Cancer Therapy with Checkpoint Inhibitors: Establishing a Role for Ophthalmology

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Objective: *To discuss interprofessional collaboration between the primary oncology clinicians and specialists in the management of immune-related ocular toxicities.*

Data Sources: *Peer-reviewed articles, case reports and systematic reviews.*

Conclusion: *Accurate ophthalmologic assessment is critical for the prevention and treatment of ocular toxicities associated with immunotherapy.*

Implications for Nursing Practice: *Oncology nurses play a key role in early identification and management of ocular symptoms from immunotherapy; early referral to ophthalmic specialists can enhance recovery and preserve sight.*

Key Words: *immunotherapy, checkpoint inhibitor, eye, toxicity, interprofessional collaboration, management.*

Immunotherapeutic agents are designed to "harness" the patient's own immune system to target cancer. Recent successes in the treatment of melanoma, non-small cell lung cancer, and renal cell carcinoma have been profound and immunotherapeutic agents are currently being used in practice and clinical trials in the treatment of many other cancers.

Immunotherapy for cancer treatment manipulates adaptive immunity processes. Adaptive immunity involves the B cells recognizing antigens from tumor cells and forming antibodies that bind to circulating antigens; these antigens are present on major histocompatibility molecules expressed on the surface of macrophages and dendritic cells known as antigen presenting cells. The T cell

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recognizes the antigens and then determines them as "self" or "non-self." CD4 T cells make cytokines to help amplify the immune system, while CD8 cells recognize foreign antigens and stimulate cell destruction.[1]

Immune "checkpoints" are pathways within the immune system that regulate response. When the receptor on the T cell binds to a ligand, T cells receive and respond to signals that can activate an immune response (for example, determining a bacterium as non-self and stimulating T cells to fight it) or inhibit a response (determining something is self and not stimulating an attack). The inhibitory mechanisms are essential because without them autoimmune diseases would occur. Immunotherapy drugs called *checkpoint inhibitors* circumvent these inhibitory signaling mechanisms; they block the inhibitory response, allowing the immune system to recognize the cancer as non-self and stimulate a response.

Currently there are two classes of US Food and Drug Administration-approved monoclonal antibody checkpoint inhibitors. One class is aimed at the inhibitory programmed death (PD-1) receptor and its ligand PD-L1; examples include nivolumab (Opdivo, Bristol-Myers Squibb, Princeton, NJ), pembrolizumab (Keytruda, Merck Sharp & Dohme Corp, Whitehouse Station, NJ), and atezolizumab (Tecentriq, Genentech, Inc., South San Francisco, CA). PD-1 is a cell surface receptor that functions as an immune checkpoint by preventing the activation of T cells. Thus, PD-1 inhibitors activate the immune system by releasing this inhibition. The second class is heralded by ipilimumab, (Yervoy, Bristol-Myers Squibb, Princeton, NJ), a human monoclonal antibody that works to block the inhibitory cytotoxic lymphocyte antigen 4 (CTLA-4). CTLA-4 is a protein receptor that downregulates the immune system and inhibits cytotoxic T lymphocytes from destroying cancer cells. By blocking CTLA-4, ipilimumab allows for cancer cell devastation by these cytotoxic T lymphocytes.

Side Effects of Checkpoint Inhibitors

The most common adverse events seen with checkpoint inhibitors include fatigue, arthralgia, and anorexia, similar to cytotoxic chemotherapy agents.[1] Although initially advocated as having fewer side effects than conventional therapies, these agents can trigger immune reactions against normal tissues known as immune-related adverse events (irAEs). IrAEs can range from relatively minor effects, such as dermatitis or skin depigmentation, to severe toxicities against crucial organ systems, such as liver, bowel, and lung.[2] Of patients treated with ipilimumab, approximately 64% experience an irAE of any grade,[3] with autoimmune colitis, endocrinopathies, hepatitis, and cutaneous irAEs the most frequently reported.[4-6] Cutaneous irAEs were common in patients treated with pembrolizumab and autoimmune thyroiditis and pneumonitis with those treated with nivolumab.[4] Differences in the side-effect profiles of checkpoint inhibitors are likely caused by different mechanisms of action, with the PD-1 inhibitors, nivolumab and pembrolizumab, appearing to have a more tolerable profile than the CTLA-4 inhibitor ipilimumab.[7] While ophthalmologic irAEs have been reported in only about 1% of patients treated with checkpoint inhibitors,[8] some have been described as severe[3] and potentially visually threatening.

Ocular Toxicity

Immune-related ocular toxicity manifests as inflammation in various anatomic segments of and around the eye (see Fig. 1). Moving from anterior to posterior, side effects seen include orbital inflammation (sometimes diagnosed as euthyroid Graves ophthalmopathy), ulcerative keratitis, dry eye syndrome, episcleritis, uveitis (anterior and posterior), retinopathy (Vogt-Koynangi-Harada syndrome and serous detachments), and choroidopathy.[9-39] Tables 1, 2 and 3 highlight published case reports of ocular side effects related to ipilimumab, pembrolizumab, and nivolumab therapy. No specific case reports of ocular toxicity related to atezolizumab were found; the company prescribing information does note that ocular inflammatory toxicity occurs in <1% of patients.[40] Atezolizumab, along with newer agents durvalumab (Imfinzi, Astra Zeneca Pharmaceuticals, Wilmington, DE) and avelumab (Bavencio, Merck KGaA, Darmstadt, Germany), were recently approved by the US Food and Drug Administration; specific case reports related to ocular toxicity may be forthcoming.

Orbit. The orbital tissues surrounding the eye are composed of extraocular muscles (which control movement of the eye), the soft tissue adnexal structures, lacrimal gland, and nasolacrimal duct system that are bound by the confines of the cave-like orbital bones. The dermis and eyelids cover the