Recent Developments in Oncology Immunotherapy, Adverse Effects Part 2

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ABSTRACT

Immunotherapy has emerged as a promising treatment for cancer survivors in the past few years. This new treatment is associated with unique immune-related toxicities that can range from mild to life-threatening. Early recognition, referral, and monitoring by primary care nurse practitioners may improve the quality of life and survival of cancer survivors.

Keywords: cancer, immune-related adverse event, immunotherapy, primary care, toxicities

It is estimated that there are more than 15.5 million cancer survivors living in the United States today and that this number will increase to 20 million by 2026.[1] *Cancer survivor* is a term used to describe anyone who has ever had cancer, from the time of diagnosis to death.[1] The increase in cancer survivors is due in part to improvements in the early detection of cancer, as well as emerging treatments such as immunotherapy that help cancer survivors live longer.[1-7]

For instance, a study conducted by Brahmer et al[8] that compared nivolumab with docetaxel in patients with squamous non–small-cell lung cancer found that patients on nivolumab had a survival rate nearly double (42%) that of patients who received docetaxel alone (24%). Similarly, in a study that evaluated the clinical usefulness of an autologous tumor lysate-pulsed dendritic cell vaccine plus ex vivo–activated T-cell transfer in an adjuvant setting for postoperative hepatocellular carcinoma found that the median recurrence-free survival and overall survival were 24.5 months and 97.7 months, respectively, in patients receiving adjuvant autologous tumor lysate-pulsed dendritic cell vaccine plus ex vivo–activated T-cell transfer compared with 12.6 months and 41.0 months, respectively, in the group receiving surgery alone ($P = .011$ and .029).[9]

To date, more than 15 cancer immunotherapies have been approved for use as monotherapy in various solid and hematologic cancers.[10] The goal of immunotherapy is to boost or restore the ability of the immune system to detect and destroy malignant cells by overcoming the mechanisms by which malignant cells evade and suppress the immune response.[11] However, boosting the immune system may result in a hyperactivated nonspecific T-cell immune response against normal tissue, resulting in organ damage that may present as immune-related adverse events (irAEs).[11]

The most common irAEs associated with immunotherapy are mild to severe, including dermatologic effects (rash and pruritus), pulmonary effects (pneumonitis), gastrointestinal effects (diarrhea and colitis), hepatotoxicity, and endocrinopathies (hypophysitis, thyroid dysfunction, and diabetes) (Table).[12-14] Although irAEs can occur in other systems, their incidence is less frequent, and they are less likely to be seen in the primary care setting (Figure).[15]

Given that cancer survivors often visit primary care nurse practitioners (PCNPs) for non–cancer-related medical conditions, it is essential that PCNPs have a basic knowledge of the immune system and immune response to tumor cells to understand the clinical application of immunotherapy. Additionally, the PCNP's role may involve monitoring, recognition, and management of irAEs associated with immunotherapy.

IMMUNE SYSTEM REVIEW

The immune system is a highly specialized and adaptive system of physical barriers, organs, cells,

Table. Common Immune-related Adverse Event (irAE) Median Onset, Symptoms, and Diagnostic Technique

irAE	Median Onset	Presenting Symptoms	Diagnostic Technique
Dermatologic toxicity	Around 5 weeks	Erythematous, maculopapular rash Pruritus Mucositis, gingivitis Vitiligo	R/O viral or bacterial infection R/O nutritional deficit or other medication effect R/O complications from cancer or comorbid conditions Laboratory tests: complete blood count, complete metabolic panel, thyroid panel, cortisol level, etc CT or MRI scan, lumbar puncture, and as indicated
GI toxicity, enterocolitis	6-8 weeks	Diarrhea Abdominal pain Per rectal bleeding or mucous	
GI toxicity, hepatitis	8-12 weeks	Usually asymptomatic elevation of AST, ALT, bilirubin Periportal edema or hepatomegaly in severe cases	
Endocrinopathy	6-11 weeks	Nonspecific: fatigue, weight change, nausea, depression Symptoms of hypothyroidism or hyperthyroidism Elevated blood glucose Hypophysitis: fatigue, headache, hypogonadism (amenorrhea or impotence), hypotension	
Rheumatologic toxicity	Around 1 month	Muscle and joint stiffness, pain, edema, limited range of motion	
Pneumonitis	2-5 months	Cough, upper respiratory infection symptoms, dyspnea, chest pain Hypoxia: pulse oximetry $< 90\%$	
Neurotoxicity	10-14 weeks	Symptoms of neurologic deficit involving central and peripheral nervous systems	
Nephrotoxicity	15 weeks	Usually asymptomatic elevation of creatinine	

AST = aspartate aminotransferase; ALT = alanine aminotransferase; CT = computed tomography; GI = gastrointestinal; MRI = magnetic resonance imaging; R/O = rule out.

and molecules that guards the human body against foreign substances or antigens.[16] The first tier of defense is physical barriers, such as skin and mucous membranes. This physical line of defense is followed by 2 types of immunity: innate and adaptive. Innate or nonspecific immunity consists of cells (phagocytes, macrophages, dendritic cells, and natural killer cells) that kill and eliminate foreign antigens.[16,17] Innate immunity is short-lived and does not form an immunologic memory.[18] In contrast, adaptive immunity involves immunologic memory and uses 2 methods to defend against antigens, humoral and cell-mediated responses.[16] A humoral response is mediated by antibodies, which are produced by B lymphocytes. Generally, antibodies are secreted into the circulation and mucosal fluids where they neutralize and eliminate extracellular antigens or foreign substances.[16] Meanwhile, a cell-mediated response is facilitated by T lymphocytes known as $CD4^+$ helper T cells and $CD8^+$ cytotoxic T lymphocytes, which destroy intracellular protein-based antigens via phagocytosis.[16,18]

Two self-tolerance immune mechanisms protect against B- and T-cell responses to self-antigens: central and peripheral tolerance.[19] Central tolerance occurs during lymphocytic maturation and involves the physical destruction of self-reactive cells, whereas peripheral tolerance ensures that cells do not react to self-antigens in the secondary lymphoid tissues.