ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Management of Toxicities Due to Immune Checkpoint Inhibitors

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H&O Could you briefly describe your background and expertise in immune checkpoint inhibitors (ICIs)?

PR I am a rheumatologist and clinical immunologist, and a graduate of the University of Chicago Committee on Clinical Pharmacology and Pharmacogenomics training program. I currently lead the Immune-Related Adverse Event Clinic at my institution, where I collaborate very closely with my subspecialty colleagues and oncologists on a wide variety of ICI toxicities. I also serve on the National Comprehensive Cancer Network (NCCN) Guidelines for the Management of Immune-Checkpoint Inhibitor-Related Toxicities panel.[1]

H&O What are the most and least common immune-related adverse events (irAEs) seen with ICIs?

PR The most common ICI irAEs are endocrinopathies, such as thyroid abnormalities, and cutaneous side effects, such as dermatitis. The most common high-grade toxicity, when toxicities are graded according to the Common Terminology Criteria for Adverse Events (CTCAE), is colitis. Of the less common toxicities, myocarditis carries the highest mortality rate, especially myocarditis associated with peripheral myositis or myasthenia gravis/myasthenia gravis–like syndrome. The simultaneous occurrence of myocarditis, myositis, and myasthenia gravis/myasthenia gravis–like syndrome in a patient receiving immune checkpoint inhibition is termed triple-M ("3 Ms") or ICI-associated myocarditis/myositis/myasthenia gravis overlap syndrome (IM3OS). Another severe toxicity is pneumonitis, which is notable because pneumonitis is the most common cause of treatment-related death in patients who receive programmed death 1 (PD-1) inhibitor or programmed death ligand 1 (PD-L1) inhibitor monotherapy.[2]

Other uncommon side effects include, but are not limited to, hematologic abnormalities and presentations that mimic rare autoimmune conditions, such as eosinophilic fasciitis. Because it is difficult for any clinician to remain abreast of all the various subspecialty-related manifestations of immune checkpoint inhibition, especially the rare ones, it is worth reaching out to a specialist in the affected organ and/or an autoimmune disease subspecialist if something unexpected develops in the ICI treatment path that raises concern for an irAE.

H&O What are the management options for the irAEs that occur with ICI treatment?

PR Therapy is driven by both the severity of the irAE and the organ system(s) involved, with the patient's underlying cancer and comorbidities taken into consideration. For severity, we rely on the CTCAE grades. We usually try to manage grade 1 AEs with local therapy. For example, for a skin manifestation, we can use topical corticosteroids, or if a single joint is inflamed, we may try an intra-articular corticosteroid injection. We generally continue the ICI therapy.

The management of grade 2 AEs depends on the organ or system involved but generally consists of holding the ICI and considering systemic therapy, such as oral corticosteroids. If these measures relieve the symptoms, we can feel comfortable resuming the ICI.

For patients with a grade 3 or higher AE, we need to consider a prolonged hold or even discontinuation of the ICI. Therapy often requires systemic immunosuppression with glucocorticoids in addition to considering the addition of steroid-sparing immunosuppression.[3]

Not all toxicities require systemic corticosteroids or immunosuppression, however. For example, treatment for a thyroid abnormality involves hormone replacement rather than immunosuppression. Endocrinopathies are unique in that therapy most often consists of hormone replacement rather than immunosuppression. Patients with endocrinopathies can resume ICI therapy in most cases after initiation of hormone replacement therapy, but it should be noted that endocrinopathies are the most common chronic irAEs, and hormone replacement tends to be lifelong therapy.

Furthermore, irAE management requires ongoing evaluation to determine what organ systems are affected, as patients can develop more than one irAE. In addition to decisions regarding immunosuppression, organ-specific therapeutics and supportive measures should be considered. For example, a patient who has ICI-myocarditis with signs and symptoms of heart failure may need diuresis and other cardiac-specific management along with systemic immunosuppression. A patient with ICI-colitis and severe hypovolemia requires fluid and electrolyte repletion. For all of these reasons, irAE management often requires a multidisciplinary team approach.

H&O What second-line management approaches are used?

PR Second-line management is considered for a few key reasons: a steroid-refractory irAE, a steroid-resistant or steroid-dependent irAE, steroid intolerance, and/or a chronic or recurrent irAE requiring prolonged courses of systemic corticosteroids. For example, a patient who has very poorly controlled diabetes or decompensated heart failure may not be able to tolerate systemic glucocorticoids and will require a steroid-sparing immunosuppressive agent for irAE management. In other cases, a patient will have a good response to corticosteroids but will experience a worsening of their irAE as we taper the corticosteroids, a situation that the Society for Immunotherapy of Cancer has termed a steroid-resistant or steroid-dependent irAE.[3] For both types of patients, we often borrow treatment options that are used for preexisting autoimmune diseases that clinically most closely resemble irAEs, while keeping in mind that irAEs have different pathomechanisms than preexisting autoimmune diseases, so treatment may not be a simple copy-and-paste situation. Well-powered, prospective randomized controlled trials will be essential to identify the most effective and safe therapeutics for irAE management.

One of the most successful steroid-sparing agents we have for ICI-induced colitis (ICI-colitis) is the tumor necrosis factor alpha (TNF-α) inhibitor infliximab. We usually see an excellent response after just 1 to 3 doses of infliximab. For ICI-colitis, we have also seen excellent outcomes with the gut-specific immunomodulator vedolizumab (Entyvio, Takeda). Vedolizumab is promising because its gut-specific nature allows us to treat without systemic immunosuppression. For ICI-arthritis, disease-modifying antirheumatic drugs that are approved for rheumatoid arthritis such as interleukin 6 axis inhibitors, infliximab, and antimetabolites such as methotrexate and leflunomide, have shown promise.[4] We have long used the T-cell suppressor mycophenolate mofetil for autoimmune hepatitis, so this could be a logical choice for managing ICI-hepatitis because ICIs engage T-cell communication. Finally, a steroid-sparing combination that has been shown to be useful for life-threatening myocarditis consists of the cytotoxic T-lymphocyte–associated antigen 4 immunoglobulin (CTLA-4-Ig) fusion protein abatacept (Orencia, Bristol Myers Squibb) plus the JAK inhibitor ruxolitinib.[5]

> Immunotherapy-related adverse event management often requires a multidisciplinary team approach.

The take-home message is that we do not have large pool of prospective data to guide second-line therapy, so the second-line management of irAEs often relies on expert-driven judicious repurposing of medications successfully used to treat clinically comparable primary autoimmune diseases.

H&O Are certain ICI combinations, such as PD-1 inhibition plus CTLA-4 blockade, riskier in terms of the toxicity profile?

PR If I were to rank individual ICIs from least to most risky, I would say that PD-L1 inhibitor monotherapy is the least toxic, followed by PD-1 inhibitor monotherapy and then CTLA-4 inhibitor monotherapy. From there, it gets more nuanced because not all combination regimens

are more toxic than monotherapy. The toxicity rates for anti–CTLA-4 monotherapy differ according to dosing; the toxicity rate with ipilimumab at the 3-mg/kg dose is approximately 20%, which is comparable to the high-grade irAE rates with the combination of the LAG3 inhibitor relatlimab plus the PD-1 inhibitor nivolumab (Opdualag, Bristol Myers Squibb). Grade 3 to 4 treatment-related toxicity rates for ipilimumab at 10 mg/kg are higher, but the riskiest toxicity profile is with the combination of the CTLA-4 inhibitor ipilimumab (Yervoy, Bristol Myers Squibb) and nivolumab (Opdivo, Bristol Myers Squibb), so the specific agents in an ICI combination therapy matter a great deal. That said, a pharmacovigilance analysis noted that the combination of relatlimab plus nivolumab carried a higher myocarditis signal than ipilimumab plus nivolumab, even though the latter combination was linked to a broader range of immune-related toxicities overall.[6]

H&O Which toxicities do you consider to be the most life-threatening and the most time-sensitive to manage?

PR Myocarditis is probably the scariest toxicity. If we see any cardiac abnormality, there is a low threshold for rapid evaluation and we take a cross-collaborative approach to management that often involves cardiology, rheumatology, and neurology (for concurrent manifestations of peripheral myositis and/or myasthenia gravis). Progression to respiratory compromise by way of decompensated heart failure, life-threatening arrhythmia, or diaphragmatic weakness can be quick. The manifestations can present sequentially, so it is important to be vigilant for the development of myasthenia gravis–like symptoms or myositis, with repeat physical examinations and serial measurements of negative inspiratory force, for example.

Pneumonitis is also very concerning and unfortunately we do not yet have reliable options for second-line therapy. The use of infliximab has raised concerns, given its association with a high risk for mortality and infection. Although emerging data suggest that intravenous immunoglobulin, tocilizumab, and mycophenolate mofetil may be helpful, ICI-pneumonitis continues to carry a high mortality risk.

Neuropathy is very concerning, especially in the case of a Guillain-Barré syndrome–like or myasthenia gravis–like presentation. We worry about diaphragmatic weakness and respiratory compromise, which can progress very quickly.

For all these irAEs, the threshold for rapid specialty involvement and possibly even inpatient admission must be low.

H&O How can oncologists best balance maintaining antitumor efficacy with managing a serious irAE?

PR I am passionate about the central question of maximizing the efficacy of ICI therapy while minimizing toxicities. I wish we could identify all the patients who are at highest risk of developing irAEs before ICI initiation and mitigate their ICI toxicity risk while simultaneously optimizing the ICI antitumor efficacy.

So far, much of the data show that the development of an irAE is associated with a favorable tumor response. This finding presents a big challenge to oncologists, suggesting that the optimal situation may be the development of toxicities that are low-grade and easily addressed, so that the ICI can be restarted. However, even though some research shows that high-grade toxicity is associated with a good tumor response, it is also associated with worse overall survival.

The immunosuppression used to treat irAEs raises concerns for potential abrogation of ICI's antitumor effectiveness as well as risk of infection and other potential AEs specifically associated with the individual agents, although it could present an opportunity if we were able to find an immunomodulating agent that allowed us to decouple ICI toxicity from ICI efficacy.

Corticosteroids mechanistically raise concern for diminishing ICI efficacy by way of their broad, indiscriminate immunosuppression. Research shows that higher peak corticosteroid levels and earlier corticosteroid use are associated with worse outcomes, although it should be noted that in one meta-analysis, the outcomes were worse when the corticosteroids were used for brain metastases or other supportive care than when they were used to treat irAEs.[7] Additionally, in the national, multi-institutional RADIOS study, we found that corticosteroids at the level prescribed for ICI-associated inflammatory arthritis did not affect cancer progression-free survival, but the earlier use of corticosteroids did seem to affect outcomes.[8] The concern that systemic corticosteroids negatively affect tumor outcomes remains, and this is one reason we need to think about the use of steroid-sparing therapies.

Research on these steroid-sparing agents shows that interleukin 6 inhibition may adjunct antitumor immunity, making it an option to facilitate the decoupling of ICI efficacy and toxicity.[9] In vitro research suggests that TNF-α inhibitors also might be effective at decoupling efficacy from toxicity in ICI therapy, although the clinical data have been controversial. A large study of a melanoma cohort suggested that TNF-α inhibition might lead to worse outcomes than systemic corticosteroids for patients with colitis due to an ICI, but the findings were confounded by treatment practice patterns because the

patients who received infliximab had more severe, corticosteroid-refractory disease and may have received higher cumulative doses of corticosteroids.[10] Multiple other observational studies analyzing the use of infliximab for ICI-related colitis have not found worse cancer outcomes with infliximab.

Ultimately, the answer regarding the safety and efficacy of any of these irAE therapeutics is going to be answered best by carefully designed, multi-institutional, prospective randomized controlled trials.

H&O Is there a role for prophylactic corticosteroids or other treatments in high-risk patients?

PR Although it may be of value to use lower doses of corticosteroids to decrease ICI toxicities, no prospective large trials have addressed this question, and the guidelines do not recommend this approach. As previously mentioned, there is significant concern regarding systemic corticosteroids and their effect on tumor response and overall survival. In addition, long-term corticosteroid therapy has the potential to cause a litany of other steroid-associated toxicities, such as infection, heart disease, osteoporosis, and diabetes.

H&O What does the evidence indicate about rechallenging patients with a checkpoint inhibitor after a grade 3 or 4 irAE?

PR When we look at rechallenge, the risk that the irAE will recur is about 30%. I would not recommend rechallenge for any patient with an irAE that was life-threatening or that required intensive care, and I would worry about rechallenge for a patient with a high-grade toxicity if recurrence could lead to a life-threatening situation such as high-grade triple-M or IM3OS, a neuropathy such as Guillain-Barré syndrome, or myasthenia gravis, pneumonitis, or colitis.

When we deem rechallenge to be safe, one approach is to rechallenge along with an immunomodulating agent. For example, if a patient had ICI-colitis and the only cancer therapeutic option was cancer immunotherapy, we could consider ICI rechallenge along with vedolizumab.

H&O Is there anything you would like to add?

PR An emerging area in the irAE landscape is survivorship. ICIs have been so effective that patients live longer, and we now see irAEs that progress to chronicity, with ICI-endocrinopathies and rheumatic toxicities the most common of the chronic irAEs.[11] Although it is promising that our patients are living much longer, we need to be mindful that they may be experiencing prolonged, sometimes lifelong, consequences of immune modulation due to ICI treatment and are living with additional long-term diagnoses.

Beyond the management of the irAE itself, there is the decision of whether or not the ICI rechallenge can or should be considered. This relies on oncology and subspecialty collaboration, along with key factors such as the patient's oncologic diagnosis, cancer stage, and available therapeutic alternatives, as well as candid conversations with the patient for a shared decision-making approach.

Disclosures

Dr Reid reports financial relationships with AbbVie, Amgen, and UCB, and has a patent pending regarding the use of interleukin 6 axis inhibitors for viral infection–associated pneumonitis.

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