Pneumonitis After Precision Oncology Therapies: A Concise Review

Abstract
With greater understanding of the molecular biology of cancer, precision oncology therapies are becoming increasingly prevalent. Adverse events associated with these therapies may cause significant harm to patients if not promptly recognized and treated. In this review, we focus on pneumonitis that occurs as a side effect of treatment with precision oncology agents. We discuss the incidence and time to onset of pneumonitis associated with a broad array of precision oncology agents. We highlight the common patterns of pneumonitis and offer a comprehensive approach to evaluation and treatment with therapy-specific guidelines where available.

Keywords: Pneumonitis, precision oncology agent, pulmonary adverse events

Introduction
Almost 40% of individuals will be diagnosed with cancer at some point in their lives.\(^1\) In the United States of America, the incidence of new cases of cancer is estimated at 455 cases per 100,000 individuals per year, and an estimated 171.2 deaths per 100,000 individuals are attributed to cancer.\(^2\) Surgery, chemotherapy, and radiation are the mainstays of therapy for most cancers. However, despite improvements in outcomes for many early-stage cancers, survival rates for late-stage cancers have plateaued.\(^3\) For example, 5-year survival rates have remained stable for late-stage non-small cell lung cancers over the last decade despite numerous clinical trials of conventional therapies.\(^4\) New strategies are needed to mitigate the morbidity and mortality associated with late-stage cancers.

Late-stage cancers are often resistant to conventional chemotherapy and radiation.\(^5\) Molecular profiling of late-stage cancer may identify specific mutations which can be targeted for treatment.\(^6\) The strategy of identifying mutations in pathways associated with cancer progression and then directly targeting them is broadly termed “precision oncology.”\(^7\) Prominent examples of improvements in early survival with precision oncology approaches include BRAF inhibitors in melanoma and epidermal growth factor receptor (EGFR) inhibitors in EGFR-mutant lung adenocarcinoma.\(^8,9\) However, improvements in long-term survival remain elusive.

With the advent of precision oncology therapies, oncologists now face a new array of adverse effects that may require prompt recognition and treatment.\(^10\) The purpose of this review is to highlight pulmonary adverse events with common precision oncology agents. We propose a standardized clinical algorithm to evaluate and treat cancer patients receiving precision oncology therapies who are suspected of having pneumonitis. Furthermore, we highlight common manifestations of pneumonitis after treatment with EGFR inhibitors, HER2/neu receptor inhibitors, mammalian target of rapamycin (mTOR) inhibitors, anti-CD20 and anti-CD30 monoclonal antibodies, breakpoint cluster (BCR)-Abelson tyrosine kinase inhibitors (TKIs), anaplastic lymphoma kinase (ALK) inhibitors, and Bruton’s tyrosine kinase (BTK) inhibitors.

Patterns of Pneumonitis After Precision Oncology Therapies
Interstitial lung diseases (ILDs) are a collection of various diseases of the lung parenchyma with varying incidences, manifestations, and prognoses.\(^11\) Pulmonary complications of precision oncology therapies often mimic certain ILDs seen in the general population. In this section, we...
choose three specific patterns of pneumonitis – nonspecific interstitial pneumonitis (NSIP), organizing pneumonia (OP), and diffuse alveolar damage (DAD) – that are commonly seen in patients receiving precision oncology therapies and discuss the pathophysiology, clinical features, and prognosis [summarized in Table 1]. Figure 1 shows representative images from patients who developed NSIP, OP, and DAD after precision oncology therapies. A more complete discussion of the clinical features and pathophysiology of various ILDs is available elsewhere.\textsuperscript{[12,13]}

Nonspecific interstitial pneumonitis

NSIP may be idiopathic or arise in association with various conditions such as autoimmune disease, human immunodeficiency virus infection, or after exposure to certain drugs. NSIP is one of the most common manifestations of drug-induced ILD.\textsuperscript{[14]} NSIP typically presents with nonspecific symptoms of cough and dyspnea. Histologically, NSIP is characterized by dense fibrosis with diffuse inflammatory cell infiltration and uniform and diffuse thickening of alveolar walls, but without loss of alveolar structural integrity.\textsuperscript{[15]} High-resolution computed tomography (HRCT) imaging of NSIP most commonly shows increased reticular markings, traction bronchiectasis, and ground-glass opacities.\textsuperscript{[16–18]} Subpleural sparing of pulmonary opacities helps distinguish NSIP from idiopathic pulmonary fibrosis, but is neither sensitive nor specific for the diagnosis.\textsuperscript{[19]} These radiologic and histopathologic patterns may be seen in other ILDs such as hypersensitivity pneumonitis (HP). However, the presence of poorly formed granulomas or multinucleated giant cells on surgical biopsies and the presence of air trapping on inspiratory and expiratory imaging may help distinguish HP from NSIP.\textsuperscript{[20]} HP is a less common manifestation of pneumonitis after precision oncology therapies than NSIP, but HP and NSIP are similar in terms of clinical presentation and course. Therefore, for the purposes of this review, we considered radiologic HP to be a subtype of NSIP.

Treatment of NSIP depends on the severity of disease, the underlying cause, and the rate of progression. For drug-related NSIP, drug interruption is generally recommended for symptomatic patients and in certain cases may be curative.\textsuperscript{[21]} Optimal dosing and duration of corticosteroid treatment for NSIP have not been established, and the following are our

Table 1: Clinical, radiological, and histopathological features of common patterns of pneumonitis in patients receiving precision oncology therapies

<table>
<thead>
<tr>
<th>Type of ILD</th>
<th>Clinical features</th>
<th>Radiological features</th>
<th>Histopathological features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>OP</td>
<td>Nonproductive cough, dyspnea, weight loss, usually for &lt;2 months</td>
<td>Patchy areas of consolidation or ground-glass opacities which are often seen in the lung periphery</td>
<td>Proliferation of granulation tissues in the distal bronchus and alveoli along with mild-to-moderate infiltration of plasma cells and lymphocytes</td>
<td>Mild OP with no pulmonary function impairment – resolution can occur spontaneously. Close monitoring of respiratory symptoms, imaging, and/or pulmonary function is required</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple alveolar opacities, solitary opacities, or infiltrative opacities can be seen</td>
<td></td>
<td>Progressive and/or persistent symptoms with evidence of pulmonary function impairment – corticosteroid therapy with doses usually starting at 0.5–1 mg/kg/day of prednisone or equivalent for 3–6 months</td>
</tr>
<tr>
<td>NSIP</td>
<td>Nonproductive cough and dyspnea which develop over weeks to months. Bibasilar crackles are also heard in majority of patients</td>
<td>Reticular markings, traction bronchiectasis, and ground-glass opacities are seen mostly in lower lung zones</td>
<td>Fibrosis with diffuse inflammatory cell infiltration and uniform and diffuse thickening of alveolar walls, but without loss of alveolar structural integrity</td>
<td>Patients with minimal symptoms and no change in pulmonary function – observation Moderate symptoms or impairment in pulmonary function test – corticosteroid therapy (0.5–1 mg/kg/d of prednisone or equivalent) for 8–12 weeks. Steroid-refractory disease therapy with intravenous corticosteroids and/or cytotoxic therapies</td>
</tr>
<tr>
<td>DAD</td>
<td>Rapid onset of progressive dyspnea and cough over days to weeks</td>
<td>Widespread airspace opacities may be more prominent in the dependent areas of the lung</td>
<td>Alveolar thickening with hyaline membrane deposition and infiltration with inflammatory cells</td>
<td>Respiratory failure – Supportive therapies and intravenous corticosteroids</td>
</tr>
</tbody>
</table>

ILD: Interstitial lung diseases, OP: Organizing pneumonia, NSIP: Nonspecific interstitial pneumonitis, DAD: Diffuse alveolar damage

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recommendations. Patients with NSIP who have minimal symptoms and no change in pulmonary function may be observed, but most patients require corticosteroid therapy (0.5–1 mg/kg/day of prednisone or its equivalent) for 8–12 weeks. Steroid-refractory disease is more commonly seen in NSIP than in OP and may require further therapy with intravenous corticosteroids and/or cytotoxic therapies, though the efficacy of noncorticosteroid agents has not been well established.[22]

Organizing pneumonia

OP is an ILD that mainly affects distal respiratory bronchioles and alveoli.[23] Clinical features of OP include nonproductive cough, dyspnea, and weight loss.[24-27] In some patients, symptoms of malaise and fatigue may be present for weeks prior to diagnosis, but are nonspecific for the diagnosis of OP. Respiratory infections are often implicated as a cause of OP, though the mechanism remains unclear.[28] On histopathology, OP is characterized by excessive proliferation of granulation tissues in the distal bronchus and alveoli along with mild-to-moderate infiltration of plasma cells and lymphocytes.[29,30] HRCT imaging of the chest in patients with OP may reveal patchy areas of consolidation or ground-glass opacities which are often seen in the periphery.[25,31-42] The reverse halo sign can be seen in OP but is not pathognomonic.[43]

Treatment of OP is dependent on the severity of disease. In mild OP, resolution can occur spontaneously, but requires close monitoring of respiratory symptoms, imaging, and/or pulmonary function.[22] For patients who have progressive and/or persistent symptoms with evidence of pulmonary function impairment, corticosteroid therapy is typically highly efficacious, with doses usually starting at 0.5–1 mg/kg/day of prednisone or its equivalent for 3–6 months.[29] Interruptions in corticosteroid treatment may result in recurrence of OP, and rarely OP can be resistant to corticosteroid therapy.[44] Optimal treatment regimens for OP have not been studied in randomized trials. Treatment recommendations are generally based on clinical experience and observations from small case series and are based on symptom severity, pulmonary function impairment at presentation, disease progression, and radiographic extent of disease. Withholding the offending agent is generally recommended, for patients with asymptomatic or mild disease. Drug withdrawal and initiation of systemic corticosteroids is recommended among patients with progressive symptoms and/or moderate-to-severe disease. The addition of other therapies, such as cyclophosphamide, cyclosporine, rituximab, and macrolides, has been associated with anecdotal success in small case series of steroid-refractory patients.[45-48]

Diffuse alveolar damage

DAD is a rare and fulminating form of ILD caused by alveolar injury leading to noncardiogenic pulmonary edema.[21-49] DAD usually occurs more rapidly than NSIP or OP and is characterized by progressive dyspnea and cough over days to weeks. The diagnosis of DAD is suggested by clinical evidence of acute respiratory distress syndrome and its histopathologic correlate, DAD. The histopathology of DAD is characterized by an inflammatory interstitial infiltrate associated with thickened alveolar membranes, edema of the alveolar septa, and hyaline membrane deposition.[50,51] HRCT images of DAD show widespread bilateral airspace opacities which may be more prominent in the dependent areas of the lung.[52,53] Clinical, pathologic, and microbiologic evaluations are important to exclude competing diagnoses such as infection, heart failure, DAH, and other rare ILDs such as acute eosinophilic pneumonia. Supportive therapies, including noninvasive or invasive mechanical ventilation, are often the mainstay of treatment for DAD, as respiratory failure is common. Early initiation of high-dose systemic corticosteroids is generally recommended, although data supporting this practice are very limited. Despite aggressive therapy, DAD often has a fulminant course with high rates of mortality.[54]

Clinical Algorithm for Diagnosis of Pneumonitis after Precision Oncology Therapies

Symptoms of pneumonitis may be subtle and masked by other comorbid symptoms of the underlying malignancy. Chest radiography is not sufficiently sensitive to detect subtle findings of pneumonitis. Thus, new or worsening cough, shortness of breath, chest tightness, or pleurisy should prompt HRCT imaging of the chest.[55] Pulmonary consultation for bronchoscopic examination with bronchoalveolar lavage should be sought early among patients with compatible clinical histories and/or suspicious findings on chest CT imaging to rule out alternative diagnoses, such as pneumonia.[56] If there is no evidence of infection and there are no other contraindications, surgical biopsies of the involved lung parenchyma should be considered in select patients to determine the pattern of ILD. Transbronchial biopsies are not recommended due to low sensitivity for detection of ILD and poor diagnostic yield.[57]

A general approach to the management of pneumonitis with drug-related adverse effects is provided by the Common Terminology Criteria for Adverse Events (CTCAEs) criteria [Table 2].[58] Indications for drug interruption and resumption vary according to the specific agent in question. In general, when specific guidelines are not available, we recommend corticosteroid treatment in Grade 2 or higher pneumonitis, guided by the radiologic or histopathologic pattern of ILD. In the following section, we provide the incidences and patterns of pneumonitis seen with common precision oncology agents and, when available, provide unique strategies associated with each class of drugs. We highlight specific nuances, such as the timing of drug interruption and whether resumption of therapy is advisable.
### Pneumonitis after Precision Oncology Therapies

**Epidermal growth factor receptor inhibitors**

The EGFR belongs to the tyrosine kinase family and is expressed in various tissues such as the lung, breast, gastrointestinal tract, and the oropharynx.[59-61] Activation of the EGFR pathway by any of its ligands induces increased cellular proliferation and survival and angiogenesis through the activation of several downstream mediators such as KRAS, phosphoinositide 3-kinase, phospholipase C, and AKT.[62-66] Not surprisingly, cancers can increase activity of the EGFR pathway to promote tumor cell proliferation and survival through increased tumor expression of EGFR or mutations in EGFR leading to increased activity.[67,68]

Anticancer agents target the EGFR pathway in two distinct ways. Monoclonal antibodies bind to the extracellular part of EGFR receptor and block ligand binding, while small molecule TKIs target the intracellular component of the EGFR receptor and prevent downstream signaling.[69] Commonly used drugs include the TKIs gefitinib, erlotinib, osimertinib, and afatinib, and the monoclonal antibodies, namely, cetuximab and panitumumab.[70]

**EGFR TKIs** are more commonly associated with pneumonitis than anti-EGFR monoclonal antibodies.[71] Pneumonitis occurs in about 1% of cases of erlotinib and gefitinib therapy, with fatality being reported in up to one-third of cases.[72-78] Pneumonitis after afatinib therapy has been reported, but is rare.[79] Cases of pneumonitis after gefitinib and osimertinib therapy more commonly present as NSIP,[80-82] while pneumonitis after erlotinib is more commonly presents as OP.[83] The incidence of pneumonitis due to osimertinib is 2%–4%, and 0.4%–0.5% of patients develop fatal pneumonitis.[84]

**EGFR TKIs** are also associated with radiation recall pneumonitis.[85] Radiation recall pneumonitis is a poorly understood phenomenon, whereby pneumonitis is triggered by a precipitating drug within lung tissue that has been previously irradiated.[86] The diagnosis is made if the area of pneumonitis corresponds closely to the fields of radiation exposure during treatment. Radiation recall pneumonitis may be more common if the time interval between radiation treatment and systemic chemotherapy is <3 months.[85] Radiation recall pneumonitis may resolve spontaneously, but symptomatic cases require treatment with corticosteroids, potentially withholding the EGFR inhibitor.[86]

Studies have suggested that pneumonitis-related mortality associated with EGFR TKI therapy may be higher in Japanese populations as compared to non-Japanese population (approximately 1.6%–4.3% in Japanese populations and 0.3%–1.0% in non-Japanese populations). This may be related to the higher frequency of EGFR-driven lung cancers, and therefore more frequent use of EGFR-inhibitors in Asian individuals rather than an increased genetic susceptibility to EGFR-related drug toxicity in the Asian population.[87,89]

The incidence of pneumonitis with the anti-EGFR monoclonal antibodies cetuximab and panitumumab has been reported to be around 1.7% and 1.3%, respectively.[90,91] Cetuximab most commonly presents with NSIP.[92] However, panitumumab-related pneumonitis most commonly presents with DAD, followed by NSIP and OP.[91] Fatalities associated with cetuximab and panitumumab are around 41% and 36%, respectively,[93] suggesting that pneumonitis after these monoclonal antibodies may present with a more fulminant course.

**Treatment of pneumonitis after EGFR inhibitor therapy** includes corticosteroids and withholding the offending drug.[94] Grading schemes specific to EGFR inhibitors have not been established, but we recommend using the NCI CTCAE [Table 2].[95] Grade 1 pneumonitis may be managed by close observation with serial imaging.[96] For Grade ≥2 pneumonitis, we would recommend drug interruption, with consideration of changing anti-EGFR therapies when the pneumonitis resolves.[97]

**HER2/neu inhibitors**

HER2/neu inhibitors are a special class of EGFR inhibitors used in HER2/neu-positive breast cancer.[98] HER2 is a member of the EGFR family gene which activates several signaling pathways which lead to cell proliferation and anti-apoptosis.[99,100] About 20%–30% of breast cancers are HER2/neu positive, and mutations in this gene are associated with poorer prognoses.[98,101]

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**Table 2. Grading of pneumonitis as outlined by the Common Terminology Criteria for Adverse Events v5.0 and general recommendations for treatment**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Asymptomatic</td>
<td>Symptomatic limitations in instrumental activities of daily living</td>
<td>Severe symptoms limiting self-care or activities of daily living</td>
<td>Life-threatening respiratory compromise</td>
<td>Death</td>
</tr>
<tr>
<td>Intervention required</td>
<td>No intervention is indicated, only clinical or diagnostic observation is recommended</td>
<td>Corticosteroid therapy in select cases</td>
<td>Corticosteroid therapy is indicated</td>
<td>Urgent intervention is indicated (e.g., tracheostomy or intubation).</td>
<td>Corticosteroid therapy is indicated. High-dose intravenous corticosteroids should be considered</td>
</tr>
</tbody>
</table>

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In this review, we will focus on trastuzumab and ado-trastuzumab emtansine. Pertuzumab, which is also approved by the Food and Drug Administration (FDA) for HER2/neu-positive breast cancer, has not been reported to cause pneumonitis. Trastuzumab is a monoclonal antibody which binds to the HER2/neu receptor and causes internalization and downregulation of HER2 and is FDA approved for use in HER2/neu-positive breast cancers. The incidence of pneumonitis is rare, estimated at about 0.5%. However, there have been cases of life-threatening pneumonitis. Ado-trastuzumab emtansine is an antibody drug conjugate which contains trastuzumab and the tubulin inhibitor emtansine. Ado-trastuzumab emtansine is FDA approved for use in metastatic HER2/neu-positive breast cancer that did not respond to trastuzumab or recurred after trastuzumab therapy. The frequency of pneumonitis with ado-trastuzumab is 1.2, higher than with trastuzumab alone. DAD has been reported with HER2/neu inhibitors, but given the rarity of pneumonitis, it is not clear whether this is the most common manifestation. The median time for onset of pneumonitis is 3–4 months after initiation of treatment. Radiation recall pneumonitis has also been reported with trastuzumab.

Treatment of pneumonitis due to HER2/neu inhibitors includes permanent discontinuation of drug and supportive management. There are no specific grading criteria for pneumonitis after HER2/neu inhibitors. Therefore, we recommend use of the NCI CTCAE [Table 2]. The safety of treating those who develop trastuzumab-related pneumonitis subsequently with ado-trastuzumab emtansine is unknown.

Mammalian target of rapamycin inhibitors

mTOR is a serine/threonine kinase which has broad effects on cell survival, cell growth, and cell proliferation. Mutations in several genes can activate the mTOR pathway, which increases the risk of developing several cancers. Treatment with rapamycin analogs has the potential to inhibit the growth of many cancers that rely on aberrant mTOR signaling for survival. Several mTOR inhibitors have been approved by the FDA or are in clinical trials. In this review, we will focus on the FDA-approved mTOR inhibitors, namely sirolimus, temsirolimus, and everolimus.

Sirolimus is rarely used as a chemotherapeutic agent, but it is more commonly used at lower doses as an immunosuppressive agent. Pulmonary complications after sirolimus are exceedingly rare. Both NSIP and OP have been reported after sirolimus therapy, but imaging and histopathology give discrepant results as to which pattern is more common. The incidence of pneumonitis is higher in the mTOR inhibitors, everolimus and temsirolimus. Larger studies have reported the incidence of pneumonitis after everolimus to be about 10%–23% and in temsirolimus to be about 2%–6%. The median time to onset of pneumonitis is about 3 months. The most common patterns of pneumonitis after everolimus and temsirolimus therapy are OP and NSIP. The mechanism by which pneumonitis occurs after mTOR inhibition remains unclear. Of note, mTOR inhibitors are also rarely associated with radiation recall pneumonitis.

Treatment of pneumonitis after mTOR inhibitor therapy is dependent on the grade of pneumonitis, which varies slightly from the NCI CTCAE [Figure 2]. Asymptomatic pneumonitis (Grade 1) only requires observation. Mild symptoms of cough or shortness of breath (Grade 2a) require close observation and possibly a temporary dose reduction, while more severe symptoms (Grade 2b) require dose reduction and institution of corticosteroid therapy. The need for oxygen or the inability to perform activities of daily living defines Grade 3 and higher pneumonitis from mTOR inhibitor therapy and requires prompt discontinuation of the drug, hospitalization, and corticosteroid therapy. For any patient with life-threatening pneumonitis (e.g., those requiring mechanical ventilation), the mTOR inhibitor should be permanently discontinued.

Anti-CD20 and anti-CD30 monoclonal antibodies

The advent of monoclonal antibodies that target cellular markers expressed on B- and T-cells has revolutionized the treatment of lymphomas. The monoclonal antibody, rituximab, binds to the CD20 antigen on B-cells and induces cell death through antibody- and complement-mediated cytotoxicity. Similarly, brentuximab vedotin is comprised of the anti-CD30 antibody, brentuximab, and an anti-mitotic agent, monomethyl auristatin E, which disrupts microtubule function. The FDA has approved rituximab for use in CD20+ lymphoma and chronic lymphocytic leukemia and brentuximab vedotin for use in relapsed Hodgkin’s lymphoma and anaplastic large cell lymphoma. The incidence of rituximab-related pneumonitis is estimated at <0.03% by the manufacturer of the drug. However, in case series of patients receiving rituximab therapy as part of a chemotherapy regimen, incidence rates of rituximab-related pneumonitis have ranged from 4% to 10%. Furthermore, the incidence of pneumonitis in regimens using rituximab with pegylated doxorubicin can exceed 20%. The median time of onset of pneumonitis is 15 days (interquartile range: 7–31 days), and the most common patterns are NSIP, followed by OP and DAD. In a systematic literature review of cases of rituximab-related pneumonitis, there were 18 fatalities out of 99 cases with available outcome data. The mainstays of therapy in rituximab-related pneumonitis are corticosteroids, depending on the pattern of ILD and withholding of the drug. Although data are scant, pneumonitis recurs in about 20% of patients who are re-challenged with rituximab after being treated for rituximab-related pneumonitis.
Brentuximab vedotin is more commonly associated with pneumonitis than rituximab, particularly in the context of bleomycin-containing regimens used in advanced-stage Hodgkin’s lymphoma, where the incidence of pneumonitis has been reported to be 44%. As a result, the FDA has placed a black box warning for the use of brentuximab vedotin with bleomycin-containing regimens. In a Phase I study, two out of 11 patients died due to pneumonitis, though the pattern of pneumonitis was not clearly described. Replacing bleomycin with brentuximab vedotin in patients with advanced-stage Hodgkin’s lymphoma who are receiving doxorubicin, vinblastine, and dacarbazine reduces the incidence of pneumonitis from 7% to 2% and results in improved progression-free survival. The incidence of pneumonitis after brentuximab vedotin therapy is substantially lower in the absence of bleomycin. The most common patterns of pneumonitis after brentuximab vedotin therapy have not been well described, but cases of DAD have been reported. The safety of re-challenging patients with brentuximab vedotin-related pneumonitis is unknown.

**Break point cluster-ABL1 tyrosine kinase inhibitors**

The Philadelphia chromosome, also known as the BCR-ABL1 fusion gene, is caused by a reciprocal translocation of the BCR gene on chromosome 22 and the ABL1 gene on chromosome 9. This aberrant chromosome 22 results in constitutive activation of ABL1 and abnormal tyrosine kinase signaling, causing the cell to divide uncontrollably. The BCR-ABL1 mutation is seen in nearly all patients with chronic myelogenous leukemia and may be found in some patients with acute lymphoblastic leukemia or acute myelogenous leukemia. In this section, we will discuss toxicities of the BCR-ABL1 TKIs such as imatinib, dasatinib, nilotinib, and bosutinib.

The overall incidence of imatinib-related pneumonitis is rare, with severe reactions of Grade 3 and Grade 4 occurring in 0.2% and 1.3%, respectively, in one small series. The most common CT presentations of imatinib-related pneumonitis are NSIP, followed by OP. The median interval between drug exposure and the development of pneumonitis is about 2 months. The incidence of dasatinib may as high as 17%. Dasatinib-related pneumonitis most often appears radiographically as NSIP. Rare reports of pneumonitis associated with nilotinib and bosutinib therapies have also been documented, but no studies of incidence exist.

Treatment of pneumonitis after imatinib or dasatinib therapy involves discontinuation of the drug and corticosteroids for persistent pneumonitis. Guideline recommendations are needed for the management of pneumonitis after BCR-ABL1 TKI therapy. Guidelines for the management of pneumonitis after BCR-ABL1 TKI therapy have been proposed by the European Leukemia Net investigators and are summarized in Table 3. Grade 1 pneumonitis requires observation but no change in management. Grade 2 and higher pneumonitis require withholding of TKI therapy, and Grades 3 and 4...
4 pneumonitis should prompt a change in TKI therapy if possible.\cite{95,166,163,164} Corticosteroid therapy should be considered in Grade 2 pneumonitis and is indicated in Grades 3 and 4 pneumonitis.

**Anaplastic lymphoma kinase inhibitors**

ALK is a tyrosine kinase receptor which activates several pathways that lead to cell proliferation, growth, and survival.\cite{165,166} Mutations in the ALK gene have been identified in adenocarcinomas of the lung and in large-cell lymphomas.\cite{166} Four ALK receptor inhibitors have been approved by the FDA for treatment of ALK-positive lung cancer – crizotinib, ceritinib, alectinib, and brigatinib.\cite{167-171} The incidence of pneumonitis is about 2% following crizotinib therapy,\cite{172} 4% following ceritinib therapy,\cite{169} 0.4% following alectinib therapy,\cite{170} and 6% following brigatinib therapy.\cite{171} The median time to development of pneumonitis after crizotinib therapy is 23 days.\cite{172} Acute pneumonitis following brigatinib therapy has been described and occurs with a median onset of 2 days after brigatinib is initiated.\cite{171} Re-challenge with brigatinib and crizotinib may be feasible in some patients after resolution of pneumonitis.\cite{173} No studies clearly describe the median time to pneumonitis in ceritinib and alectinib. The most common pattern of pneumonitis is NSIP.\cite{172,174-176} We recommend following the NCI CTCAE to grade the severity of pneumonitis [Table 2].

**Bruton’s tyrosine kinase inhibitors**

BTK is a protein made by BTK gene which has a critical role in B-cell development and maturation.\cite{177,178} Mutations in the BTK gene are associated with a variety of disorders related to aberrant B-cell function, including X-linked agammaglobulinemia (loss of function), B-cell lymphomas, chronic lymphocytic leukemia, and Waldenstrom’s macroglobulinemia (gain of function).\cite{179,183} The FDA has approved ibrutinib and acalabrutinib for use in chronic lymphocytic leukemia.\cite{184} Pneumonitis has not been reported after acalabrutinib therapy, but has been reported after ibrutinib therapy.\cite{184-186} Ibrutinib-related pneumonitis is rare,\cite{187-190} and both OP and NSIP have been reported after ibrutinib treatment.\cite{189,191} We recommend the NCI CTCAE to grade pneumonitis severity and to determine the approach to treatment [Table 2].

**Conclusions**

Pneumonitis is a rare, but potentially severe complication of precision oncology therapies. Increased awareness of pneumonitis following precision oncology therapies is necessary as these therapies are increasingly employed in the treatment of cancer. Further work is necessary to develop frameworks for detection of early pneumonitis and to help distinguish pneumonia from pneumonitis.

**References**


**Table 3: European LeukemiaNet recommendations for the management of pneumonitis after therapy with breakpoint cluster region-Abelson tyrosine kinase inhibitors**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Asymptomatic</td>
<td>Symptomatic</td>
<td>Severe symptoms</td>
<td>Life-threatening respiratory compromise</td>
</tr>
<tr>
<td>Management</td>
<td>No change in therapy or dose is required. Treat adverse effect</td>
<td>Withhold the drug until severity falls to &lt; Grade 2, with weekly monitoring</td>
<td>Withhold the drug until severity falls to &lt; Grade 2, and resume at the same dose. If there is no resolution within 4 weeks, discontinue the drug, and switch to another when appropriate.</td>
<td>Stop the drug and switch to another TKI when appropriate</td>
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</table>

TKI: Tyrosine kinase inhibitor


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