The Latest Cancer Agents and Their Complications

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KEYWORDS

• Cancer • Immunotherapy • Checkpoint modulators • Cancer vaccines
• Adoptive immunotherapy • CAR-T • Immune-related adverse events
• Oncologic emergency

KEY POINTS

- Cancer immunotherapy is a new class of cancer agents that leverages the immune system to combat cancer.
- The mechanisms of action are vastly different than traditional cytotoxic chemotherapy.
- Complications related to immunotherapy, termed immune-related adverse events (IRAEs) occur frequently, affect almost any organ system, but most are mild to moderate in severity and are self-limited or respond to steroids.
- Emergency physicians must be aware of IRAEs and be able to diagnose and manage them in consultation with oncologists.

INTRODUCTION

Emergency physicians have grown comfortable with diagnosing and treating the various infectious, cardiovascular, gastrointestinal, dermatologic, and other complications of traditional cytotoxic chemotherapies, but the armamentarium of cancer therapeutics available to oncologists has grown exponentially over the last decade. There is now an entirely new class of cancer therapeutics, known as cancer immunotherapy, and it works by entirely different mechanisms and has completely different complications. New drugs and new indications are being approved at a rapid pace, and it is imperative that emergency physicians become familiar with the diagnosis and management of complications associated with these drugs.

The cornerstone difference between cancer immunotherapy and traditional chemotherapy is that the primary goal of immunotherapy is to interfere with growth signals produced by cancerous cells, rather than directly destroy them (and other healthy cells

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in the process). The mechanism by which immunotherapy achieves this goal is by enhancing antitumor immune responses of the patient's immune cells.

OVERVIEW OF IMMUNE-BASED THERAPIES

Several strategies have been developed, aimed at priming the immune system's response to tumor cells, leading to the genesis of several different immunotherapy agents. A familiarity with these modalities will enable emergency physicians to not only understand the mechanisms of action, but also to anticipate potential complications when patients undergoing immune therapy present to the emergency department.

To date, there are 3 main immunotherapeutic strategies.[1] These include nonspecific stimulation of immune reactions, active immunization to enhance antitumor reaction, and passive transfer of activated immune cells with antitumor activity. **Table 1** summarizes these methods.

Nonspecific Stimulation

Interleukin-2 (IL-2) is a T-cell growth factor that was first identified in 1980,[2] then became more widely studied in 1983 when a recombinant form was developed.[3] A landmark trial by Rosenberg and colleagues[4] was the first to document regression of advanced solid cancers using immunotherapy in people. The trial analyzed effects of IL-2 and LAK (nonspecific lymphokine-activated natural killer) cells together, but a follow-up trial[5] showed that the response was in fact due to IL-2 alone. IL-2 works by stimulating T and natural killer cells in order to act on tumor cells recognized as foreign. IL-2 was originally approved in the 1990s as monotherapy to treat metastatic renal cell cancer and metastatic melanoma. Today, treatment is approved for several other malignancies including nonsmall cell lung cancer (NSCLC) using IL-2, typically in combination with other therapies (other methods of immune therapy as well as with chemotherapy).[6]

The other subcategory of nonspecific immune system stimulation is recognized as checkpoint modulator therapy (also called checkpoint inhibitors but will be referred in this article as checkpoint modulators). To date, there are 3 mechanisms of checkpoint modulators: anticytotoxic T-lymphocyte antigen 4 (anti-CTLA-4), antiprogrammed death 1 (anti-PD-1), and antiprogrammed death ligand 1 (anti-PDL1). They differ in mechanism from IL-2; instead of stimulating the immune cells directly, these antibody drugs remove inhibitory mechanisms that are typically in place to dampen the immune response. In other words, they modulate the points that keep the immune system in check, effectively taking the brakes off of the system. Currently, available checkpoint inhibitors include ipilimumab (anti-CTLA-4), nivolumab and pembrolizumab

Table 1
Summary of methods, mechanism, and agents of cancer immunotherapy

Method	Mechanism	Agent
Nonspecific	Stimulation of effector cells Inhibition of regulatory factors ("checkpoint modulators")	IL-2 Anti-CTLA4 (ipilimumab), Anti-PD1 (nivolumab, pembrolizumab), Anti-PDL1 (atezolizumab, durvalumab)
Cancer vaccine	Active immunization to enhance antitumor reactions	Sipuleucel-T, talimogene laherparepvec
Adoptive immunotherapy	Passive transfer of activated immune cells with antitumor activity	CAR-T (tisagenlecleucel, axicabtagene ciloleucel)