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REVIEW

Checkpoint Inhibitor-Induced Pneumonitis: Incidence and Management

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Abstract

Purpose of Review Despite immune checkpoint inhibitors' (ICIs) many notable benefits, they carry the risk of immune-related adverse events (irAEs). Checkpoint inhibitor pneumonitis (CIP) is an irAE with significant morbidity and mortality. Early recognition and understanding of treatments are essential for those who prescribe ICIs or manage patients on therapy.

Recent Findings Early detection of pneumonitis may be aided by increased serum CRP and IL-6 levels. Additionally, immunosuppressive treatment for patients failing steroids demonstrates that infliximab and tocilizumab provide some benefit, but outcomes remain poor. IVIG might be a better option.

Summary CIP remains a challenging diagnosis. Certain risk factors have been identified for CIP development. Diagnosis is confounded by lack of pathognomonic radiology and pathology findings. Severity of disease guides treatment, which initially involves discontinuation of ICP and addition of steroids. For more severe cases, immunosuppression has a role but requires further study.

Keywords Immunotherapy · PD-1 · PD-L1 · CTLA-4 · Immune-related pneumonitis · Checkpoint inhibitor pneumonitis

Introduction

Immune checkpoint inhibitors (ICI) are a class of monoclonal antibodies focused on the counterregulatory mechanisms of T cell activation. The principal targets are T cell program death 1 receptor (PD-1), its associated ligand (PD-L1), and cytotoxic T lymphocyte antigen-4 (CTLA-4) (Table 1) [1]. Both the PD-1/PD-L1 and CTLA-4/CD28 axes are part of T cell regulation, and activation of the PD-1/PD-L1 or CTLA-4/CD28 pathways results in T cell suppression [2]. This counterregulatory pathway plays an important role in the tolerance of self and prevention of excessive autoimmunity and may play a role in modulating immune response for chronic infections. However, this pathway is often exploited by tumor cells through overexpression of PD-L1 or CTLA-4 to promote tumorigenesis by suppression of T cell activity [3, 4].

Immune checkpoint inhibitors block the signal pathways that suppress T cell-mediated tumor destruction. A tumor cell will activate antigen-presenting cells (e.g., dendritic cells and macrophages) to present the tumor antigen through a major histocompatibility complex, which then binds to a T cell receptor. T cells are then activated and result in anti-tumor activity [5].

In 2011, the CTLA-4 inhibitor ipilimumab was FDA approved after demonstrating survival benefit in metastatic melanoma. Since that time, the number of different immunotherapy agents and indications has continued to expand, including non-small cell lung carcinoma (NSCLC), renal cell carcinoma, Hodgkin's lymphoma, head and neck carcinoma, colorectal cancer, urothelial carcinoma, and hepatocellular carcinoma, and it continues to grow. In 2019, Haslam and colleagues estimated that 44% of patients with metastatic solid and hematological tumors in the United States could be eligible for treatment with ICI, with approximately 13% having response to these drugs [6].

While enhanced activation of the immune system is responsible for the therapeutic efficacy of ICIs, it may also

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Table 1 FDA-approved immune checkpoint inhibitors

Mechanism of action	Drug name
PD-1 inhibitor	Pembrolizumab (Keytruda)
	Nivolumab (Opdivo)
	Cemiplimab (Libtayo)
PD-L1 inhibitor	Atezolizumab (Tecentriq)
	Avelumab (Bavencio)
	Durvalumab (Imfinzi)
CTLA-4 inhibitor	Ipilimumab (Yervoy)
	Tremelimumab (Imjudo)

Comprised of information from The American Cancer Society webpage. https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/immune-checkpoint-inhibitors.html [1]

cause immune-related adverse events (irAEs). irAEs can affect a wide array of systems including pulmonary, dermatologic, gastrointestinal, endocrine, hepatic, neurologic, and rheumatologic [7]. The mechanism has not been fully delineated but may be a direct result of its intended purpose of bolstered immune response to neoplastic growth. In fact, there is evidence to suggest that the presence of irAEs is associated with better treatment response [8].

Checkpoint Inhibitor Pneumonitis

Epidemiology

Overall CIP incidence ranges from 3 to 6% for all grades and 0.8% to 1% for grade ≥ 3 in clinical trials settings [9–11]. However, real-world data suggests the actual incidence may be higher, with rates variable between 10 and 19% and possibly even higher, as there are no strict exclusion criteria for therapy [12–15].

Time of onset from ICI use ranges from 1 week up to 2 years [14, 16–18]. Delaunay and colleagues identified a median onset of existing interstitial lung disease (ILD) after immunotherapy introduction of 2.3 months, though 42.2% in that population developed ILD < 2 months after initiating [17]. Additionally, there are reports of CIP occurring several months after cessation of therapy [19]. Time of onset of CIP was not correlated to its severity [17].

Risk Factors

Multiple studies and case reports have identified various risk factors for CIP, including patient factors, specific ICI choice, tumor type, baseline lung function, and prior radiation therapy.

Male gender, former or current smokers, advanced age, and autoantibodies are all associated with increased CIP risk [14, 18, 20].

CIP is more often associated with PD-1 and PD-L1 ICIs (4%) vs. anti-CTLA-4 therapy (1%) [21, 22]. Within non-small cell lung cancer (NSCLC), PD-1 inhibitors cause CIP at a higher incidence than PD-L1 inhibitors in NSCLC patients and may also result in more severe presentations of pneumonitis [23]. In meta-analyses, PD-L1-treated NSCLC and renal cell carcinoma patients had a higher risk of developing pneumonitis than patients with melanoma [16]. Additionally, squamous cell types were associated with higher incidence of CIP [13, 16, 24]. CIP is also more common with combination immunotherapy versus monotherapy, at 7% [9, 13, 16].

Decreased FEV1 and FVC may increase risk for future CIP [25, 26]. Preexisting ILD, pulmonary fibrosis, COPD, and asthma have all been identified as CIP risk factors [11, 14, 20, 24, 27–30].

The risk of CIP was much higher in those who received radiation therapy prior to ICI vs. ICI alone (13% vs. 1%) [24, 31]. Additionally, there is a predilection for ICI development in the regions of prior radiation treatment, termed radiation recall, which is multifactorial but may include vascular permeability changes leading to local accumulation of systemic agents such as ICIs [32, 33].

There appears to be an additive effect of risk factors as well. For example, in patients with preexisting ILD and NSCLC, the incidence of CIP has been reported to be as high as 31% [34, 35].

Clinical Presentation

Checkpoint inhibitor pneumonitis is defined as respiratory symptoms with chest radiograph infiltrates, temporally related to ICI use, and in the absence of infection. It can have a wide range of symptoms and radiographic findings. Most common symptoms include dyspnea, cough, fever, and hypoxia (which can lead to respiratory failure in some cases) [18]. Diagnosis is challenging as about one-third of patients may be asymptomatic at onset, and a high index of suspicion is required for accurate diagnosis [22].

More than 50% of patients also develop other irAEs including skin rash, colitis, hypophysitis, arthritis, thyroiditis, hepatitis, esophagitis, duodenitis, hyperthyroidism, nephritis, myositis, vitiligo, pernicious anemia, and hemolytic anemia [36].

Diagnostic Workup

Patients who develop new or progressive respiratory symptoms, particularly with hypoxia, in the setting of ICI use, must be considered at risk for CIP. Beyond exposure history

and physical examination with pulse oximetry measurement, diagnostic workup should include testing to rule out other lung pathology, including progression of disease or pseudo-progression, other drug-induced pneumonitis, reactivation of TB or other infections, pleural effusions, and pulmonary embolism. Another challenge is differentiating acute exacerbations of ILD from checkpoint inhibitor pneumonitis.

Prior literature has reported increased serum IL-6 and CRP levels could predict irAEs, particularly CIP [37, 38]. In a single-center setting, Cheng and colleagues demonstrated that CT radiomics and machine learning could also be a promising option to better delineate CIP from radiation pneumonitis [39].

When ≥ grade 2 disease is present, further investigation into infectious etiologies with nasopharyngeal, sputum, urine, and blood cultures should be pursued [5, 40]. The SARS-CoV-2 pandemic resulted in multiple CT findings of bilateral ground glass and areas of consolidation, which must be carefully differentiated from CIP [41].

Radiographic Findings

Though chest radiography may be a starting point for testing, CT chest, particularly high-resolution CT, can delineate subtle findings of pneumonitis. CIP does not have distinct pathognomonic radiographic findings (Fig. 1) [5].

Overall, organizing pneumonia (OP) is the most prominent radiographic pattern, regardless of tumor type, and was associated with intermediate (CTCAE grade 2) toxicity [5, 16, 42]. OP pattern is one of bilateral patchy opacities (consolidative or ground glass) with a peripheral or peribronchovascular predominance predominantly in the mid-lower lung fields [5]. These airspace opacities may also be migratory. Pulmonary nodules (usually < 1 cm) in a peribronchovascular pattern may also be evident though occasionally mass-like consolidations are seen. These must be differentiated from progression of malignancy [5].

Non-specific interstitial pneumonia (NSIP) is the second most common presentation of CIP and often associated with

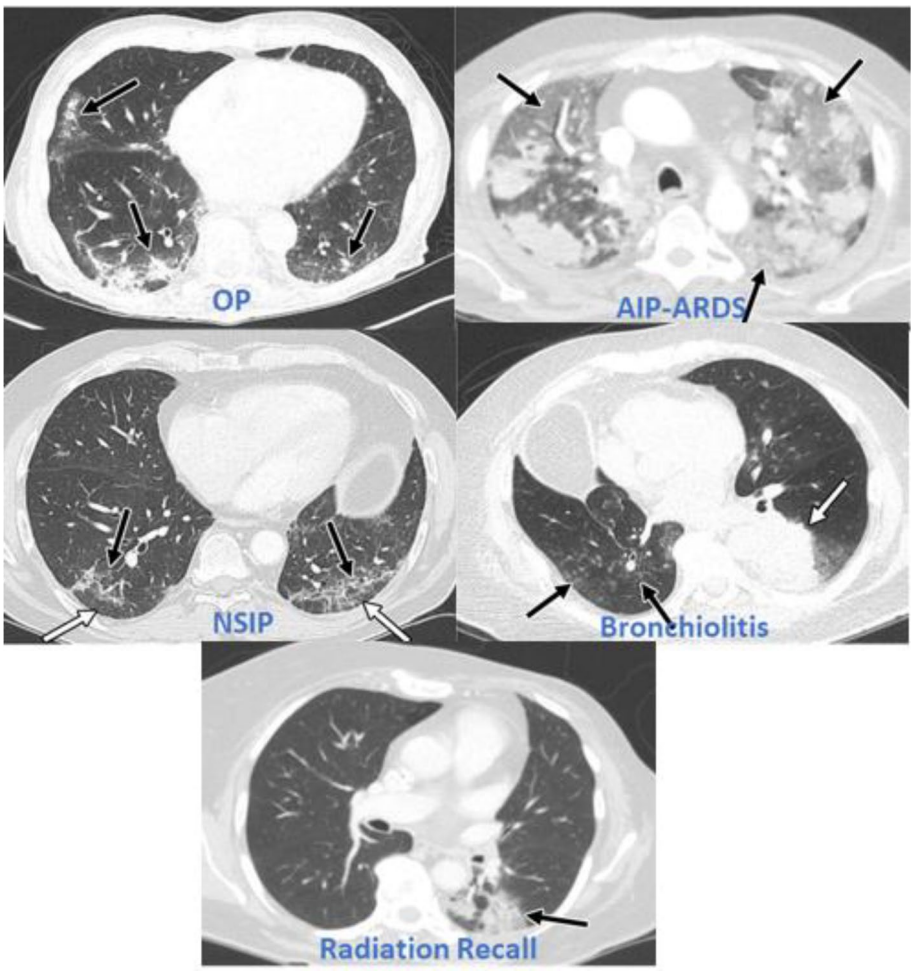

Fig. 1 Some common radiographic patterns seen with checkpoint inhibitor pneumonitis. OP, organizing pneumonia; NSIP, non-specific interstitial pneumonia; ARDS, acute respiratory distress syndrome. Adapted from Kalisz K, Ramaiya N, Laukamp et al. Immune checkpoint inhibitor therapy-related pneumonitis: patterns and management. *RadioGraphics* 2019;39:1923–1934 [4]

lower toxicity grade (CTCAE grade 1) [5, 16–18, 42]. It presents as ground glass and reticulations with a lower lobe predominance and occasionally with subpleural sparing. Architectural distortion as seen in fibrotic NSIP is usually not a feature of CIP, likely due to acute presentations of these diseases [5, 43].

Hypersensitivity pneumonitis (HP) pattern is less common in CIP but is associated with lower grade of toxicity and symptoms (CTCAE grade 1) [5]. CT reveals upper lobe or diffuse centrilobular nodules, tree in bud changes, and evidence of mosaicism. Detailed exposure history must be obtained to rule out HP from other allergens [44].

Additional patterns that have been reported include acute interstitial pneumonia/ARDS, bronchiolitis pattern, radiation recall (an inflammatory reaction occurring in a prior field of radiation after exposure to ICI or other inciting agents), and sarcoid-like reaction with anti-CTLA-4 (which presents with mediastinal and hilar lymphadenopathy, as well as perilymphatic lung nodules in an upper lung predominant fashion) [5, 16, 18, 45–47].

Pulmonary Function Testing

Pulmonary function testing often demonstrates restriction and reduced diffusion capacity. Some studies advocate for baseline and monitoring pulmonary function testing on individuals treated with ICI [25, 48, 49].

Pretreatment pulmonary function testing with lower FEV1 and FVC may identify patients at increased risk for CIP [25, 26]. More recent studies have identified pretreatment reduction in TLC as strongly associated with development of CIP [50]. Additionally, subtle changes in diffusion capacity may be the first indicator of subclinical pneumonitis (even before radiographic changes) and help further screening for evolving pneumonitis [49]. This is particularly important for individuals with preexisting interstitial lung disease, who are at greater risk for future CIP.

Bronchoscopy

Bronchoscopy and bronchoalveolar lavage (BAL) may be indicated for further workup particularly with grade ≥ grade 2 CIP and often reveals lymphocytosis (as high as 30%) with CD8 + or CD4 + T cells in CIP patients as well as increased IL-6 [17, 51–53]. However, it is not often performed. In fact, even in a relatively robust population of CIP, Delaunay and colleagues reported only 35 individuals (55.6%) had BAL, with 15 cases of immunochemistry demonstrating PD-L1 tumor expression in 12 [17]. Interestingly, in CIP patients, BAL analysis may reveal an M2 predominant macrophage population as well as increased CCL18 gene expression (also seen in idiopathic pulmonary fibrosis), which may help further delineate accurate diagnosis [54].

Routine lung biopsy is not recommended unless there is uncertainty of radiographic or clinical findings [55]. A range of pathologic presentations have been described, including organizing pneumonia, diffuse alveolar damage, eosinophilic pneumonia, cellular interstitial pneumonia, and non-specific granulomatous inflammation [40, 52, 53, 55]. Transbronchial biopsy samples may also demonstrate inflammatory and lymphocytic infiltration [17, 53].

Management

Grading of CIP, like other irAEs, is based on severity. Management recommendations are largely based on expert opinion and observational data. The grading criteria are based on both radiographic and clinical findings (Table 2) [48, 56].

According to the American Society of Clinical Oncology and the Society for Immunotherapy of Cancer, with grade 1 CIP, there are no symptoms and radiographic findings are confined to one lobe or less than 25% of lung parenchyma [22]. Withholding of ICI therapy is the first step. Short-term imaging in 3–4 weeks may be indicated to assess for radiographic resolution [22, 55]. ICI may be resumed with radiographic improvement or resolution. If there is no improvement, these individuals should be treated as grade 2 disease [22, 55].

Grade 2 CIP criteria include onset of respiratory symptoms or involvement of 25–50% of lung parenchyma. Oral prednisone is recommended, consistent with our practice, initially at 1–2 mg/kg/d with taper by 5–10 mg/week over 4–6 weeks [22, 55, 57]. These patients need further workup to rule out infectious causes with cultures and possible bron-

Table 2 CTCAE pneumonitis grading system

Grade	Symptom
1	Asymptomatic, clinical or diagnostic observations only, intervention not indicated
2	Symptomatic with medical intervention indicated, limited some ADL
3	Severe symptoms limiting self-care ADL, with oxygen need
4	Life-threatening respiratory compromise with urgent intervention required (e.g., intubation)
5	Death

Reproduced from Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, November 2017, National Institutes of Health, National Cancer Institute [54]

choscopy with BAL, and addition of antibiotics should be considered. Symptoms should be monitored closely with pulse oximetry, and if there is no improvement in 48–72 h, care should be escalated to grade 3 treatment. ICI must be held until resolution to grade 1 or less or discontinued if recurrent or persistent grade 2 events [22, 56]. Lower serum CRP and IL-6 levels may support safe ICI rechallenge in appropriate patients [58].

With grade 1 and 2 disease, patients can often be managed as outpatients. In fact, in a study performed by Naidoo and colleagues, CIP improved or resolved in all 17 cases of grade 1 CIP and 13/14 (93%) of grade 2 CIP cases [18].

With grade 3 and 4 CIP, severe respiratory symptoms require hospitalization and there is involvement of all lung lobes or > 50% of lung parenchyma [22]. In this setting, empiric antibiotics should be initiated along with IV methylprednisolone. Doses are variable—some individuals may receive pulse dose steroids, and others may start at 1–2 mg/kg/day [22, 59]. Unfortunately, the optimal steroid dosing is unknown and is often adjusted based on clinical response [40]. ICI must be discontinued permanently, and steroids can be tapered over 4–6 weeks [3, 22, 57].

If there is no improvement after 48–72 h, these patients are considered steroid refractory. In the case of initial improvement on steroids and subsequent recurrence, they may be termed steroid resistant. In these cases, other therapies may be indicated. Consensus guidelines from multiple groups recommend immunosuppression with either (1) infliximab 5 mg/kg, (2) cyclosporine 2.5 mg/kg/day in divided doses, (3) mycophenolate mofetil 1–1.5 g twice daily, (4) intravenous immunoglobulin (IVIG) or (5) tocilizumab 0.6 mg/kg added to the patient's steroid [15, 48, 55, 60]. Most of these agents have various efficacy in CIP, and experience is largely based on extrapolation from other irAEs and ILDs [13]. There is no preferred initial regimen or optimal duration of therapy [15].

There are case reports of successful IVIG use in pneumonitis based on its utility in other ICI-related toxicities such as myasthenia gravis, thrombocytopenia, and some CTD-ILD, as it may regulate immune cell function, bind and neutralize autoantibodies, and downregulate various chemokines and cytokines [61]. Balaji and colleagues demonstrated that patients receiving IVIG monotherapy had improved oxygenation requirements and reduced level of care, as well as fewer deaths [62]. As it is less immunosuppressive, it may also have a role in refractory CIP with concurrent infection [13].

Infliximab, a TNF α agent, is often preferred due to its success in colitis and other irAEs, though limited data exists in steroid-refractory checkpoint inhibitor pneumonitis [15]. We will often use infliximab for our higher-grade CIP patients, albeit this is based on limited data. In Beattie's study of 26 patients with steroid-refractory or steroid-resistant CIP, addition of immunosuppression with infliximab and/or mycophenolate mofetil resulted in durable improvement in 38% of patients and complete resolution, allowing for cessation of immunosuppression, in 12% of these individuals [63]. Other papers have also reported favorable response to infliximab [64, 65]. However, steroid-refractory patients may have earlier onset and more severe pneumonitis, with less chance for durable treatment response [63]. 50% of the overall population of 26 in Beattie and colleagues' study had only transient improvement with immunosuppression; another 12% had no benefit [63]. Moreover, a study of irAEs managed with infliximab + steroids vs. steroids alone demonstrated decreased survival with infliximab [66]. Additionally, in another study of 12 steroid-refractory CIP patients, all 5 patients treated with infliximab died from pneumonitis or infectious complications [62].

Cyclophosphamide use is based on its history in other steroid-refractory ILDs, but there is limited information on utility specifically in CIP. In various studies, cyclophosphamide in combination with other immunosuppressive agents had variable efficacy. While it may be a reasonable option for steroid-refractory CIP, further studies are required [9, 67, 68]. Based on its mechanism of action as an IL-6 receptor antagonist, tocilizumab has also been identified as effective in irAE and may have a role in CIP management, but further randomized trials are lacking [69, 70].

If longer term steroids or other immunosuppression are needed, then trimethoprim and sulfamethoxazole can be considered for *Pneumocystis jirovecii* prophylaxis. The role of fluconazole prophylaxis for prolonged steroid need is less clear [71].

Many of these steroid-refractory CIP patients have diffuse alveolar damage on radiographic imaging and neutrophilic and lymphocytic predominant BAL fluid [15, 62, 63]. The steroid-refractory population with ongoing pneumonitis is consistent with chronic CIP, affecting about 2% of individuals with NSCLC or melanoma treated with ICIs, and some require lifelong immunosuppression [50]. Beyond immunosuppression, nintedanib, based on its anti-VEGF mechanism with known antitumor effect and antifibrotic effects, may have a role in steroid-refractory, "chronic" CIP, though this has only been reported in individual cases [72].

Worsened clinical outcomes in CIP were seen in current or former smokers and those with underlying lung conditions [18, 53]. But other publications have proposed that despite higher incidence of CIP with pretreatment interstitial changes, decreased TLC (< 80% predicted) and DLCO (corrected for hemoglobin < 80% predicted), CIP severity was unchanged compared to those with normal radiology and lung function [50, 73]. Additionally, Ichimura and colleagues demonstrated a decreased risk of acute exacerbation of idiopathic interstitial pneumonia after ICI use [74]. Other reports suggest the addition of antivascular endothelin growth factor (anti-VEGF) therapy to ICI may help prevent CIP development by protecting against alveolar fluid

and protein extravasation from vasculature [75]. This may allow cautious use of ICIs in individuals with certain types of interstitial lung disease and restrictive physiology, albeit with closer monitoring.

Multiple studies have demonstrated lower overall survival in individuals who developed CIP with an overall fatality rate of 10–17% [40, 51, 76]. This remains true even though short-term survival may not be significantly altered, and, in fact, about 2/3 of patients with ≥ grade 3 CIP will have clinical response to steroids, though 25–33% may experience recurrent disease after initial resolution [9, 22, 57]. One possible explanation for the reduced survival may be the need to stop ICI therapy as well as increased pulmonary symptoms limiting continued antitumor treatment [40].

Lastly, primary steroid-refractory CIP has a higher mortality and worse prognosis than recurrent CIP. In one study, 90-day all-cause mortality/hospice referral was 50% [63]. Escalating therapy may allow for more sustained improvement, but not complete resolution, in up to 30–40% of patients [15].

Conclusions

Over the past decade, immune checkpoint inhibitor therapy has been a pivotal part of cancer care. Therapeutic effect is related to enhanced immune system activation, but this same mechanism can also result in various immune-related adverse events, including checkpoint inhibitor pneumonitis. CIP can be a challenge to diagnose due to variable symptoms, radiographic and pathologic findings. Optimal treatment strategies are unclear, particularly for steroid-refractory and resistant cases. Moreover, treatment options for immunosuppression beyond steroids remain unclear.

The many gaps in our understanding of CIP extend to all aspects of the disease, including the following. (1) What is the exact mechanism underlying CIP? (2) Which patients are most at risk for CIP (existing data has some discrepancies which might deprive appropriate patients of CIP therapy)? (3) How should patients at higher risk be screened for CIP (should all patients have pretreatment PFTs and then periodic testing)? (4) How can we identify reliable biomarkers to allow for earlier detection and monitoring (is there a role for routine serum CRP and IL-6)? (5) Do the variable radiologic and pathologic patterns truly represent the same mechanism of CIP? (6) In patients with underlying ILD treated with ICI, how can an acute exacerbation be differentiated from CIP (this has great implications for future rechallenge with ICI)? (7) What is the optimal duration and type of immunosuppression for a given patient (and should IVIG be monotherapy or part of combination therapy with other immunosuppression)?

The use of machine learning and radiomics has some potential utility in diagnosing CIP and differentiating CIP from other entities, but there is still immense variability in quality of imaging input and other technical factors such as lack of external validation, which limit more widespread use [77]. Perhaps, combination of radiomics with additional BAL and serologic testing would allow more accurate clinical diagnosis [77]. Additional studies to define the roles of immunosuppressive treatments with infliximab IVIG, rituximab, and tocilizumab are in process (NCT04438382, NCT04375228) [15].

Despite multiple new studies on CIP, further literature, particularly randomized controlled trials, is essential to guide best practices with regard to the early identification and management of checkpoint inhibitor pneumonitis.

Compliance with Ethical Standards

Conflict of Interest Kunal Gada and Chaofan Yuan declare that they have no conflict of interest. Alpa G. Desai has received speaker honorarium from Boehringer Ingelheim and Mallinckrodt.

Human and Animal Rights and Informed Consent. All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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Selected More Recent References of Interest

78. Gatti-Mays M, Gulley JL. Real-world insights on preferred treatments for steroid-refractory immune checkpoint inhibitor-induced pneumonitis. J Immunother Cancer [Internet]. 2021 Feb 1 [cited 2023 Mar 26];9(2):e002252. Available from: https://doi.org/10.1136/jitc-2020-002252. This was a summary of treatment for steroid-refractory pneumonitis. It built on work by Balaji and Beattie (also reviewed and in the reference list above), which is helpful re: their experience with Infliximab and Mycophenolate mofetil, though I felt it left more questions than answers about optimal treatment.
79. Wong A, Riley M, Zhao S, Wang JG, Esguerra V, Li M, et al. Association between pre-treatment chest imaging and pulmonary function abnormalities and immune checkpoint inhibitor pneumonitis. Cancer Immunol Immunother. 2023 Jan 14. Available from: https://doi.org/10.1007/s00262-023-03373-y. This was a retrospective study of patients who received at least dose of ICI. 46/1097

had CIP. Pretreatment PFTs and chest imaging were reviewed. Increased CIP seen with patients who had preexisting interstitial changes and reduced TLC. There is not much data on the role of screening and pretreatment PFTs but this study is intriguing that perhaps it should be more standardized to help risk-stratify patients re: best time to initiate ICI or whether to start at all.

80. Lin X, Deng H, Chu T, Chen L, Yang Y, Qiu G, et al. Safety and efficacy of immunotherapy rechallenge following checkpoint inhibitor-related pneumonitis in advanced lung cancer patients: a retrospective multi-center cohort study. Transl Lung Cancer Res. 2022 Nov;11(11):2289–305. Available from: https://doi.org/10.21037/tlcr-22-732. A multicenter retrospective study of advanced lung cancer individuals who had grade ≥1 CIP and either received rechallenge with ICI or not. It demonstrated that grade ≥3 and ground glass opacity pattern had worse outcomes with rechallenge. Of 107 patients who were rechallenged, 9 had recurrent pneumonitis. This was an interesting study that also looked at factors of the recurrent pneumonitis patients and found that elevated white blood cell count as well as neutrophils and IL-6 and CRP levels in the serum portended higher recurrence rate. It provides some guidance on how to manage rechallenge in patients with CIP.