adverse effect of thalidomide and lenalidomide is pulmonary embolism. Venous thromboembolism, including pulmonary embolism, has been reported in as high as 12% of patients taking these agents [81]. Case reports describe interstitial pneumonitis, organizing pneumonia, and eosinophilic pneumonia that typically resolve with steroids and drug discontinuation [82–85]. A report on the expanded safety experience of lenalidomide in patients with myeloma described infectious pneumonia in 7.1% [86].

Conclusions

Although rare, a variety of pulmonary toxicities are seen with targeted therapies (Table 3). Acute interstitial lung disease is seen with gefitinib and less frequently with erlotinib. Over one third of reported cases are fatal. Patients from Japan and those with pre-existing lung disease are at increased risk. Imatinib and dasatinib can cause an exudative pleural effusion. Patients with pre-existing cardiovascular disease and those treated in the accelerated phase seem to be at increased risk. Pleural effusions resolve with discontinuing therapy. The mTOR inhibitors ever-

olimus and temsirolimus are associated with pneumonitis in up to 13.5% of patients. Most patients experience mild symptoms that usually promptly resolve with dose reduction or discontinuation. An expert panel has developed recommendations for managing everolimus-induced pneumonitis. Hemoptysis and a slight increased risk of pulmonary embolus have been reported with bevacizumab in patients with advanced non-small cell lung cancer. Patients who develop hemoptysis on bevacizumab tend to have squamous histology and centrally located tumors that are close to main pulmonary vessels. Infusion-related bronchospasm is most common pulmonary side effect of rituximab but acute respiratory distress syndrome and diffuse alveolar hemorrhage have also been reported. Reversible interstitial pneumonitis that is independent of concurrent cytotoxic therapy has also been reported with the treatment of both malignant and benign conditions. Rare case reports describe bronchospasm, bronchiolitis, and pulmonary fibrosis with cetuximab and panitumumab; interstitial pneumonitis with trastuzumab; pneumonitis with sorafenib and sunitinib; and infusion-related dyspnea and alveolar hemorrhage with alemtuzumab.

Targeted therapies often have unique side effect profiles and are usually better tolerated than conventional cytotoxic agents. Our understanding of the mechanism of these adverse effects is poor. Pulmonary toxicities caused by targeted agents are rare but important to recognize. Including these less common adverse effects into the differential for patients receiving these agents with otherwise unexplained pulmonary symptoms could aid in timely diagnostic and therapeutic decisions.

Conflict of interest statement None of the authors has any conflict of interest with the information presented in this manuscript.

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