Pulmonary toxicities of biologics: a review

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With the advancement of research in cancer treatment more and more drugs are being introduced for the treatment of cancer. In this review study, we have tried to look at some of the relatively newly introduced drugs, commonly referred to as biologics. The aim of this study was to review the very rare but fatal pulmonary toxicities (mostly interstitial lung disease) caused by these drugs. The drugs that were reviewed are rituximab, cetuximab, bevacizumab, alemtuzumab, and trastuzumab. This review basically aims at presenting a basic introduction (mechanism of action and indications of use) of these drugs followed by a summary of the incidence, various clinical presentations, diagnosis, treatment options, and outcome of patients around the world who presented with pulmonary toxicities caused by these drugs. *Anti-Cancer Drugs* 21:131–139 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Methods

Manuscripts were searched on Pubmed using keywords, pulmonary toxicities/lung toxicities/pulmonary side effects of rituximab/trastuzumab/cetuximab/alemtuzumab/bevacuzimab.

Rituximab

Food and Drug Administration (FDA)-labeled indications

(1) Non-Hodgkin's lymphoma, diffuse, large B-cell, CD20-positive, in combination for first-line treatment.
(2) Non-Hodgkin's lymphoma, follicular, CD20-positive, B-cell, in combination with cyclophosphamide, vincristine, and prednisone chemotherapy for first-line treatment.
(3) Non-Hodgkin's lymphoma, low grade, CD20-positive, B-cell, stable or responsive to earlier CVP cyclophosphamide, vincristine, and prednisone chemotherapy.
(4) Non-Hodgkin's lymphoma, relapsed or refractory, low grade or follicular, CD20-positive, B-cell.
(5) Rheumatoid arthritis (moderate to severe), in combination with methotrexate, in patients who had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies.

Mechanism of action

Rituximab is a monoclonal antibody directed against the CD20 antigen on B-lymphocytes. CD20 regulates cell cycle initiation and, possibly, functions as a calcium channel. Rituximab binds to the antigen on the cell surface, activating complement-dependent B-cell cytotoxicity; and to human Fc receptors, mediating cell killing through an antibody-dependent cellular toxicity (A list of cases of suspected rituximab-induced lung toxicity is given in Table 1).

Rituximab, though rarely, is known to cause life-threatening pulmonary complications that can be dealt with by prompt initiation of therapy. Lung toxicity presents with a rate of less than 0.03% among 540 000 patients [25]. The pattern of rituximab-related pulmonary toxicities in Table 1 included 29 patients with interstitial pneumonia [1,4,5,7–9,11,13–15,18,20,23,24], five patients with bronchiolitis obliterans with organizing pneumonia (BOOP) [2,4,16,25], two patients had an interstitial process characterized by loosely formed granulomata and diffuse alveolar damage [10,17]. Six patients had bilateral infiltrates on imaging (19, 3, and 6) and two patients presented as acute respiratory distress syndrome [21,22]. Clinicians should be aware of the pulmonary toxicities such as interstitial pneumonitis caused by rituximab. Once a patient develops fever of unknown origin, cough, or even the slightest shortness of breath, a computed tomography (CT) scan of the chest should be performed immediately to make an early diagnosis of the disease. Bronchoscopy and bronchoalveolar lavage should be performed to rule out infectious disease. The exclusion of all known etiological factors associated with pulmonary interstitial infiltrates is essential for diagnosing rituximab-induced interstitial pneumonitis. Immediate discontinuation and prompt initiation of steroid therapy seems to confer benefit when rituximab toxicity is suspected. Clinicians should be on the look out for the various signs and symptoms (as mentioned in Table 1 in each case) to prevent any fatal pulmonary complications. As stated in each case in Table 1, many of the patients did respond favorably to high doses of steroids. Elderly people may be at a particularly high risk for rituximab-induced lung disease. The clinical, lung function test and imaging findings in BOOP lack specificity, so that the definitive diagnosis is dependent on obtaining a histological specimen. A gradually worsening

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Table 1 List of cases of suspected rituximab-induced lung toxicity

Ref.	Patients	Age/sex	Diagnosis	Rituximab	Time since last dose	Clinical features	Imaging	Lung pathology	Treatment and outcome
[1]	1	55/F	MCL	Rituximab	4 months	Fever, cough, dyspnea and hypoxemia	Bilateral reticulonodular infiltrates	OLBx/desquamatve alveolitis and sinusoidal histiocytosis	Spontaneous remission
[2]	1	NA	Bulky NHL	Rituximab	NA	NA	NA	NA, patient labeled as bronchiolitis obliterans	Died 10 months after the start of therapy
[3]	1	56/M	Relapsed MCL	Rituximab and methylprednisolone	6 days after 1st dose	Fever, dyspnea and hypoxemia	Bilateral infiltrates	NA	Mechanical ventilation, complete resolution after 2 months
[4]	3	NA	B cell CLL	Rituximab and fludarabine	After 2, 3 and 5 cycles	NA	NA	Interstitial pneumonitis Interstitial pneumonitis with cardiomyopathy BOOP	Fludarabine stopped and short course of steroids with improvement, 1 patient received further rituximab
[5]	2	82/M 69/M	MCL Testicular NHL	Rituximab Rituximab–CHOP	0[a] 4 months	Dyspnea and hypoxemia fever and dyspnea	GGO NA	No biopsy, both had restrictive pattern and low DLCO	Prednisone 20 and 40 mg daily with dramatic improvement
[6]	2	NA	NHL	Rituximab–VNCOP-B	NA	Respiratory failure	Bilateral infiltrates	NA	High-dose steroids, death
[7]	1	77/F	ITP	Rituximab–prednisolone	2 weeks	Increasing SOB over 4 weeks. On presentation dyspneic on rest and hypoxemic	Bilateral upper zone alveolitis	None. Mixed restrictive and obstructive pattern, Low DLCO	Prednisolone tapered over 2 months with resolution
[8]	1	66/F	Parotid lymphoma	Rituximab–CHOP	15 days	Fever, cough, dyspnea and hypoxemia	Bilateral lower lobe alveolar opacities and subpleural GGO	No Biopsy	Prednisone1 mg/kg/day with resolution in 4 weeks
[9]	1	56/M	Abdominal follicular cell NHL	Rituximab	3 weeks	Cough, dyspnea and hypoxemia	Bilateral infiltrates from hila to periphery, most prominent at the bases	TBBx: interstitial fibrosis. OLBx: extensive interstitial fibrosis with focal chronic inflammation and organization, extensive arterial thrombosis	High-dose steroids, patient required mechanical ventilation and expired.
[10]	1	65/M	Diffuse B cell lymphoma	Rituximab–CHOP	0[a]	Cough, macular rash, fever, eosinophilia, dyspnea, hypoxemia	Diffuse GGO, small right pleural effusion	Lung biopsy: loose nonnecrotic granulomata in a background of mild fibrosis and rare eosinophils. Autopsy: extensive intraalveolar hemorrhage, severe DAD, dense peribronchial and alveolar lymphocytic infiltrate	Prednisone 40 mg daily, mechanical ventilation, complicated with *Staphylococcus aureus* bacteremia, MOF and death
[11]	1	80/M	Diffuse large B cell lymphoma	Rituximab–CHOP	10 days	Fever	Bilateral GGO	NA	NIPPV, methylprednisolone pulse therapy, dramatic recovery, D/C after 3 weeks
[12]	2	52/M 59/M	Diffuse large cell B lymphoma Diffuse large cell B lymphoma	Rituximab–ACVBP Rituximab–ACVBP	12 days after 3rd cycle 10 days after 4th cycle	Fever, hypoxemia Initially neutropenic fever then after 4 days developed SOB, cough, severe hypoxemia[b]	Bilateral GGO Left pneumothorax and diffuse bilateral confluent infiltrates	No lung biopsy done in either case	High dose methylprednisone (3 mg/kg) administered after 7 days of admission. Improvement observed within 17 days. Steroids stopped after 45 days with no recurrence of pulmonary abnormalities Patient sent to ICU. Received methylprednisone (1 mg/kg). Died 21 days after beginning of respiratory symptoms
[13]	1	80/M	Follicular grade 3 NHL	Rituximab–CHOP	After 3 doses	Dyspnea, cough and hypoxemia	Bibasilar subpleural consolidation, GGOs, small cysts and interlobular septal thickening	Interstitial inflammation and edema, type II pneumocyte hyperplasia and atypia and foamy vacuolated histiocytes in air spaces	Methylprednisolone 1 mg/kg and mechanical ventilation, death after 10 days
[14]	1	64/M	Diffuse large B cell lymphoma	Rituximab–CHOP and G-CSF	7 days	Fever and dyspnea	Bilateral infiltrates	OLBx: DAD, fibrosis and extensive organizing pneumonia	Mechanical ventilation and high dose prednisolone with improvement 7 days later

Table 1 ***(continued)***

Ref.	Patients	Age/sex	Diagnosis	Rituximab	Time since last dose	Clinical features	Imaging	Lung pathology	Treatment and outcome
[15]	2	73/M 66/M	Diffuse large B cell lymphoma Testicular diffuse large B cell lymphoma	Rituximab–CEOP Rituximab–CEOP	After 7 cycles After 5 cycles	Cough, dyspnea Cough and dyspnea	Bilateral subpleural GGO, reticular infiltrates and traction bronchiectasis Multifocal patchy consolidation, subpleural GGO and basilar reticular opacities	No biopsy, mild restriction and low DLCO No biopsy, mild obstruction and low DLCO	High-dose steroids tapered over 5 weeks. Normalization of DLCO Prednisone 10 mg daily for 2 months, normalization of DLCO and imaging
[16]	1	61/M	NHL	Rituximab	2 months	Dry cough and dyspnea	Multifocal dense nodules	BOOP	Prednisone 40 mg daily with slow taper and resolution of symptoms and nodules
[17]	1	88/M	Waldenstrom's macroglobulinemia	Rituximab–fludarabine and cyclophosphamide	8 weeks	Dyspnea, cough, hemoptysis and hypoxemia	Bilateral alveolar and interstitial infiltrates, bilateral pleural effusions	Interstitial pneumonitis with scattered, loosely formed granulomata	Prednisone (60 mg/day) with rapid resolution of symptoms and hypoxemia
[18]	1	69/M	Stage 1 V extranodal marginal zone B cell lymphoma	Rituximab–CHOP	After 5th course	Neutropenic fever, generalized weakness and mucositis followed by SOB aggravation and hypoxemia despite antibiotics	Bilateral patchy GGO	TBBx: interstitial thickening and type II pneumocyte activation	Prednisolone (1 mg/kg) for 2 weeks. Patient improved and was discharged after 42 days on a tapering dose of prednisolone regimen. Had complete resolution of dyspnea and dyspnea on exertion
[19]	3	77/M 79/M 54/F	All three had Asian variant of intravascular large B cell lymphoma	Rituximab [all three were premedicated with IV injections of betamethasone (4 mg), diphenhydramine 30 mg and oral acetaminophen before starting IV rituximab infusion 1 day before the induction chemotherapy]	Within 24 h of the prechemotherapy rituximab infusion[c]	Severe systemic reactions including dyspnea, hypoxia, tachycardia and hypotension	Not given Newly developed bilateral lung infiltrates Newly developed bilateral lung infiltrates	Not done TLBx: acute capillaritis but no microorganisms or lymphoma – cell proliferation Not done	Respiratory distress subsided 2 days after commencement of supportive care Required endotracheal intubation and mechanical ventilation support. Complicated by postoperative hemopneumothorax and uncontrolled hemophagocytosis. Patient died 3 weeks after rituximab treatment Required endotracheal intubation and mechanical ventilation support. Lung infiltrates cleared 10 days after initiation of supportive care
[20]	9	62/F 63/M 54/M 49/M 58/F 51/M 81/M 50/M 52/M	DLBCL DLBCL MCL FL DLBCL MCL Small-B NHL DLBCL DLBCL	Rituximab–CEOP Rituximab–CEOP Rituximab–CEOP Rituximab–CEOP Rituximab–CEOP Rituximab–CEOP Rituximab–CVP Rituximab–CEOP Rituximab–CEOP	9 days after 4th cycle 12 days after 3rd cycle 9 days after 2nd cycle 19 days after 2nd cycle 14 days after 5th cycle 18 days after 1st cycle 14 days after 2nd cycle 15 days after 2nd cycle 15 days after 3rd cycle	Fever, dry cough Fever Asymptomatic Fever, dry cough, dyspnea Fever Fever, dry cough, dyspnea Fever, dyspnea Fever, dyspnea	Bilateral pulmonary diffuse interstitial infiltrates were seen on CT scans in seven patients and unilateral flaky interstitial infiltration in one patient. One patient was found to have bilateral diffuse interstitial infiltrates on a routine midtreatment CT scans	Not done	[d]All patients were treated with either 5 mg of DXM or 40 mg of methylprednisolone DXM, Azithromycin. Patient recovered DXM, azithromycin. Patient recovered Methylprednisolone, azithromycin. Patient recovered Methylprednisolone, azithromycin. Patient recovered Methylprednisolone. Patinet recovered Methylprednisolone, Azithromycin. Patient recovered Methylprednisolone, azithromycin, tienam and itraconazole were used because of aggravation. Patient died after 41 days after he developed secondary pulmonary infection initially and pleural effusion and hypoxemia later DXM, azithromycin. Patient recovered Methylprednisolone, azithromycin.

Table 1 ***(continued)***

Ref.	Patients	Age/sex	Diagnosis	Rituximab	Time since last dose	Clinical features	Imaging	Lung pathology	Treatment and outcome
[21]	1	43/M	ITP	Rituximab	1 day (low grade fever and chills accompanied the infusion)	Dyspnea, pleuritic chest pain, hypoxemia	Diffuse pulmonary GGO	Not done	Diagnosis of ARDS was made. He received 500 mg of methylprednisolone intubated. Complicated by pseudomonas infection and pneumothorax. Died 3 weeks after receiving rituximab
[22]	1	66/M	Grade 2 follicular lymphoma	Rituximab–THP–COP and prednisolone	3 h after 3rd infusion	Fever, chills, dyspnea with hypoxemia, tachycardia and tachypnea	Infiltrative shadow, massive bilateral pleural effusion and mild cardiomegaly	Not done	Diagnosis of ARDS made. High-dose methylprednisolone (100 mg/day) and mechanical ventilation. Extubated on day 4. Patient improved
[23]	2	63/M 61/M	DLBCL DLBCL	Rituximab–CHOP Rituximab–CHOP	10 days before 6th cycle 2 weeks after completion of 5th cycle	Fever, dyspnea Fever, dyspnea, nonproductive cough	Diffuse bilateral pneumonitis Diffuse interstitial lung pattern	Biopsy showed reactive changes consistent with alveolar damage and interstitial fibrosis Not done	Started on 250 mg of IV prednisolone every 4 h. Condition improved in 24 h. Sent home on oral steroids Received IV prednisolone 60 mg every 6 hrs, intubated and mechanical ventilation. Died after 1 week of treatment without improvement (family withdrew care)
[24]	2	64/F 55/F	Rheumatoid arthritis Monotypic Castleman's disease	Rituximab–methotrexate and prednisone (10 mg/day) Rituximab–prednisone and hydroxychloroquine for 4 weeks	21 weeks after starting Rituximab After 4 months of initiation of therapy	Dry cough, chest pain and asthenia No respiratory symptoms	Bilateral alveolar densities GGO	BOOP BOOP	Prednisone 40 mg/kg was started. Tapered over 5 months. Right lung densities resolved Prednisone started at 0.75 mg/kg for 15 days then tapered. The lung densities alternately improved and worsened

ACVBP, adriamycin, cyclophosphamide, vindesine, bleomycin, prednisone; ARDS, acute respiratory distress syndrome; BOOP, brochiolitis obliterans with organizing pneumonia; CEOP, cyclophosphamide, epirubicin, vincristine and prednisolone; CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone; CLL, chronic lymphocytic lymphoma; CT, computed tomography; CVP, cyclophosphamide, vincristine, prednisone; DAD, diffuse alveolar damage; DLCO, carbon monoxide diffusion capacity; DLBCL, diffuse large B cell lymphoma; DXM, dexamethasone; F, female; FL, follicular lymphoma; G-CSF, granulocyte colony stimulating factor; GGO, ground glass opacities; ITP, idiopathic thrombocytopenic purpura; IV, intravenous; M, male; MCL, mantle cell lymphoma; MOF, multiorgan failure; NA, not available; NHL, Non-Hodgkin lymphoma; NIPPV, noninvasive positive pressure ventilation; OLBx, open lung biopsy; SOB, shortness of breath; TBBx, transbronchial biopsy; THP-COP, pirarubicin, cyclophosphamide, vincristine; VNCOP-B, etoposide, mitoxantrome, cyclophosphamide, vincristine, prednisone and bleomycin.

[a]Symptoms started while patient was still receiving rituximab but were not related to the infusion.

[b]Neutropenia resolved after 4 days of anti-infectious treatment but patient remained febrile.

[c]The pulmonary complications did not seem to be an allergic reaction to rituximab as repeated administration of the same drug in the two surviving patients did not reproduce the adverse response.

[d]Azithromycin, an antibiotic against atypical pneumonia was given to eight of the nine patients because some of the tests to rule out opportunistic infections are not widely available in China (this was a Chinese study).

dry cough with dyspnea, a fever, and asthenia are the most common clinical manifestations. Chest pain may be a feature [24]. Three radiographic patterns have been identified [26,27]. The most typical consists of multiple, peripheral, nonsystematized alveolar densities whose most suggestive feature is their migratory nature. The other two forms consist of a solitary nodule and diffuse infiltrates with reticulonodular densities. CT is useful for determining the exact location of the densities. The CT appearance ranges form marked consolidation to a ground glass appearance [26,27]. Differentials to be considered in a patient who has multiple alveolar densities include infection, pulmonary lymphoma, pneumonic-type adenocarcinoma, and chronic idiopathic eosinophilic pneumonia [25]. Corticosteroids remain the mainstay of therapy. Physicians should be aware that fludarabine, cyclophosphamide, and bleomycin (given as a combination with rituximab many times) can also cause pulmonary toxicities. Their presentations will not be discussed here. The pathogenesis of rituximab-induced interstitial lung disease (ILD) is largely unknown and cytokine release is postulated to be the mechanism. Several studies showed that rapid lymphocyte lysis, complement activation, and TNF-α release occur after rituximab infusion [28–30]. TNF-α has been implicated as a key cytokine in many inflammatory lung diseases. On the basis of the proposed pathophysiology of the lung injury, some investigators propose to use anti-TNF-α-directed therapy in patients whose clinical condition worsens despite corticosteroids [23]. Retreatment with rituximab should be carefully

Table 2 In summary characteristics of rituximab-induced interstitial lung disease [22]

Characteristic	Findings in patient with R-ILD
Incidence	Rare
Symptoms	Dyspnea, fever, and cough
Evaluations	Pulse oximetry or blood gases HRCT of chest looking for interstitial infiltrates PFT documenting a restrictive pattern and decreased diffusion capacity Bronchoscopy with bronco-alveolar lavage might help rule out an infectious etiology, and lung biopsy can show interstitial fibrosis
Therapy	Immediate discontinuation of rituximab corticosteroids Any other clinically necessary measures Might consider TNF-α directed therapy (infliximab) in severe cases and in patients whose clinical condition worsens despite corticosteroids
Outcome	Can be fatal

HRCT, high resolution CT scan; ILD, induced interstitial lung; PFT, pulmonary function test; TNF, tumor necrosis factor.

considered based on benefit and risk ratio. A summary of the characteristics of rituximab-induced interstitial lung disease is given in Table 2.

Cetuximab

FDA-labeled indications

(1) Head and neck cancer, locally or regionally advanced squamous cell, in combination with radiation therapy.
(2) Head and neck cancer, metastatic or recurrent squamous cell; as monotherapy in patients who failed earlier platinum-based therapy.
(3) Metastatic colorectal cancer, epidermal growth factor receptor (EGFR) expressing, as monotherapy, in patients intolerant to irinotecan-based chemotherapy.
(4) Metastatic colorectal cancer, EGFR expressing, as monotherapy in patients who failed both irinotecan-based and oxaliplatin-based regimens.
(5) Metastatic colorectal cancer, EGFR expressing, in combination with irinotecan, in patients refractory to irinotecan-based chemotherapy.

Mechanism of action

Recombinant human/mouse chimeric monoclonal antibody, which binds specifically to EGFR, human epidermal growth factor receptor protein 1 (HER1) and c-ErbB-1 and competitively inhibits the binding of EGF and other ligands. Binding to the EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in the inhibition of cell growth, induction of apoptosis, and decreased matrix metalloproteinase and vascular endothelial growth factor (VEGF) production.

Two cases of fatal diffuse alveolar damage that developed in lung transplant recipients after the administration of cetuximab for metastatic cutaneous squamous cell carcinoma have been reported [31]. The patients had similar characteristics: older, white, and male with a smoking history who had undergone left lung transplantation for emphysema.

Time of onset of symptoms: within 1 month of starting cetuximab.

Symptoms: shortness of breath, hypoxemia, and nonproductive cough.

Radiology: ground glass opacification throughout the transplanted lungs.

Treatment and outcome: methylprednisolone, mycophenolate mofetil, and sirolimus and antibiotics (intravenous pentamidine, ganciclovir, voriconazole, vancomycin, and zosyn) in the first case. No infectious etiology was observed. His condition worsened and patient died 10 days after hospitalization. The Second case received methyprednisolone, sirolimus, and received empirical therapy for bacterial, fungal, and cytomegalovirus. Sputum grew methicillin-sensitive *Staphylococcus aureus*, for which he was treated. His condition worsened and the patient expired 22 days after admission.

Both the patients succumbed to respiratory failure. Except for one sputum culture, which grew *S. aureus*, all respiratory, blood and bronchoalveolar lavage cultures, nasal washings, serum antibody tests, and autopsy specimens failed to reveal an infectious agent. The autopsies showed only diffuse alveolar damage, with no evidence of infection, rejection, or cancer in the lungs. Although both the patients were receiving sirolimus at the time of their presentation neither case was consistent with sirolimus-associated pulmonary toxicity. With no evidence to support an infectious etiology, metastatic disease of the lungs, or other drug-associated pulmonary toxicity, the precipitating cause of death in both cases was believed to be cetuximab-associated ILD.

Whether transplant recipients are at increased risk of developing EGFR inhibitor-associated ILD remains unclear. Perhaps an interaction between cetuximab and an immunosuppressive agent such as sirolimus increases the risk of diffuse alveolar damage or prevents recovery from lung injury in lung transplant recipients. Possibly, increased EGFR expression in transplanted lungs, which has been observed in animal studies, increases susceptibility to the development of diffuse alveolar damage in lung transplant recipients exposed to an EGFR inhibitor [32]. The radiological and pathologic findings were more prominent in the transplanted lung compared with the native lung in both the reported cases, suggesting an increase in the transplanted lung. Until toxicities of EGFR inhibitors are better understood caution is recommended when considering the use of EFGR inhibitors in lung transplant recipients.

Bevacizumab

FDA-abeled indications

(1) Metastatic breast cancer, HER-2-negative, as first-line therapy in combination with paclitaxel.
(2) Metastatic colorectal cancer, first-line or second-line therapy, in combination with 5-fluorouracil-based chemotherapy.
(3) Nonsmall-cell lung cancer, first-line treatment in combination with paclitaxel and carboplatin for unresectable, locally advanced, recurrent or metastatic nonsquamous cell disease.

Mechanism of action

Bevacizumab is a recombinant, humanized monoclonal antibody, which binds to and neutralizes VEGF, preventing its association with endothelial receptors, FMS like tyrosine kinase and kinase insert domain receptor. VEGF binding initiates angiogenesis (endothelial proliferation and the formation of new blood vessels). The inhibition of microvascular growth is believed to retard the growth of all tissues (including metastatic tissue).

Neutropenia, fatigue, hypertension, and infection are the most common adverse effects, but hemoptysis requiring medical intervention is seen in 2.3% of patients receiving bevacizumab and it can be fatal [33]. As hemoptysis may be caused by malignant or infectious cavitary lung disease or by metastatic airway lesions, it is critical to identify the relationship of hemoptysis to the drug itself in cancer patients treated with angiogenesis inhibitors before stopping therapy. Life-threatening hemoptysis has been observed in patients enrolled in a randomized study for nonsmall-cell lung cancer treated with bevacizumab. The incidence of bleeding events was 9% (six of 66 patients) and four of these events were fatal. The subset analysis of this study suggested that hemoptysis occurred more frequently in squamous carcinomas compared with adenocarcinoma, but it is not clear whether histology alone is a central risk factor for bleeding [34]. In a study sponsored by the National Cancer Institute that led to FDA approval of bevacizumab for nonsmall-cell lung cancer, the rate of pulmonary hemorrhage requiring medical intervention for the carboplatin and paclitaxel (CP) plus bevacizumab arm [2.3% (10 of 427)] compared with [0.5% (2 of 441)] for the CP arm alone. There were seven deaths owing to pulmonary hemorrhage reported by investigators in the CP plus bevacizumab arm compared with one in the CP-alone arm. Generally, these serious hemorrhagic events were presented as major or massive hemoptysis without an antecedent history of minor hemoptysis during bevacizumab therapy [35]. It is therefore extremely important for physicians treating patients with lung cancer not only to be aware and recognize the risk of life-threatening pulmonary hemorrhage associated with bevacizumab, but also to be able to attribute this adverse effect to the drug itself.

Bevacizumab binds to all biologically active isoforms of VEGF and neutralizes their biologic properties including endothelial cell mitogenic activity, vascular permeability-enhancing activity, and those that promote angiogenesis [36]. Inhibition of VEGF results in the inhibition of vascular development and significant alteration in epithelial development, suggesting that VEGF coordinates proper development of normal lung epithelium and vasculature [37]. Therefore, it seems possible that antagonizing VEGF might decrease the renewal capacity of the endothelial cell, which in turn causes endothelial dysfunction in the supporting layers of the blood vessel. Consequently, the final event of anti-VEGF might be a tendency for bleeding from normal tissues leading to central nervous system hemorrhage, epistaxis, or gastrointestinal bleeding [38]. Further research is needed to elucidate the exact mechanism of hemoptysis related to bevacizumab [39].

Early bronchoscopy has been used not only as a first diagnostic approach but also in the management of massive hemoptysis [40]. If bronchoscopy reveals a localized bleeding mucosal lesion, laser photocoagulation, electrocautery, or other alternative bronchoscopic techniques may be considered for therapy [41]. The Nd:YAG laser (LASAG Industrial lasers, Thun, Switzerland) is widely used for the treatment of endobronchial tumors and other airway lesions and is also effective for tissue coagulation. During laser application, light energy is transmitted through the optical fibers to the targeted tissues, where energy is absorbed, transmitted through the tissue, scattered or reflected. Tissue effect is the result of wavelength (1064 nm for Nd:YAG), tissue color (Nd:YAG energy is rapidly absorbed by dark colored tissues), laser power, and power density (power/surface area). The Nd:YAG laser also causes deep tissue vasoconstriction minimizing further bleeding [42,43]. It is therefore an efficient tool for photocoagulation of the abnormal airway mucosal bleeding.

A case of interstitial pneumonitis has also been associated with the administration of bevacizumab and docetaxel. Three weeks after receiving the dose of bevacizumab and docetaxel the patient presented with fever, tachycardia, tachypnea, and was found to have basal crepitant rales in lung auscultation. Arterial blood gases showed pH of 7.41, with an oxygen partial pressure of 66 mmHg, and a carbon dioxide partial pressure of 34 mmHg. A CT scan of the chest revealed ground glass opacities predominantly in the lower lobes of both lungs. The patient responded well to prednisone (1 mg/kg). A CT scan after 1 week showed complete resolution of parenchymal opacities. Infectious etiology was excluded and transbronchial biopsy revealed expanded alveoli with an infiltrate consisting of intra-alveolar macrophages and surrounded by thickened alveoli septa without malignant cells, viral inclusions, or other specific inflammation [44].

Alemtuzumab

FDA-labeled indications

B-cell chronic lymphocytic leukemia, as monotherapy.

Mechanism of action

Binds to CD52, a nonmodulating antigen present on the surface of B and T lymphocytes, a majority of monocytes, macrophages, NK cells, and a subpopulation of granulocytes. After binding to $CD52^+$ cells, an antibody-dependent lysis of leukemic cells occurs. Adverse effects commonly include neutropenia and lymphopenia, occurring in more that 50% of patients, and consequent opportunistic infections, occurring in up to 43% of patients [45,46]. Infusion site reactions and a flu-like syndrome are common during the initiation of therapy.

There has been a case report of alemtuzumab-associated interstitial pneumonitis [47]. A 36-year-old Caucasian female presented to the hospital with progressive dyspnea. The patient was a known case of chronic lymphocytic leukemia and despite earlier chemotherapy with PCR chemotherapy (pentostatin, cyclophosphamide and rituximab) and R-CHOP chemotherapy (rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone) her disease recurred. One month before presentation, she underwent alemtuzumab salvage therapy in preparation for potential stem cell transplantation. She received 3, 10, and 30 mg of alemtuzumab over sequential days, followed by 30 mg three times weekly for 3 weeks. An erythematous, nonpruritic local skin reaction occurred with her first dose; no further complications were observed. Her vital signs at presentation included a temperature of 36.8 °C; pulse rate, 110 bpm; respiratory rate, 22 per min; blood pressure, 130/80 mmHg; and pulse oximetry, 95% at room air temperature. Physical examination findings were significant for cervical lymphadenopathy and coarse breath sounds bilaterally, without wheezing or rhonchi; the other findings were unremarkable. Cultures of urine and blood from port and lines were negative and no cytomegalovirus DNA was detected in her blood. CT scan of the chest revealed new, patchy ground glass opacities at the lung bases, suggestive of an inflammatory etiology. Pulmonary function testing revealed a 30% reduction in her adjusted diffusion capacity and 32% reduction in her forced vital capacity compared with her baseline from 1 year earlier. Echocardiography showed normal cardiac function. Bronchoscopy with bronchoalveolar lavage was negative for malignant cells and microbial organisms, and transbronchial biopsy revealed interstitial inflammation without evidence of infection. Despite broad-spectrum antibiotics, her respiratory status continued to decline. Wedge biopsy revealed prominent nonspecific interstitial pneumonitis and inflammation with no evidence of infectious etiology consistent with chemotherapy-induced pneumonitis. The patient began receiving intravenous methyprednisone (80 mg/day) with minimal improvement in symptoms. A nasotracheal viral culture showed parainfluenza virus type 3, and although there was no evidence of parainfluenza viral changes on biopsy, she was treated with intravenous immunoglobulin without improvement. Her respiratory distress gradually worsened despite continued empiric antibiotic coverage, and she was intubated 2 months after admission. Later, the family withdrew care and a request for autopsy was declined. Chemotherapy-induced respiratory failure is a difficult diagnosis. It is important to exclude infectious etiology, cardiac dysfunction and also the possibility of interstitial pneumonitis induced by multiple drugs. All these factors have to be looked into before attributing lung pathology to the drug. A good history of other chemotherapeutic agents received and knowledge of their lung toxicity patterns are important. Blood, urine, and bronchoalveolar lavage cultures and echocardiogram should be performed. Specific stains for neoplastic and viral changes on open lung biopsy are also helpful in excluding other etiologies. Bronchospasm has also been reported with alemtuzumab [48,49].

There has also been a case reported of diffuse alveolar hemorrhage following alemtuzumab [50]. A 26-year-old man with X-linked Alport syndrome underwent retransplantation with a cadaveric renal allograft. He received alemtuzumab therapy as part of an immunosuppressive induction protocol. On the second postoperative day mild hemoptysis and dyspnea developed in the patient along with new onset anemia (hemoglobin, 7.3 g/dl) and thrombocytopenia (platelet count, 54 000 cells/μl) compared with his hospital admission values of 9.1 g/dl and 127 000 cells/μl). Arterial blood gas levels obtained with a 0.4 fraction of inspired oxygen showed a PaO_2 of 74 mmHg, with a PaO_2/fraction of inspired oxygen ratio of 185. A physical examination of the chest revealed bilateral late, fine, inspiratory crackles in the mid-to-lower lung fields. A chest CT scan showed diffuse alveolar opacities. Bronchoalveolar lavage fluid, which showed a characteristic increasingly bloody return in the sequential aliquots and an RBC count of 239 500 cells/μl, was obtained from the right middle lobe. There was no growth of pathogenic bacteria or evidence of opportunistic infection in the bronchoalveolar lavage fluid. A peripheral smear did not reveal any significant schistocytes, and the serum haptoglobin level was 70 mg/dl. There was no clinical or laboratory evidence of vasculitis, and it was suspected that the thrombocytopenias caused by the drug and direct epithelial lung toxicity producing diffuse alveolar damage may have a role to play in this patient [51]. The patient required intubation and mechanical ventilation for 5 days secondary to acute respiratory failure and clinical improvement occurred with the initiation of steroids.

Trastuzumab

FDA-labeled indications

(1) Breast cancer, adjuvant, HER-2 overexpression.
(2) Metastatic breast cancer, HER-2 overexpression, monotherapy in patients who have received at least one earlier chemotherapy regimen.
(3) Metastatic breast cancer, HER-2 overexpresssion, first-line treatment in combination with paclitaxel.

Mechanism of action

Trastuzumab is a monoclonal antibody, which binds to the extracellular domain of the HER-2; it mediates antibody-dependent cellular cytotoxicity by inhibiting proliferation of cells which overexpress HER-2 protein.

In several series, trastuzumab has been well tolerated, and the addition of trastuzumab to chemotherapy does not significantly increase the frequency of side effects [52]. Infusion-related events are common but rarely severe, and they are more common during the first administration [53]. In an analysis of the safety of the administration of trastuzumab to 25 000 patients, the only respiratory-associated serious adverse event was bronchospasm [54]. These reactions occurred usually within 2.5 h of administration. However, apart from infusion-related bronchospams that have been described, rare cases of interstitial pneumonitis have been reported. One patient presented with an organizing pneumonia (earlier known as BOOP) [55]. In trial B-31, four patients in the trastuzumab group had interstitial pneumonitis, one of whom died [56]. In the N9831 trial, five patients in the trastuzumab group had grade 3+ pneumonitis or pulmonary infiltrates, one of whom died [56].

Trastuzumab-associated pneumonitis can present as hypoxemia, cough, dyspnea, and respiratory failure. Bronchoalveolar lavage differential cell count shows marked neutrophilia, suggesting neutrophilic alveolitis. Treatment-related death has also been reported in clinical trials [56,57]. A CT scan of the chest can show diffuse ground glass opacities [57] or patchy foci of airspace consolidation [55]. The drug is withdrawn immediately and corticosteroids are used to suppress the inflammatory reaction. Resolution of radiographical findings can lag 3 months behind treatment [55]. The diagnosis of drug-associated ILD should be based on the combination of clinical, radiological, and histological findings. As a matter of fact, advanced imaging techniques such as high-resolution CT are not sufficient for a correct diagnosis of ILD; the imaging and pathological pattern did not correspond in more than 40% of the cases [58].

Drug-induced ILD is the most common form of all forms of antineoplastic agent-induced respiratory disease. Patterns of drug-induced ILD are nonspecific interstitial pneumonitis, eosinophilic pneumonia, hypersensitivity pneumonitis, pulmonary fibrosis, or organizing pneumonia [59]. Early withdrawal of causative drug will often lead to improvement or even cure of the ILD. Corticosteroids may suppress the inflammatory reaction [60,61].

The mechanism of trastuzumab-associated lung injury is not clear. Acute lung injury is characterized by damage to alveolar epithelium. Successful recovery of alveolar epithelium requires proliferation and differentiation of type II pneumocytes. It has been shown that the keratinocyte growth factor can enhance alveolar epithelial repair, and these effects are mediated, in part, by the EGF receptor pathway [62]. As EGF receptors are present on human type II pneumocytes, HER-2 inhibitors can potentially impair the ability of type II pneumocytes to respond to injury. This may explain why patients with intrinsic lung disease or extensive tumor involvement of the lungs with preexisting lung injury may be at greater risk for severe pulmonary reactions [63].

Altogether, the reports of apparent trastuzumab-related pulmonary interstitial disease in B-31, N9831, and four other reports [55,64–66] are highly suggestive that this syndrome is a rare, but real, complication of this therapy. In one case, the patient subsequently developed Guillian–Barre syndrome [66]. Clinicians should be aware of it and be prepared to respond appropriately, including discontinuation of further treatment or cautious coadministration with corticosteroids [64].

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