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Multidisciplinary Approach of Immune Checkpoint Inhibitor–Related Pneumonitis: A Key to Address Knowledge and Management Gaps

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The growing understanding of the interactions between the tumor cells and the immune system has led to major disruptive innovations in oncology. Immune checkpoint inhibitors (ICIs) inhibiting the programmed death-ligand 1 (PD-L1)–programmed cell death-protein 1 (PD-1) axis allowed enhancement of an existing antitumor immune response and were reported to generate durable responses in approximately 18% of patients with advanced NSCLC, some of them being alive 4 years after starting treatment.[1,2] Their development as first-line treatment of advanced NSCLC established anti–PD(L)-1 as the new cornerstone of frontline treatment, notably in combination with chemotherapy.[3-5] Therefore, their use is rapidly increasing, especially as their benefit might be greater in earlier stages of the disease.[6]

The clinicians have, thereby, to more frequently face unpredictable immune-related adverse events (irAEs) resulting from antigen mimicry leading to crossreactivity between tumor and normal tissue or the release of T cell activity against self-antigens. In clinical trials, ICI-related pneumonitis (ICI-P) seems to be a rare, but potentially severe, irAE with a reported overall incidence between 2.7% and 3.5%[7] and recently evaluated at 4.5% when including trials with chemotherapy combinations.[8] Pneumonitis with a grade greater than or equal to three represents more than one-third of these events,[9] with a significant mortality rate of 17.5% in WHO pharmacovigilance database,[10] accounting for 35% of anti–PD(L)1-related deaths.[11] The risk of pulmonary toxicity is also consistently earlier (mean time of 2.1 mo)[12] and higher in NSCLC than in other tumor types, estimated at 4.1% compared with 1.6% in melanoma.[7,9,12,13,14] This might suggest an impact of the tumor location within the lung tissue or the role of a specific microenvironment owing to previous exposures or underlying lung diseases. In contrast to other irAEs, ICI-P does not seem to correlate with a better patient outcome.[15]

The knowledge of ICI-P remains limited.[16] Risk factors are not clearly identified as clinical trials excluded patients with previous interstitial lung disease (ILD) or systemic autoimmune diseases. Retrospective case series studies inconsistently pointed out risks factors in underlying pulmonary conditions, such as ILD,[17,18] previous radiation therapy,[19] and nonadenocarcinoma histologic subtype.[20] Occurrence of ICI-P seems more frequent with anti–PD-1 than anti–PD-L1[14,21] and with anti–CTLA-4 combinations.[14] Radiologic features include a wide spectrum of abnormalities with cryptogenic organizing pneumonia, nonspecific interstitial pneumonitis, hypersensitive pneumonitis, ground-glass opacities, or for more severe cases, acute interstitial pneumonitis.[12] It is unknown whether these different clinical phenotypes correlate with specific mechanisms and require distinct therapeutic approaches. The diagnosis of ICI-P is challenging in patients with lung cancer and must exclude infectious causes, especially at the time of severe acute respiratory syndrome coronavirus 2 pandemic, cardiac disease, other causes of ILD, and tumor progression. Management is usually based on ICI cessation and corticosteroids, but the optimal management of asymptomatic grade 1 pneumonitis and steroid-resistant severe forms remains still undefined.[16]

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Disclosure: Dr. Pérol reports grants, personal fees, and nonfinancial support from Roche Holdings AG, AstraZeneca, Chugai, Takeda, Boehringer Ingelheim, and Bristol-Myers Squibb; personal fees and nonfinancial support from Pfizer, Eli Lilly, and Merck Sharp & Dohme; and personal fees from Novartis and Amgen outside of the submitted work.

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ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2020.05.007

The incidence of ICI-P in daily clinical practice and the identification of patients at risk of this potentially life-threatening AEs are, therefore, critical to address the more at-risk patients with lung cancer. Real-world data (RWD) have become increasingly important in this field considering the accelerated approval of cancer immunotherapies. Suzuki et al.[22] report in this issue of the *Journal of Thoracic Oncology* the first prospective study aiming to specifically assess the incidence of anti–PD-1-related pneumonitis in clinical practice and the risk factors in 138 patients with advanced NSCLC, mainly treated with nivolumab as second or later line. The first finding was a 14.5% incidence of ICI-P (with approximately 6% of grade $\geq$3 events occurring earlier than low-grade events) which is much higher than that usually described in clinical trials or meta-analyses but similar to that of retrospective studies, including one performed in a Western country suggesting ethnicity cannot explain this discrepancy. Several other reasons can account for a higher incidence in RWD, including older patients with poorer performance status and more comorbidities as preexisting ILD or autoimmune conditions than those in clinical trials. One can think that a careful, multidisciplinary, prospective detection of pneumonitis would lead to detection of more events than in clinical trials in which only symptomatic events (grade $\geq$2) may be reported but grade 1 pneumonitis can be missed. Nevertheless, a similar proportion of severe events than in clinical trials does not suggest that this higher incidence is linked to an increase of mild pneumonitis. The incidence reported here, however, remains much higher than that of 3.3% recently reported from RWD coming from across a multisource approach,[8] illustrating the plausible impact of a thorough multidisciplinary assessment of ICI lung toxicity. Three of the 20 patients with ICI-P eventually died from lung toxicity; this 15% fatality rate supports the data of both the WHO database[10] and the Johns Hopkins retrospective cohort, concluding that the development of lung toxicity was independently associated with an increased risk of death.[23]

This potential severity of ICI-P emphasizes the need to detect baseline predictive factors contributing to the assessment of the individual risk-benefit ratio of a treatment. No clinical or biological patient characteristics were predictive of pneumonitis in contrast to some retrospective studies in which underlying lung condition, such as ILD,[18] or a baseline fibrosis score on chest computed tomography scan[24] was a predictor of lung toxicity. A higher risk of ICI-P in patients with a previous history of noninfectious pneumonitis (14.3% versus 2.9%) has been recently underscored in RWD.[8] Unlike that in the KEYNOTE-001 trial,[19] previous radiation therapy was not identified here as a predictive factor for ICI-P. PD-L1expression was not correlated with pneumonitis risk, even if there was a trend toward a higher proportion of PD-L1 greater than or equal to 50% tumors and responders to anti–PD-1 in patients with lung toxicity. The only disease characteristic linked to the risk of pneumonitis is adenocarcinoma histologic subtype (hazard ratio 3.00 [95% confidence interval: 0.99–9.01]), contrary to a retrospective study revealing a lower incidence in adenocarcinoma.[20] The use of treatment combinations in a later study, ethnicity, and different smoking habits might explain these opposite findings.

The originality of the study of Suzuki et al.[22] beyond its prospective design is to focus on pretreatment pulmonary function tests and dyspnea scale as potential predictive markers for ICI-P risk. Both forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) expressed in % of predicted values (%FVC, %FEV1) and the Modified Medical Research Council questionnaire daily dyspnea score were significantly lower in the subset of patients developing a lung toxicity. Baseline decreased %FVC and %FEV1, both as continuous and dichotomic variables with cutoffs determined based on receiver operating characteristic curves (at 77.6% and 75.6% of predicted values for %FVC and %FEV1, respectively), were found significant predictors of cumulative risk of pneumonitis using the Gray test, taking into account disease progression as a competitive event. By combining both %FVC and %FEV1, the authors were, then, able to define three subsets of patients based on the pneumonitis cumulative risk with rates of 26.7%, 13.0%, and 4.8%, respectively. The similar magnitude of %FVC and %FEV1 reduction, together with %total lung capacity diminution and a normal FEV1-to-FVC ratio in patients with pneumonitis, mainly indicates a reduction of lung static volumes and not an airflow obstruction. As very few patients had baseline previous ILD, this restrictive disorder probably reflects the impact of lung cancer on pulmonary function and, indirectly, the tumor volume or its consequences on lung ventilation owing to atelectasis, lymphangitis, or pleural effusion. The authors speculate that in such cases, activated lymphocytes might be retained in the lungs owing to an impairment of thoracic lymphatic drainage creating lung injury. This hypothesis is consistent with proinflammatory lymphocytosis, upregulation of lymphocyte chemoattractants, and attenuated Treg suppressive phenotype with decreased CTLA-4 and PD-L1 expression found in bronchoalveolar lavage of patients with ICI-P.[25]

Nevertheless, the low sensitivity and specificity of both baseline %FVC and %FEV1 at the selected cutoffs remain inadequate to formally rely on these values to categorize patients as low or high risk for ICI-P. The

authors underscore the high negative predictive value of %FVC greater than 77.6% or %FEV1 greater than 75.6% for pneumonitis risk, but a negative predictive value is also linked to the low incidence of ICI-P in the study population. As there is no evidence that obstructive lung disease was a risk factor in this cohort, combining %FVC and %FEV1 to refine patient categorization by identifying a preexisting restrictive lung disorder is debatable because these two parameters are collinear and not independent. The fact that only %FVC seems predictive in multivariate analysis also illustrates that FEV1 and FVC are linked and redundant.

What are the implications of these findings for clinical practice? Suzuki et al.[22] are to be commended for this important prospective work bringing a new insight: with prospective detection, the incidence of anti–PD-1-related pneumonitis seems much higher than that usually reported in clinical trials, with an early occurrence of severe events. Unlike other irAEs, onset of lung toxicity is not predictive of a better patient outcome, probably as a result of its own severity with a significant mortality and the subsequent reduction in access to subsequent treatments. Physicians must keep in mind that baseline reduction of lung static volumes seems to be predictive of a higher pneumonitis risk and should closely monitor patients with large thoracic tumor volumes after ICI initiation. Nonetheless, critical knowledge gaps in the mechanisms, diagnosis, and management of ICI-P remain to be addressed; multidisciplinary approach involving pulmonologists, as illustrated by this work, is one of the keys to improve our understanding of this adverse effect that limits ICI benefit in lung cancer.

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