Triple M Syndrome: Implications for Hematology-Oncology Advanced Practice Providers

Lisa A. Kottschade, MSN, APRN, CNP, Casey Fazer-Posorske, PA-C, and Anna J. Schwecke, MS, APRN, CNP

During the past decade, immune checkpoint inhibitors (ICIs) have revolutionized the landscape of cancer treatment. ICI-related side effects occur via direct overactivation of the immune system, and patients can experience symptoms akin to autoimmune disease. These symptoms can range in severity from mild to severe and can be fatal. Advanced practice providers require a heightened awareness of the wide range of immune-related adverse events that can occur with ICI therapy.

AT A GLANCE

- ICIs are a treatment for almost every malignancy and exert cytotoxic effects through activation of the patient's immune system.
- A rare overlap syndrome consisting of myocarditis, myositis, and myasthenia gravis (triple M syndrome) can occur, which has a high fatality rate despite treatment.
- Symptoms of triple M syndrome can be vague and overlap with other immune-related adverse events; therefore, advanced practice providers can identify this syndrome, proceed with diagnostic testing, and facilitate early intervention.

KEYWORDS
immune checkpoint inhibitor; myositis; myocarditis; myasthenia gravis

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Immune checkpoint inhibitors (ICIs) exert their effects through upregulation of the immune system (Sharma & Allison, 2020). The most common ICIs include those affecting cytotoxic T-lymphocyte antigen 4, programmed cell death protein 1 (PD-1), and programmed cell death-ligand 1. Cytotoxic T-lymphocyte antigen 4 usually affects the immune system during the priming phase of T-cell activation, whereas PD-1 and programmed cell death-ligand 1 work with T-cell responses during the effector stage (Sharma & Allison, 2020). ICIs are approved for treatment for a variety of malignancies as single-agent therapy, as dual checkpoint inhibition, and in combination with chemotherapy or targeted therapy. The latest ICI to receive approval from the U.S. Food and Drug Administration is the lymphocyte activation gene 3 inhibitor relatlimab, which restores function of exhausted T cells during the effector phase (Tawbi et al., 2022). To date, lymphocyte activation gene 3 is approved in combination with nivolumab for the treatment of metastatic melanoma (Tawbi et al., 2022).

Because of the mechanism of action of ICIs, their adverse effect profile is vastly different than that for standard chemotherapy or targeted therapy. The most common immune-related adverse events (irAEs) are those affecting the skin (e.g., rash), gastrointestinal tract (e.g., diarrhea, colitis), liver (e.g., hepatitis), and endocrine system (e.g., thyroid, pituitary) (Michot et al., 2016). However, there are less common but more severe and life-threatening irAEs requiring early recognition and intervention.

Purpose

This article reviews the recognition and management of the following three life-threatening irAEs: myocarditis, myositis, and myasthenia gravis. Although myocarditis, myositis, and myasthenia gravis can occur in isolation, they often occur together in a pair or triad and tend to have overlapping symptoms. This phenomenon is referred to as overlap syndrome or triple-hit syndrome (Lipe et al., 2021; Pathak et al., 2021). This syndrome has also been referred to clinically as triple M syndrome in reference to the three irAEs it encompasses. Because of the rarity of irAE-related side effects, the literature consists primarily of case series and retrospective reviews. Consequently, treatment and immunosuppression recommendations for diseases outside of irAEs are extrapolated from these case series.