Checkpoint inhibitor hepatotoxicity: pathogenesis and management : Hepatology

Reviews

Checkpoint inhibitor hepatotoxicity: pathogenesis and management

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Abbreviations: AIH, autoimmune hepatitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANA, antinuclear antibody; AST, aspartate aminotransferase; ATG, antithymocyte globulin; CMV, cytomegalovirus; CTCAE, Common Terminology for Clinical Adverse Events; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; DILI, drug induced liver injury; EBV, Epstein-Barr virus; G, grade; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; IST, immune suppressive therapy; MHC, major histocompatibility complex; MMF, mycophenolate mofetil; PD-1, programmed cell death protein-1; PD-L1, programmed death-ligand 1; SMA, smooth muscle antibody; TCR, T-cell receptor; Treg, regulatory T cell; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

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Abstract

Immunotherapy, including immune checkpoint inhibitor (ICI) therapy, has been a paradigm shift in cancer therapeutics, producing durable cancer responses across a range of primary malignancies. ICI drugs increase immune activity against tumor cells, but may also reduce immune tolerance to self-antigens, resulting in immune-mediated tissue damage. ICI-associated hepatotoxicity usually manifests as hepatocellular enzyme elevation and may occur in 2%–25% of ICI-treated patients. Although ICI-associated hepatotoxicity is clinically and pathologically distinct from idiopathic autoimmune hepatitis, our understanding of its pathogenesis continues to evolve. Pending greater understanding of the pathophysiology, mainstay of management remains through treatment with high-dose corticosteroids. This approach works for many patients, but up to 30% of patients with high-grade hepatotoxicity may not respond to corticosteroids alone. Furthermore, atypical cholestatic presentations are increasingly recognized, and rare cases of fulminant hepatitis due to ICI hepatotoxicity have been reported. Optimal management for these challenging patients remains uncertain. Herein, we review the current understanding of pathogenesis of ICI-associated toxicities, with a focus on hepatotoxicity. Based on the existing literature, we propose evolving management approaches to incorporate strategies to limit excess corticosteroid exposure, and address rare but important presentations of cholestatic hepatitis and fulminant liver failure. Finally, as ICI hepatotoxicity frequently occurs in the context of treatment for advanced malignancy, we review the impact of hepatotoxicity and its treatment on cancer outcomes, and the overall safety of re-challenge with ICI, for patients who may have limited treatment options.

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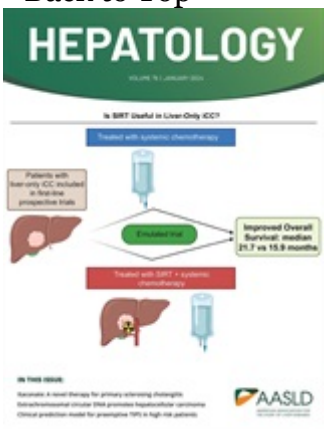

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