Immune-Related Adverse Events (irAEs): Implications for Immune Checkpoint Inhibitor Therapy

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Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of advanced malignancies, including non-small cell lung cancer (NSCLC). Although these agents have improved clinical outcomes in NSCLC, they have also led to unique toxicities, termed immune-related adverse events (irAEs).^{1–3} irAEs are the result of nonspecific immune activation and can affect any organ system, although they most commonly occur in the skin, liver, gastrointestinal tract, and endocrine systems.⁴

In this issue of *JNCCN*, Kichenadasse et al⁵ evaluate the incidence of irAEs occurring in a group of 1,548 patients with NSCLC treated with atezolizumab monotherapy on 4 clinical trials.^{6–9} The authors used individual patient data from these trials to explore the incidence and timing of single-organ and multiorgan irAEs, the latter defined as either concurrent or sequential depending on whether irAEs arose within 7 days of one another. The primary objectives were to evaluate the incidence, grade, and time course of irAEs, in addition to assessing correlation with clinical outcomes (overall and progression-free survival). Kichenadasse et al⁵ also conducted an in-depth evaluation of multiorgan irAEs, which is of particular interest because information regarding these types of AEs is currently sparse.

Among the 4 atezolizumab NSCLC trials evaluated, multiorgan irAEs occurred in 5.4% of patients. To date, very little information is available on the frequency, significance, and management of multiorgan irAEs. Studies that have reported frequency of multiorgan irAEs have cited incidences from 5% to 43% across multiple tumor types, encompassing both single-agent and multiagent ICI treatment modalities.^{10–18} Interestingly, previously published reports have shown that the development of irAEs correlates with patient response rate and survival.^{19,20} In a 2019 study, Cortellini et al¹² found that overall survival, progression-free survival, and objective response rates were higher among patients with NSCLC who experienced irAEs during treatment with anti-PD-1 agents; however, no significant difference in these endpoints was observed when comparing single-site versus multiple-site irAEs. In contrast, Kichenadasse et al⁵ found that multiorgan involvement was associated with better survival outcomes than were observed with single-organ involvement.

The question of whether multiorgan irAEs are associated with improved survival in patients with NSCLC is important because this information could potentially help guide decisions about whether to continue treatment with ICIs in the face of treatment-related toxicity. If multiorgan irAEs are truly associated with improved survival outcomes, clinicians and patients may choose to forge ahead with ICI treatment despite multiorgan toxicity, when possible. To assist with this critical decision, effective tools are needed to predict which patients are most likely to experience serious and/or fatal toxicities. Currently, however, no refined tools are available to predict development of ICI-induced irAEs, and surveillance for occurrence generally relies on traditional laboratory markers.²¹ At the very least, developing predictive tools would allow for more relevant discussion between clinicians and patients during ICI therapy. Given the dramatic improvement in

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doi: 10.6004/jnccn.2020.7640

The ideas and viewpoints expressed in this commentary are those of the author and do not necessarily represent any policy, position, or program of NCCN.

See page 1191 for related article.

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patient outcomes with ICIs in multiple tumor types, most clinicians and patients are hesitant to defer ICI therapy unless treatment risk clearly outweighs benefit, which is a difficult decision point to accurately characterize.

Although irAE management guidelines exist, they are not standardized and are widely variable. In their study, Kichenadasse et al found that approximately 15% of irAEs required systemic steroids, 7.5% resulted in hospitalization, and 2.5% required treatment discontinuation. Across tumor types, anti-PD-1 discontinuation secondary to toxicity has been reported to occur at a rate of 3% to 12%.²² Kichenadasse et al did not report the utilization rates of other immunomodulating agents, such as infliximab and tocilizumab, for the management of irAEs; however, other researchers have reported that 39.1% of patients who experienced steroid-refractory irAEs received tocilizumab.²³ Although it is clear that ICI discontinuation secondary to irAEs occurs with some frequency, the exact incidence of this clinical outcome remains unclear, as does the optimal approach to the use of steroids and immune modulators in the management of irAEs.

Kichenadasse et al found that 27% of patients with NSCLC experienced ≥ 1 irAEs. This result is consistent with a previous study that found that approximately 30% of patients with NSCLC treated with ICIs develop irAEs.¹⁹ However, significant variability in diagnosis and attribution of irAEs was seen across the 4 atezolizumab trials evaluated, as evidenced by the fact that the observed irAE rate ranged from 7% to 40% in these trials. In the pooled analysis, most patients developed irAEs with a median time of onset of 7 weeks, but some patients developed irAEs almost 2 years after the start of treatment. The development of endocrine abnormalities in Kichenadasse et al's study (11.6%) was lower than previously described (20%),²⁴ raising the question of whether these findings are secondary to undersurveillance of endocrine dysfunction or if they represent an advantage of atezolizumab over other agents with similar mechanism of action. Taken together, these findings underscore the importance of further exploring the pattern of irAE occurrence in ICI-treated advanced malignancies.

An urgent need exists to better elucidate irAEs that occur in the context of PD-1/L1 monotherapy, given the increasing use of ICIs as part of multimodality treatment regimens, such as with chemotherapy (NSCLC: KN189), radiation (NSCLC: PACIFIC), or multikinase inhibitors (renal cell carcinoma: KN426).^{25–27} A better understanding of the diagnosis and management of irAEs would be especially helpful in settings where treatment modalities have overlapping toxicities, such as pneumonitis occurring after radiation or diarrhea and skin toxicities from multikinase inhibitors. Kichenadasse et al have shed additional light on a subject that is becoming increasingly common in the clinic—namely the occurrence of irAEs during ICI therapy—but for which treatment guidelines are still based predominantly on expert opinion and retrospective studies (eg, ASCO and NCCN guidelines).^{28,29}

Finally, it should be noted that the patients with NSCLC included in Kichenadasse et al's meta-analysis were predominately treated in the second-line setting.^{7,8} As a result, some of the observed toxicity on trial, such as hematologic toxicities, may be due to prior therapies, not ICIs. In fact, as the authors point out, hematologic toxicities were not considered to be related to ICIs in these studies. However, recent studies suggest hematologic toxicities may be more common than previously thought with ICIs.³⁰ When an ICI is combined with chemotherapy to treat advanced malignancies, it will be increasingly important to ascertain reliable attributions of these toxicities. Lack of reliable attribution may otherwise result in dose reduction or omission of chemotherapy but continued ICI therapy, only to result in worsening toxicity and subtherapeutic treatment.

In summary, the study by Kichenadasse et al⁵ in this issue of *JNCCN* is an important addition to our knowledge base regarding ICI-induced irAEs, especially because this study evaluated a large atezolizumab-treated patient population from well-designed prospective studies. Undoubtedly, both single-organ and multiorgan

irAEs will be seen with increasing frequency in clinic. Studies such as this one are a reminder of the ongoing need for research strategies to predict, detect, and mitigate toxicities from ICIs.

Disclosures: Dr. Owen has disclosed that he receives grant/research support from BMS, Merck, Palobiofarma, and Genentech. Dr. Lisberg has disclosed that he has received grant/research support from Daiichi Sankyo, Calithera Biosciences, AstraZeneca, Dracen Pharmaceuticals, and WindMIL; he is a scientific advisor/consultant for AstraZeneca, Bristol-Myers Squibb, Leica Biosystems, Jazz Pharmaceuticals, Novocure, Pfizer, and MorphoSys; and his spouse is employed by and owns stock in Boston Scientific. The remaining authors have disclosed that they have no financial interests, arrangement affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

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