

Introduction to immunotherapy: What nurses need to know about emerging therapies

Understanding these rapidly evolving treatments will help you advocate for patients and manage side effects.

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IMMUNOTHERAPY is steadily becoming the standard of care for cancer patients. The rapidly advancing science behind immunotherapy offers oncology patients treatment options with durable responses and potentially less toxicity. Immunotherapy encompasses several treatment modalities, including oncolytic viruses, checkpoint inhibitors, and chimeric antigen receptor (CAR) T-cell therapy. All of these options work with the body's own immune system to identify abnormal cancer cells that can be destroyed while healthy normal cells are unharmed. Understanding these options helps nurses better care for patients, including providing education.

How immunotherapy works

The immune system is the body's defense against infectious organisms and other invaders. It's made up of a network of cells (including T cells and B cells), tissues, and organs working together to protect the body by attacking organisms and substances that in-

vade the body and cause disease.

Cancer cells, however, are able to evade cell death and escape immune recognition and subsequent destruction. They do this by developing multiple resistance mechanisms, including local immune evasion, induction of tolerance (which results in unresponsiveness of the immune system),

and systemic disruption of T-cell signaling.

Chemotherapy destroys rapidly dividing cells, such as cancer cells, but it also attacks other rapidly dividing healthy cells, such as blood and mucosal cells. This is what causes side effects such as alopecia, mouth sores, nausea, vomiting, diarrhea, and decreased blood cell counts.

Immunotherapy, on the other hand, works with the body's immune system by helping T cells to better distinguish cancer cells from healthy cells and shrink or kill them. The side effects of T-cell stimulation are inflammatory and include rash, diarrhea, liver inflammation, and hypothyroidism.

In this article, we'll review three immunotherapy treatment options—oncolytic viral immunotherapy, checkpoint inhibitors, and CAR T-cell therapy—including their indications and nursing implications.

Oncolytic viral immunotherapy Vaccines, which take advantage of the body's defensive cell-mediat-

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LEARNING OBJECTIVES

1. Identify the difference between chemotherapy and immunotherapy.
2. Differentiate three types of immunotherapy treatment: oncolytic viral immunotherapy, checkpoint inhibitors, and chimeric antigen receptor T-cell therapy.

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ed immunity response, have been developed as prophylactic treatment to prevent cancer-causing viruses—such as human papillomavirus and hepatitis B—but their use in treating malignancies is still evolving.

Cancer treatment vaccines work by stimulating T cells (usually CD8 positive or helper CD4 positive cells) and enabling them to recognize and act against specific cancer types or by inducing the production of antibodies that bind to molecules on the surface of cancer cells. Cancer vaccines are composed of weakened or killed cancer cells that carry a specific cancer antigen or an immune cell that's modified to act as an antigen. These cells can be autologous (come directly from the patient) or allogenic (from another person).

Indications

In 2010, the U.S. Food and Drug Administration (FDA) approved the use of sipuleucel-T for treating resistant metastatic prostate cancer. The vaccine is created by drawing the patient's blood and then isolating certain immune cells identified within it. That blood is then fused with an immune-cell stimulator in the laboratory and infused back into the patient.

Another FDA-approved oncolytic virus is talimogene laherparepvec—a genetically modified version of the herpes simplex virus that causes cold sores. The vaccine is administered directly into the melanoma lesion, which causes the cells to rupture and die. Several oncolytic viral agents are currently in clinical trials.

Nursing implications

The most common side effects from cancer vaccine therapy are inflammatory responses at the injection site, such as erythema, pain, edema, heat, rash, and pruritus. Other potential adverse events include flulike symptoms, low-grade fever, nausea,

Making a block

Checkpoint inhibitors block the mechanism of action of tumor cells, allowing T cells to kill the tumor cells.

Immune checkpoint	Mechanism of action that the immune checkpoint blocks
Programmed cell death protein (PD-1)	PD-1 exists on tumor cells. Binding of PD-L1 to PD-1 prevents T cells from killing tumor cells in the body.
Programmed death ligand 1 (PD-L1)	PD-L1 exists on T cells, preventing them from killing tumor cells.
Cytotoxic lymphocyte-associated molecule-4 (CTLA-4)	CTLA-4 exists on T cells, which bind to CD80 and CD86, preventing them from killing tumor cells.

vomiting, myalgia, headache, and fatigue. Because vaccines produce immune-mediated responses, the risk of a hypersensitivity reaction exists and should be considered a medical emergency.

While administering these vaccines, adhere to hazardous drug safe-handling principles. Personal protective equipment, including gloves and gowns, is required. And make sure you're familiar with your organization's guidelines for administering immunotherapy.

Checkpoint Inhibitors

Checkpoint inhibitors are among the newest agents used in cancer therapy. In a healthy human, the immune system has the innate ability to identify foreign cells and attack them while safeguarding normal tissue. Cancer cells take advantage of abnormalities that cause decreased expression of checkpoint proteins and manipulate the body's natural defensive response so they can continue to proliferate.

Recent literature discusses the concept of microsatellite instability (MSI). Cancer cells in tumors with an MSI-high (MSI-H) status have a greater than normal number of genetic markers called microsatellites, which are short, repeated sequences of DNA that may relate to defects in the cells' ability to correct

mistakes that take place when DNA is copied. This defect is most frequently found in colorectal cancer, but other types of GI cancer and endometrial cancers may have MSI-H. This can put the patient at a higher risk of other cancers and also may be relevant for genetic testing of immediate family members.

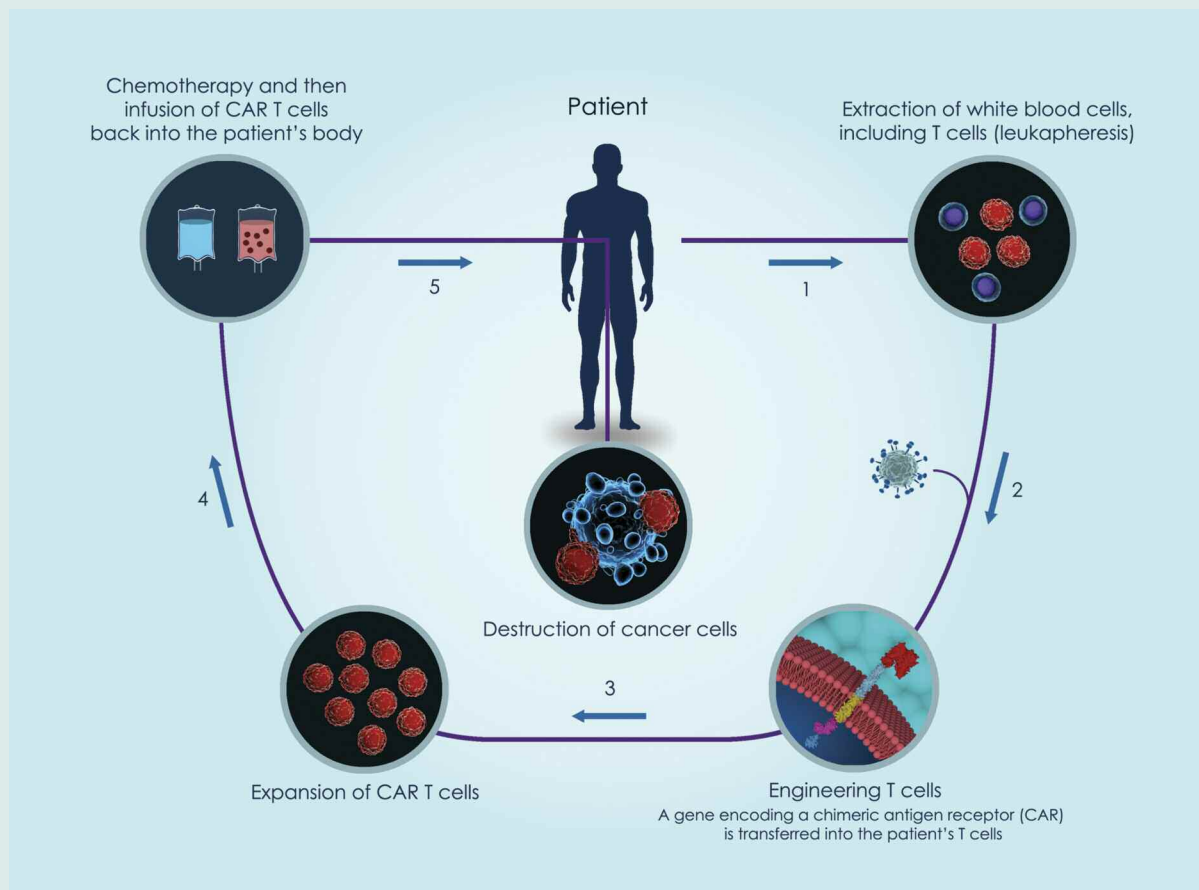
Preliminary data suggest that patients with MSI-H status cancers (which means they have high mutational tumor burden) are more likely to respond to checkpoint inhibitors. MSI-H tumors also have been shown to respond to anti-programmed cell death protein (PD-1) checkpoint inhibitors.

Immune checkpoint inhibitors approved by the FDA include atezolizumab, avelumab, durvalumab, ipilimumab, nivolumab, and pembrolizumab. These agents use different mechanisms to inhibit different checkpoints, although they're all T-cell suppressors (T-cell agonists). For example, ipilimumab is a monoclonal antibody that inhibits cytotoxic T lymphocytes. It binds to cytotoxic lymphocyte-associated molecule-4 (CTLA-4) proteins CD80 and CD86 ligands, blocking the CTLA-4 pathway and enhancing T-cell proliferation and antitumor effects. Nivolumab and pembrolizumab work on PD-1 and atezolizumab targets the programmed death ligand 1 (PD-L1). When PD-1 is bound to

CAR T-cell process

The image below outlines the steps of the chimeric antigen receptor (CAR) T-cell process.

Leukapheresis, a type of apheresis, is the process of removing the patient's whole blood and then separating the white blood cells to be manufactured into a CAR T-cell therapy CD19 infusion. The remaining blood is instilled back into the body through an apheresis catheter that's placed before the procedure. The sessions last about 3 to 4 hours, and the patient can usually return home after treatment.*



*The American Society for Apheresis, which was established in 1982, partners with providers, nurses, and allied health professionals to educate and establish qualifications for this rapidly growing field. Apheresis certification requires formal classroom instruction and training in the use of an apheresis machine. In addition, nurses in training shadow an expert nurse in the care of apheresis patients.

the PD-L1 ligand, it produces an immune response and antitumor effects. (See *Making a block.*)

Indications

Current indications for checkpoint inhibitors include melanoma, non-small cell lung cancer, renal and bladder cancer, Hodgkin's lymphoma, and head and neck cancer. The FDA indications for these agents are rapidly evolving, and new indications continue to be added to the

National Comprehensive Cancer Network Guidelines and Compendia. For patients who have cancers that aren't currently FDA approved for treatment with checkpoint inhibitors, individual drug companies may offer them via compassionate use. However, their use is up to the treating oncologist's discretion.

Nursing implications

Unlike conventional chemotherapy, checkpoint inhibitors stimulate T

cells, which elicits an inflammatory reaction in healthy organs. This, in turn, can cause inflammatory side effects, particularly in the GI tract (for example, colitis), endocrine glands (for example, pancreatitis, thyroid dysfunction, adrenal insufficiency), skin (for example, dermatitis, pruritis), and liver (for example, hepatitis).

Many of these toxicities may be mild, requiring only a short course of steroids, but severe toxicity may

CAR T-cell therapy toxicities

Patients receiving chimeric antigen receptor (CAR) T-cell therapy may experience these toxicities.

Cytokine release syndrome

Rapid proliferation of T cells can cause cytokine release syndrome, an inflammatory response that ranges from mild to severe. Signs and symptoms include fever, chill, myalgia, and tachycardia. In more severe responses, hypotension, dyspnea, and neurotoxicity, such as confusion or seizures, can occur.

Management includes I.V. fluids, electrolyte replacement, and opioids as needed. Uncontrolled coagulopathy may occur, so partial thromboplastin time, prothrombin time, international normalized ratio, and fibrinogen laboratory tests should be checked, followed by administration of fresh frozen plasma or platelets as needed.

Closely monitor intake and output while administering fluid boluses to prevent pulmonary edema. Oxygen and vasopressors may be needed. Administering methylprednisolone may solve the patient's problems clinically, but its use may block T-cell activation and reverse CAR T-cell therapy.

Tumor lysis syndrome

Laboratory results of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia indicate tumor lysis syndrome (TLS). TLS occurs when byproducts from rapid tumor lysis build up in the bloodstream, which can cause blockage in the renal tubules and subsequent acute kidney injury. If blood work shows the presence of oliguria or an increase of 0.3 mg/dL in creatinine, notify the provider immediately.

Daily labs with electrolytes are helpful, although the provider may need to increase the frequency of blood work monitoring to ensure electrolyte interventions are working. Allopurinol combined with I.V. hydration inhibits the production of uric acid, preventing renal tubule blockages. In already established TLS, rasburicase converts uric acid in the body to allantoin, a molecule that's five to 10 times more soluble in urine than uric acid.

Neurologic symptoms

Neurologic symptoms related to CAR T-cell therapy toxicity include confusion, B-cell aphasia, unresponsiveness, and seizures due to encephalopathy. Perform neurologic exams at least once per shift. To treat seizures, the provider may order anti-seizure medications, such as levetiracetam. B-cell aphasia may occur when CD19-positive cells are killed by the CAR T-cell therapy, causing hypogammaglobulinemia. (CD19 is a B-cell surface protein expressed throughout B-cell development and expressed in nearly all B-cell malignancies, such as chronic lymphocytic leukemia, acute lymphocytic leukemia, and many non-Hodgkin lymphomas.) This can be treated with I.V. immunoglobulin therapy, reorientation, and hydration.

Graft-versus-host disease

Graft-versus-host disease (GVHD) can present as diarrhea or a skin rash. It typically reveals itself 2 to 3 weeks after hematopoietic stem cell transplant once engraftment has taken place. Topical triamcinolone creams, which are less likely to be absorbed systemically, are permitted to treat skin rashes, but a discussion with the medical team should occur because systemic steroids that suppress the immune system aren't indicated with CAR T-cell therapy.

If a patient is status postautotransplantation and CAR T-cell therapy, he or she will be hospitalized for at least 30 days because of severe immunosuppression. If the patient received only CAR T-cell therapy, he or she may be released to home and should receive education about what signs and symptoms to report to the nurse or provider. In addition, instruct patients to inform their local emergency department of their transplant history, medical history, and CAR T-cell therapy to ensure proper precautions, including safe handling of hazardous drugs, are taken and that the patient is triaged appropriately.

require emergent treatment, including hospitalization and consultation with a specialist. The American Society of Clinical Oncology has released a guideline with recommendations for managing toxicities from immune checkpoint inhibitors based on grade of toxicity (ascopubs.org/doi/full/10.1200/JCO.2017.77.6385).

Side effects can occur at any time throughout treatment, and because patients typically are on these therapies for prolonged periods, ongoing monitoring is vital. Early detection (through patient assessment and laboratory testing) and prompt treatment are critical to managing checkpoint inhibitor toxicities.

Teach patients and family members about the potential toxicities, and stress the importance of notifying all healthcare providers that the patients are being treated with checkpoint inhibitors. Patients should carry a wallet card that lists the agents they are receiving. In addition, instruct patients to contact their oncology team if they experience any side effects.

Chimeric antigen receptor T-cell therapy

The revolutionary CAR T-cell therapy, which targets CD19 antigen through a specified immune response, has been used to treat patients with relapsed acute lymphoblastic leukemia (ALL).

In a healthy body, both T and B cells are active in maintaining a healthy immune system. When CAR T-cell therapy is administered, the immune antigens identify B cells that express CD19 and activate an immune response. However, the therapy can't yet differentiate between B cells infected with malignancy and healthy B cell antigen. This results in death of all B cells, which can lead to toxicity and side effects.

Memorial Sloan Kettering Cancer Center, University of Pennsylvania, National Cancer Institute, and Fred Hutchinson Cancer Research Center

CAR T-cell therapy has significant *risk*, but the treatment response rate is impressive.

enrolled 158 subjects of varying ages with B-cell ALL in their CAR T-cell therapy trials. The results revealed 134 complete responses (disappearance of all areas of disease), an 85% response rate. This is a significant tumor response, especially since ALL in pediatric patients is considered incurable. About 33% of the 134 subjects at these cancer centers have reported relapses. Research is ongoing to discover why the relapses occurred and how those who are still in remission have maintained their health.

Indications

CAR T-cell therapy has significant risk, but the treatment response rate is impressive, so the FDA granted approvals for adult and pediatric patients with relapsed refractory B-cell ALL, as well as patients with relapsed refractory diffuse large B-cell lymphoma.

Nursing implications

CAR T-cell therapy is a multistep process. (See *CAR T-cell process*.) Before initiating the CAR T-cell therapy, a certified nurse must perform leukapheresis to harvest white blood cells. After harvesting the cells, the process of engineering the CART-19 can take up to 3 weeks. In the meantime, patients begin lymphodepleting chemotherapy (such as cyclophosphamide and fludarabine) to control the disease.

About 1 week after chemotherapy administration, the CAR T-cell therapy is introduced. Patients are premedicated with acetaminophen and diphenhydramine to prevent or lessen potential toxicities. Some facilities require an overnight hospital stay to monitor patients, especially if they acquire a fever as an immune response. Continuous monitoring is required to ensure safety precautions are met, so it's not surprising that this therapy is administered only at large medical centers that participate in active oncology research or have a bone marrow

transplantation unit. A lower nurse-to-patient ratio is vital to ensure adequate monitoring.

The most common toxicities seen with CAR T-cell therapy are cytokine release syndrome (CRS), neurologic symptoms, graft-versus-host disease, and tumor lysis syndrome (TLS). Both CRS and TLS are oncologic emergencies, but they present differently. (See *CAR T-cell therapy toxicities*.) Although nursing interventions for immunologic oncologic emergencies are similar in the care of patients receiving CAR T-cell therapy, vital signs should be taken every 4 hours and labs (including electrolytes) should be drawn at least once a day.

The future of CAR T-cell therapy is evolving as long-term results, side effects, and efficacy have not yet been determined. Researchers also are developing a new approach to this therapy by determining if harvesting CD19 antibodies from healthy donors would be more beneficial than the current process of harvesting from the patient. Research also is being conducted in solid tumor studies to determine the efficacy of engineering a "super T cell" to override the immune suppressor genes in advanced solid tumors.

Evolving treatment

The advent of immunotherapy and targeted/novel agents is changing oncology care. Immunotherapy has given hope and longer survival benefits to oncology patients. The rapid evolution of these treatments means that nurses and other health-care professionals must stay abreast of research updates so they can communicate treatment options—including indications, toxicities, and self-care—to their patients. ★

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Please mark the correct answer online.**1. Which statement related to chemotherapy and immunotherapy is correct?**

- Immunotherapy helps T cells to better distinguish cancer cells from healthy cells.
- Chemotherapy helps T cells to better distinguish cancer cells from healthy cells.
- Common side effects of immunotherapy include mouth sores, nausea, and vomiting.
- Common side effects of chemotherapy include rash and liver inflammation.

2. Cancer treatment vaccines work by

- stimulating B cells.
- depressing B cells.
- stimulating T cells.
- depressing T cells.

3. Sipuleucel-T is approved by the Food and Drug Administration (FDA) for

- initial treatment of prostate cancer.
- treatment of resistant metastatic prostate cancer.
- treatment of advanced melanoma.
- initial treatment of melanoma.

4. The most common side effects of cancer vaccine therapy are

- hyposensitivity reactions.
- hypersensitivity reactions.
- systemic inflammatory responses.
- inflammatory responses at the injection site.

5. Which statement about administering cancer treatment vaccines is correct?

- They are not toxic, so personal protective equipment (PPE) is not required.
- They have minimal toxicity, so only gloves are needed.
- The only PPE required is eye protection, such as goggles.
- PPE, including gowns and gloves, are required.

6. Which of the following is a genetically modified oncolytic virus approved for treating melanoma?

- Ipilimumab
- CGTLA-4 protein
- Talimogene laherparepvec
- Atezolizumab

7. Which statement about microsatellite instability (MSI) is correct?

- Microsatellites are short, repeated sequences of DNA that may relate to defects in the cells' ability to correct mistakes that take place when DNA is copied.
- Microsatellites are long, isolated sequences of DNA that may relate to defects in the cells' ability to correct mistakes that take place when DNA is copied.
- MSI-high (MSI-H) status is most frequently found in endometrial cancer.
- MSI-H status is most frequently found in lung cancer.

8. The checkpoint inhibitor nivolumab works by

- binding to CTLA-6 proteins CD60 ligands.
- binding to CTLA-1 proteins CD70 ligands.
- targeting the programmed cell death protein (PD-1).
- targeting the programmed cell death protein (PD-2).

9. Which statement about the side effects of checkpoint inhibitors is correct?

- Side effects can occur at any time throughout treatment.
- Side effects occur only during the initial phase of treatment.
- Checkpoint inhibitors directly damage healthy cells.
- Checkpoint inhibitors rarely cause an inflammatory reaction.

10. Chimeric antigen receptor (CAR) T-cell therapy

- targets CD4 antigen through a generalized immune response.
- targets CD19 antigen through a specified immune response.
- kills only B cells affected by malignancy.
- kills only T cells affected by malignancy.

11. Which statement about leukapheresis is correct?

- A session lasts about 3 to 4 hours.
- A session lasts about 20 to 30 minutes.
- Red blood cells are separated from whole blood cells.
- The patient needs to be hospitalized for 24 hours.

12. Your patient who is receiving CAR T-cell therapy reports fever, chill, myalgia, and tachycardia. You suspect the patient is experiencing

- cytokine lysis reaction.
- graft-versus-host disease.
- cytokine release syndrome.
- tumor lysis syndrome.

13. Which of the following is the likely cause of the increased creatinine in your patient receiving CAR T-cell therapy?

- cytokine lysis reaction.
- graft-versus-host disease.
- cytokine release syndrome.
- tumor lysis syndrome.

14. Which of the following is most likely to indicate that your patient receiving CAR T-cell therapy is experiencing tumor lysis syndrome?

- Hypouricemia
- Hypokalemia
- Hypercalcemia
- Hyperkalemia