Update on New Therapies With Immune Checkpoint Inhibitors

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Background: Immunotherapy has had a long history in cancer treatment and, with recent breakthroughs, new drugs are available that have shown promising results.

Objectives: The current article discusses an overview of immune function, including immunediting and the theory of immune checkpoints, as well as specific drugs that have been approved as immune checkpoint inhibitors. Additional discussion includes a review of nursing implications and administration, side effects, adverse events, and the future of immuno-oncology.

Methods: This review of literature focused on locating, summarizing, and synthesizing data from published articles, the American Cancer Society, U.S. Food and Drug Administration, and literature from pharmaceutical manufacturers that focused on immunotherapy treatment options that use checkpoint inhibition. Search criteria included articles published from 2005–2015 and archived in CINAHL®, OVID®, and PubMed databases using the key words immunotherapy, immune checkpoint inhibition, PD-1, PD-L1, CTLA-4, and oncology.

Findings: Cancer therapy targeting immune checkpoint inhibition has shown promising results and continues to evolve. Oncology nurses need to remain abreast of new immune-modulating therapies to understand their efficacy, as well as side effect management.

With the success of new therapies using immuno-oncology agents, immunotherapy is increasingly seen as an effective treatment for cancer (Mendes, 2014). Many patients with cancer who were previously out of treatment options have new hope.

Using the immune system as a tool to battle cancer is not a new idea. As early as 1891, Coley’s toxins, an immunotherapeutic mixture of bacteria, were used with patients with cancer (Ito & Chang, 2013). When William Coley lost a patient to metastatic sarcoma after performing radical resection, he began to review medical records and identified that patients who developed postoperative infections had higher survival rates than those that did not (McCarthy, 2006). With this observation, he worked under the assumption that the immune system was triggered by the infection, which resulted in an immune response that also fought the underlying cancer. Coley continued to test his theory, claiming a five-year survival rate of 50% in patients treated with the toxins. After his death, his daughter published data from his cases, supporting a near-complete regression in 500 of 1,000 cases (McCarthy, 2006).

Clinical research in the late 19th century was not as regimented or rigorous as it is today; therefore, Coley’s results were difficult to replicate. Based on questionable results and poorly documented patient follow-up, the approach did not gain favor. As a result, the use of chemotherapy and radiation became the standard treatment modalities for cancer (Ito & Chang, 2013). Immunotherapy has been revisited a number of times since then. Many drugs have
been approved as immunomodulatory agents, including monoclonal antibodies, cancer vaccines, immune adjuvants, and cytokines (Kannan, Madden, & Andrews, 2014) (see Table 1). These different therapies manipulate the immune response in a variety of ways to prevent or attack malignancy, and some immune therapies can support the patient during cytotoxic treatments.

As the landscape of cancer treatment changes and new therapies become available, nurses will need to be aware of how new treatments will affect patients and their practice. This article reviews the immune response to malignancy, how immunotherapy modulates that response, and the management of common side effects and potential adverse events from these new agents.

### Overview of Immune Function

One role of the immune system is to destroy cancerous cells through constant surveillance and elimination of cancerous transformation (Elgert, 2009). Preclinical studies have suggested that an active immune system continuously recognizes and eliminates the vast majority of cancer cells before they form a tumor mass (Hanahan & Weinberg, 2011; Vajdic & van Leeuwen, 2009). The innate immune system (a nonspecific response) recognizes and destroys abnormal proteins through the use of phagocytes, natural killer cells, cytokines, and complement proteins. In contrast, the adaptive immune system works by mounting a targeted response to specific antigens through cell-mediated and humoral (antibody-mediated) immunity (Kannan et al., 2014). Cell-mediated immunity involves activation of antigen-specific cytotoxic T cells, macrophages, and natural killer cells, as well as release of cytokines. Humoral immunity refers to the activation of B cells that have not been exposed to an antigen by helper T cells, which then differentiate into memory cells and antibody-releasing plasma cells (Murphy, 2014).

### Immunoediting

Malignant cells that resist the multifaceted attack of the immune system are thought to do so by avoiding a process known as immunoediting (Kannan et al., 2014). Immunoediting consists of three phases: elimination, equilibrium, and escape. The elimination phase consists of the successful recognition and elimination of malignant cells by the immune response. The equilibrium phase refers to control of cancer cell growth without completely eliminating the transformed cells. Finally, the escape phase encompasses tumor cells not susceptible to destruction in the first two phases that continue to divide and grow (Prendergast, 2008). Tumor cells that are not eliminated continue to replicate and are resistant to the immune response (DuPage, Mazumdar, Schmidt, Cheung, & Jacks, 2012; Kannan et al., 2014). Immunotherapy agents are used to bolster the immune system, so it can attack these malignancies before they translate to the escape phase. Many of these therapies are molecular targeted therapies, meaning that they are directed toward well-defined molecular targets (Giaccone & Soria, 2008). This targeted therapy inhibits the...
functions of molecular targets to manipulate the immune system into fighting the malignancy.

Immune Checkpoints

Immune checkpoints are pathways in the immune system that regulate the immune response. These checkpoints modulate the immune response to reduce injury to healthy tissues when the immune response is no longer needed (Lartigue, 2012). However, cancer cells can use these pathways to bypass the immune response and proliferate. With the discovery of these key immune checkpoints in the early 1990s, researchers investigated ways to inhibit the checkpoints to fight malignancy. From this research, new targeted immunotherapies are being tested. The U.S. Food and Drug Administration ([FDA], 2016) approved three therapies for cancer treatment: anti-CTLA4, anti-PD-1, and anti-PD-L1. These drugs inhibit specific checkpoints and boost patients' immune response to attack malignancy.

Immune Checkpoint Inhibitors

Ipilimumab (Yervoy®) is a monoclonal antibody that inhibits the cytotoxic T lymphocyte–associated antigen 4 (CTLA4) pathway. Ipilimumab was approved by the FDA (2016) in 2011 for the treatment of unresectable or metastatic melanoma. The CTLA4 pathway inhibits T-cell function by binding CTLA4 to proteins CD80 and CD86, also called ligands. Ipilimumab works by blocking this interaction. This action results in proliferation of T cells, which have antitumor effects. By inhibiting this pathway, T cells are activated and able to mount a response to the cancerous cells. In the clinical trials that led to FDA approval, patients who received ipilimumab plus tumor vaccine had an overall survival rate of 10 months versus 6 months with tumor vaccine alone (Pazdur, 2013). The overall response rate of the combined therapy (ipilimumab and tumor vaccine) was 5.7% versus 1.5% response in patients who received only the tumor vaccine (Pazdur, 2013). A longer duration of survival occurred in a subset of patients who received ipilimumab beyond what would be expected with cytotoxic or targeted therapies (Schadendorf et al., 2015).

Two programmed cell death protein 1 (PD-1) inhibitors, nivolumab (Opdivo®) and pembrolizumab (Keytruda®), were approved by the FDA for patients with advanced melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma. Both of these drugs are PD-1 inhibitors that work by blocking the interaction of PD-1 with its ligands, PD-L1 and PD-L2, releasing PD-1 pathway–mediated inhibition of the immune response, including the antitumor immune response (see Figure 1).

Pembrolizumab was the first anti-PD-1 therapy to be approved in the United States. Pembrolizumab has received two breakthrough therapy designations, one for melanoma and one for NSCLC. Accelerated approval was granted by the FDA for the treatment of metastatic melanoma in September 2014 after a trial of patients, who had progressed within 24 weeks of receiving ipilimumab, showed an overall response rate of 24%, with patients showing ongoing response durability of 86% (ClinicalTrials.gov, 2015d; FDA, 2016).

Nivolumab was only a few months behind pembrolizumab, receiving accelerated FDA approval for treatment of metastatic melanoma in late 2014 and metastatic squamous NSCLC in early 2015 (FDA, 2016). Clinical trial data for nivolumab supported a 32% response rate with 87% durability of response in patients with melanoma (ClinicalTrials.gov, 2015a). In a study involving patients with lung cancer, the median overall survival with nivolumab was 9.2 months versus 6 months with docetaxel (Taxotere®) (ClinicalTrials.gov, 2015b). Another study of single-agent nivolumab in lung cancer showed a 15% response rate, with 59% of responders showing a durable response (of six months or longer) (Bristol-Myers Squibb, 2015; ClinicalTrials.gov, 2015c). With the early successes of nivolumab and pembrolizumab, additional clinical trials are underway to determine efficacy against other cancers as a single agent and in combination therapy (www.clinicaltrials.gov). Although no currently approved PD-L1 inhibitors are available on

![Figure 1. Effects of Anti-PD-1 and Anti-PD-L1 on T Cells and Tumor Cells](https://example.com/figure1.png)

Note. The top image depicts the PD-1/PD-L1 pathway showing the tumor cell inactivating the T cell. The bottom image depicts the inhibition of the PD-1/PD-L1 pathway, with anti-PD-1 and anti-PD-L1 blocking the inactivation of the T cell by the tumor cell.
Diarrhea
- Grade 1: Increase of less than 4 stools per day over baseline
- Grade 2: Increase of 4–6 stools per day over baseline
- Grade 3: Increase of 7–9 stools per day over baseline; incontinence; hospitalization indicated
- Grade 4: Increase of 10 or more stools per day over baseline; bloody stool; hospitalization indicated

Interventions
- Moderate (grade 2 for more than five days, grade 3): Withhold treatment; administer corticosteroids until resolved to grade 1 or less.
- Severe (grade 4 or greater): Discontinue treatment; administer corticosteroids until resolved to grade 1, then begin 30-day taper of steroids.

Elevated Liver Enzymes
- Grade 1 (mild): Elevated AST or alkaline phosphatase or both; total serum bilirubin less than 2.5 mg/dl; INR less than 1.5
- Grade 2 (moderate): Elevated AST or alkaline phosphatase or both; total serum bilirubin greater than 2.5 mg/dl; INR less than 1.5; without hyperbilirubinemia
- Grade 3 (moderate to severe): Elevated AST or alkaline phosphatase or both; total serum bilirubin greater than 2.5 mg/dl; hospitalization because of drug-induced liver injury
- Grade 4 (severe): Elevated AST or alkaline phosphatase or both; total serum bilirubin greater than 2.5 mg/dl; at least one of the following: prolonged jaundice beyond three months, signs of hepatic decompensation (INR greater than 1.5, ascites, encephalopathy), or other organ failure believed to be related to drug-induced liver injury

Interventions
- Mild (grade 1): Administer corticosteroids.
- Moderate (grade 2): Withhold treatment until resolved.
- Moderate to severe (grades 3–5): Permanently discontinue.

Rash
- Grade 1: Faint erythema or dry desquamation
- Grade 2: Moderate to brisk erythema or a patchy, moist desquamation, mostly confined to skin folds or creases; moderate edema
- Grade 3: Confluent moist desquamation 1.5 cm in diameter or greater and not confined to skin folds; pitting edema

Interventions
- Mild (grade 1): Observed and managed medically.
- Moderate (grade 2): Withhold treatment until resolved.
- Severe (grade 3 or greater): Discontinue and begin corticosteroids for severe side effects.

FIGURE 2. Management of Immunotherapy-Related Adverse Events

Note. Based on information from Bisanz, 2011; Bristol-Myers Squibb, 2015; Merck and Co, Inc., 2015; Postma & Heimans, 2000; Postow & Wolchok, 2015; U.S. National Library of Medicine, 2016.

Side Effects
Because immune checkpoint inhibitors “basically take the ‘brakes’ off the immune system” (American Cancer Society, 2015, para. 11), side effects can occur when the immune system begins to work against noncancerous cells, as well as malignant cells. Some more common immune-related side effects include rash, fatigue, pneumonitis, colitis, hepatitis, nephritis, and hormone problems (particularly affecting the thyroid and pituitary gland). Conducting thorough patient assessments and reviewing laboratory results help to identify problems early, which gives providers the opportunity to manage effects prior to exacerbation. Minor side effects of immune therapy can often be treated with temporary oral steroid use, interrupting treatment, or supportive care. Moderate to severe side effects (grades 3–5), which can be serious and life-threatening, necessitate more aggressive steroid therapy and lengthy tapering down of dosing of at least one month (Bristol-Myers Squibb, 2015) or possibly permanent identification and management.
discontinuation of therapy, even if the side effect is resolved (Merck and Co., Inc., 2015) (see Figure 2).

Immune-Related Adverse Events

During therapy, a unique set of adverse events may occur, termed immune-related adverse events. These differ from other side effects in severity; immune-related adverse events can lead to discontinuation of therapy and can be fatal in some cases if left untreated. Immune-related adverse events occurred in 41% of patients who received pembrolizumab in clinical trials, 36% in patients receiving ipilimumab, and 64% in ipilimumab studies (ClinicalTrials.gov, 2015a, 2015d; Tarhini, 2013). Because of immune-related adverse events, 10% of patients who received immunotherapy have therapy discontinued and/or require lengthy rounds of high-dose steroids. The most serious of these immune-related adverse events include diarrhea, pruritus, rash, and colitis (Bristol-Meyers Squibb, 2015).

A differentiator between cytotoxic therapies and immunotherapies is that immune-related adverse events do not always necessitate discontinuation of therapy like the adverse events seen with cytotoxic agents. A link between clinical benefit and immune-related adverse events has been found in patients treated with ipilimumab, with one study showing 36% of patients with grade 3 or 4 toxicities achieving a clinical response (Weber, Kähler, & Hauschild, 2012). Patients receiving immunotherapy agents have a different pattern of response to therapy. Unlike cytotoxic therapies that are discontinued with progression of disease, immunotherapy treatment can have a delayed response; therefore, progression of disease may be present early on after initiation of therapy (Oxnard et al., 2012).

The Future of Immuno-Oncology

With the state of cancer immunotherapy, many new treatments are on the horizon. Immune checkpoint inhibition is currently being heavily researched, with several pharmaceutical companies and research groups testing various drugs in clinical trials. New treatments are available for melanoma and NSCLC and are anticipated to be useful in other tumor types in the next few months to years. With the successes in approved drugs and clinical trials, pharmaceutical companies are conducting additional research into immune checkpoints, as well as other ways to stop cancer cells from eluding the immune system.

Conclusion

The field of cancer research moves quickly and is constantly changing with new breakthroughs in treatment. Immunotherapy research has opened the door to a number of possible treatment options for many patients. Drugs are being researched and approved by the FDA in short time frames because of their significant improvements in progression-free survival and response rates. With the successes of newly approved drugs, as well as drugs showing promise in clinical trials, oncology nurses should be prepared for changes in available treatment options for their patients. Administration of immunotherapy agents can have different adverse events from the traditional cytotoxic agents that oncology nurses have used to provide the best treatment. Having awareness of possible side effects can help nurses to provide the best care to their patients, and catching symptoms early can allow patients to remain on treatment longer.

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Implications for Practice

- Relate basic principles of immune response and the understanding of immune checkpoints to how they are manipulated to engage the immune system to fight cancer.
- Understand the difference between immunotherapies and cytotoxic therapies in method of action, pattern of response, and side effect profile.
- Differentiate assessment parameters to assist in identifying side effects from immunotherapies to avoid interruption or discontinuation of treatment.


