Opinion

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Expanding Clinical Utilization of Checkpoint Inhibitors for Cancer Treatments Necessitates the Development of Predictive Models for Immunotherapy-Induced Pneumonitis

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ABSTRACT

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Opinion

Immunotherapy has revolutionized treatment and improved prognosis for patients with a variety of advanced-stage cancers. Use of immune checkpoint inhibitors (ICIs) continues to increase due to this dramatic impact [1]. ICIs that target programmed cell death protein-1 (PD-1), programmed death protein ligand-1 (PD-L1), and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) have provided lasting responses and improved long-term survival in select patients with advanced non-small cell lung cancer (NSCLC) [2-6]. Despite this success, overall response rates to ICIs remain less than 50% and those patients who do not respond can experience accelerated and lethal disease progression [7,8]. In addition, ICI-mediated immune dysfunction may result in serious immunotherapy-related adverse events (irAEs) [9]. While irAEs can involve any organ system, gastrointestinal toxicities, pruritis, rash, hyphophysitis, vitiligo, dysthyroidism, hepatotoxicity, and pneumonitis are the most commonly observed complications [10]. The actual incidence of irAEs varies between agents and is likely underestimated [9,11]. Checkpoint-inhibitor pneumonitis (CIP) is a potentially life-threatening irAE more commonly seen among patients treated for NSCLC than for other malignancies [12,13]. Pneumonitis is defined as focal or diffuse inflammation of the lung parenchyma [14] and can occur with chemotherapy [15,16], targeted therapy [17,18] and radiotherapy (RT), as well as with ICIs [19]. Pre-ICI experiences with pneumonitis caused by cancer therapeutics emphasized that clinical and radiologic signatures may facilitate early recognition, treatment selection, and improvement in outcomes. Little is known about the etiology and molecular mechanisms underlying CIP [20]. While life-threatening CIP is rare, in NSCLC patients CIP can mimic conditions such as tumor progression or infection [11]. In the setting of expanding use of ICIs, clinicians should be educated regarding prompt CIP recognition and appropriate management.

Besides serious clinical consequences, pneumonitis contributes to treatment noncompliance, often requiring dose holds, immunosuppressive therapy, and/or permanent ICI cessation [12]. Most cases of CIP are mild and managed successfully in the outpatient setting, but inpatient management, long-term respiratory complications, or treatment-related deaths occur in ~ 20% of affected patients [21-23]. The time to onset of pneumonitis has a wide range (9 days to 19.2 months with a median of 2.7 months for combination ICI and 4.6 months for ICI monotherapy) [12,22], complicating recognition and classification of CIP especially for NSCLC patients. Timely identification or, even better, pre-treatment prediction, could help to mitigate or prevent serious pulmonary complications. The natural history of CIP differs from other irAES; while thyroiditis or hepatitis are illnesses that tend

to be self-limiting, most cases of CIP require immunosuppression with high dose steroids [24]. In a large retrospective study that reported overall incidence of CIP at ~5%, the majority of CIP cases improved with corticosteroids [12,25] but 9% of CIP patients died during immunosuppressive therapy due to infection or CIP itself, only 28% of patients whose CIP resolved were rechallenged with ICI, and 25% of the rechallenged cohort developed recurrent CIP and had to permanently discontinue immunotherapy.

In clinical trials for NSCLC, the incidences of all-grade CIP are typically reported at ~5% for ICI monotherapy and between 7-10% for combination therapy [13,26,27]. However, the incidence of CIP in NSCLC outside of clinical trials remains uncertain, with CIP presentation mimicking infectious pneumonia or tumor progression and radiologic patterns of pneumonitis varying greatly from case to case [12]. For patients with NSCLC, CIP signs and symptoms can be misclassified in the setting of underlying lung disease and actual incidence may be higher than reported [11,28]. The ability to identify patients at risk for CIP prior to immunotherapy could prevent significant morbidity; discovery of signatures or methods for early CIP prediction represents an unmet clinical need.

Recent advances in analysis of medical imaging have made CIP risk prediction attainable. In the emerging technology known as quantitative imaging or radiomics, medical (PET, CT, MRI) images are analyzed at voxel level to detect textural features associated with disease or health [29]. Radiomics evaluate both semantic (volume, shape, etc.) and agnostic (texture) anatomical organ features. The former can be recognized by the naked eye while the latter require computer algorithms for detection at voxel level. Radiomics allow for comprehensive characterization of the tissue of interest and its corresponding microenvironment. Quantitative imaging has been used in recent years to predict tumor response at various anatomical sites [29-33]. Less attention has been devoted however to radiomics in the context of normal tissue complication predictions [34,35].

The first publication [36] that used a radiomics model to predict CIP was a proof of principle study that retrospectively evaluated a small cohort of patients (30) treated with immunotherapy. Quantitative analysis of pre-immunotherapy baseline chest CT was able to identify the only two patients who went on to develop CIP. A study from a separate group [28] reviewed a larger cohort of NSCLC patients with higher incidence of clinically diagnosed CIP (6%) after PD-1 checkpoint-inhibitor therapy. Retrospective chart review of CIP candidates demonstrated an incidence rate closer to 20%, ~ three times higher than commonly reported. These results were observed in a patient population receiving monotherapy, suggesting that actual CIP incidence could be even higher among patients treated with combination immunotherapy [12].

With increasing use of ICIs to treat advanced cancer, comprehensive CIP predictive models that incorporate uncorrelated but complementary biomarkers are poised for clinical application. Quantitative imaging is a promising analytic technique, but it need not stand alone; laboratory-derived parameters such as blood counts, blood inflammatory biomarkers, and inflammatory biomarkers in bronchoalveolar lavage fluid [37] as well as common clinical variables such as smoking history, comorbid conditions, and performance status promise to advance and refine CIP predictive modeling.

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