CONTINUING EDUCATION

EDUCATIONAL OBJECTIVES

After participating in this activity, clinicians should be better able to

- Identify the components of the immune system
- Describe the mechanism of action of various immunotherapies
- List the names and indications of currently used immunologic agents.

Disclosure of Conflicts of Interest

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Kathy Boltz, PhD	No financial relationships to disclose

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STATEMENT OF NEED/PROGRAM OVERVIEW

Oncology nurses are aware of the increasing number of immunotherapeutic agents under development, and they need to keep their knowledge of these emerging treatments up-to-date. In addition, research continues to provide more clear explanations of how the body's natural defenses can be activated to prevent and cure cancer. This activity will review the components of the immune system, explain the mechanism of action of immunotherapies, and describe currently available immunotherapeutic agents. After refreshing their own understanding of immunotherapies, nurses can explain to patients how these treatments are used with greater confidence.

FACULTY

Kathy Boltz, PhD
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LEARNING GOAL/PURPOSE

To better understand how cancer immunotherapies use the body's natural defenses to identify and kill cancer cells.

NURSING CREDIT

Medical Education Resources is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

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METHOD OF PARTICIPATION

There are no fees for participating in and receiving credit for this activity. During the period August 2014 through August 2015, participants must 1) read the learning objectives and faculty disclosures, 2) study the educational activity, 3) complete the posttest by selecting the best answer to each question on the posttest, 4) complete the evaluation form, and 5) continue to next section to claim credits and view your certificate.

A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed posttest with a score of 70% or better. Statements of credit are available at the conclusion of the activity.

MEDIA

Journal article and Web site (myCME.com; OncologyNurseAdvisor.com)

Co-provided by Medical Education Resources and Haymarket Media Inc.

TARGET AUDIENCE

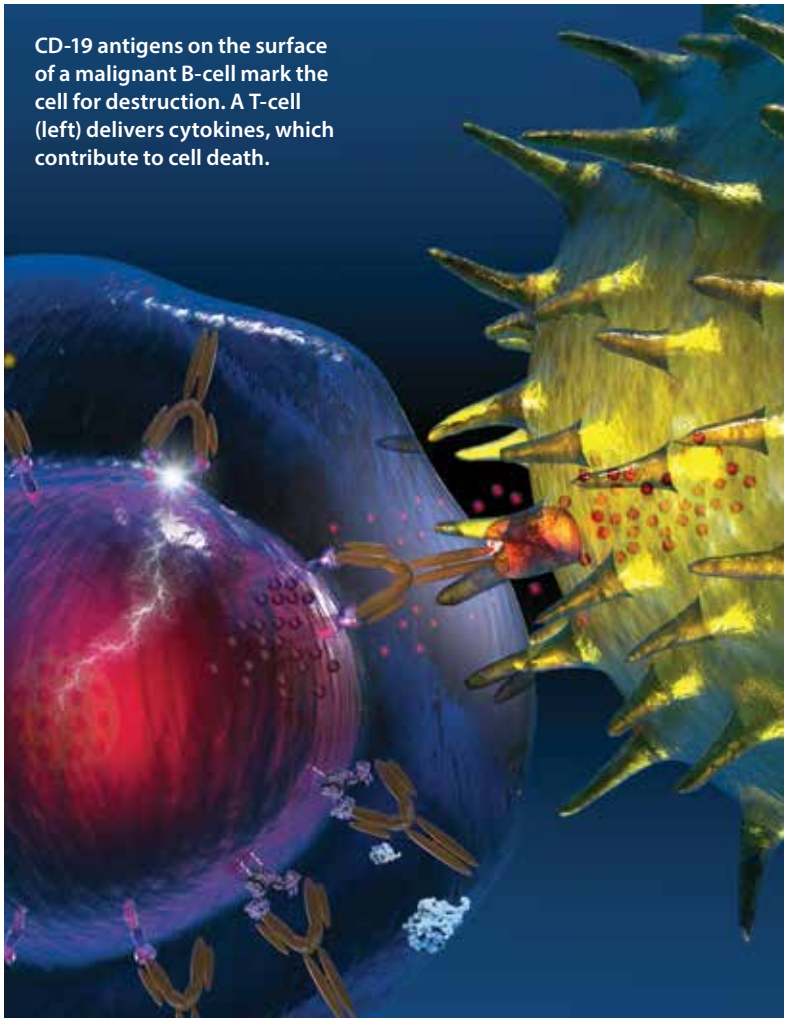
- This activity has been designed to meet the educational needs of registered nurses and nurse practitioners involved in the management of patients with cancer.

PROGRAM INFORMATION

- **Estimated time to complete this activity:** 1 hour
- **Release date:** August 2014
- **Expiration date:** August 2015

How the immune system is unleashed to fight cancer

Cancer cells hide from the body's natural defenses. This overview explains how immunotherapeutic strategies expose cancer cells to the immune system.



CD-19 antigens on the surface of a malignant B-cell mark the cell for destruction. A T-cell (left) delivers cytokines, which contribute to cell death.

KATHY BOLTZ, PHD

Strategies that unleash the immune system to attack cancer cells are being developed at a rapid pace. Maintaining an up-to-date understanding of the immune system and an awareness of new immunotherapies and changing indications for existing ones is essential to providing effective cancer care. This article aims to increase oncology nurses' knowledge of immunotherapies.

Cancer immunotherapy involves using the body's own immune system to fight cancer. Cancer cells avoid detection and elimination by the immune system, and so engaging the immune system against cancer is difficult. Foreign cells such as bacteria have proteins on their surface not normally found in the human body; however, cancer cells are more similar to normal cells and have fewer clear differences from normal cells. This makes it difficult for the immune system to recognize cancer cells as foreign. Immunotherapy treatments often seek to make cancerous cells more obvious to the immune system.

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The immune system has two parts, known as the innate and adaptive immune systems. These systems differentiate between pathogens and self. They create an immune response against antigens, which are any substance that raises an immune response.

The innate immune system is diverse. Its components include physical barriers such as skin and mucosal membranes; effector cells that include macrophages, natural killer (NK) cells, innate lymphoid cells, dendritic cells, mast cells, neutrophils, and eosinophils; pattern recognition mechanisms such as Toll-like receptors; and humoral mechanisms that include complement proteins and cytokines.[1] Cytokines are a complex group of proteins that are produced when the immune system is activated.[2] They allow immune cells to communicate and coordinate their attack on antigens. Cytokines include interleukins, interferons, and colony-stimulating factors, among others.

The innate immune system works rapidly and is usually characterized by tissue inflammation. It uses repeated patterns to recognize pathogens and employs a variety of effector mechanisms to respond quickly. One of its roles is to initiate the adaptive immune system.

The adaptive immune system consists of T and B cells. In contrast to the innate immune system, the adaptive system responds more slowly but is more specific. The adaptive immune system includes B cells, which produce thousands of highly targeted antibodies once activated; regulatory T cells, which provide checks on the activity of the immune system so it does not damage healthy cells; CD4+ helper T cells, which direct and support specialized cells such as B cells and CD8+ killer T cells; CD8+ killer T cells, which can each kill thousands of harmful cells; and antibodies, which seek and bind to antigen proteins. The innate immune system also creates memory of an antigen, which is important for cancer immunotherapy because it can decrease metastasis and limit the occurrence of a second malignancy.[3]

The innate immune system is linked to the adaptive immune system through dendritic cells.[3] When the innate immune system is activated, the dendritic cells travel to nearby lymph nodes and present antigen to T cells, activating them. When the dendritic cell presents an antigen, the response to that antigen depends on the microenvironment where the dendritic cell found the antigen. Ultimately, T cells are responsible for cell-mediated immune responses, which are considered the most important mechanism used by the immune system to kill solid tumors.[3]

CANCER VACCINES

Knowledge of how dendritic cells work has led to sipuleucel-T, which is based on ex vivo (cultured outside the body) activated dendritic cells. A patient's monocytes, a precursor of dendritic cells, are incubated with a fusion protein that links the target antigen, Prostatic Acid Phosphatase, to a cytokine known as granulocyte-macrophage colony-stimulating factor (GM-CSF). This fusion protein drives the monocytes to mature into dendritic cells. The target antigen causes the activated dendritic cells to produce an immune response against the prostate cancer. Sipuleucel-T was approved by the US Food and Drug Administration (FDA) to treat patients with metastatic prostate cancer. In a randomized, controlled trial, sipuleucel-T improved median survival by 4.1 months, compared with placebo.[4]

MONOCLONAL ANTIBODIES

Monoclonal antibodies are now standard of care for a number of tumor types. Antibodies are proteins that bind to a specific antigen. Monoclonal antibodies are designed to recognize very specific antigens on certain types of tumor cells. Monoclonals circulate in the body until they find and attach to the antigen. Once attached, some monoclonal antibodies work by attracting other immune system cells that destroy the cells containing the antigen; others block tumor antigens or molecules that promote the survival of tumors.[3,5]

Commonly used monoclonal antibodies include trastuzumab (Herceptin), which targets HER2 and is FDA-approved for the treatment of breast cancer and metastatic gastric cancer; and rituximab, which targets CD20 and is FDA-approved for non-Hodgkin lymphoma and chronic lymphocytic leukemia (CLL). Trastuzumab's target, the HER2 protein receptor, can be expressed in large amounts on the surface of some cancer cells, where it helps the cells to grow. When trastuzumab binds to the HER2 receptor, it inactivates the receptor. Antibodies such as trastuzumab and rituximab are known as *naked monoclonal antibodies,* meaning they do not have a drug or radioactive material attached to them. Most naked monoclonal antibodies work through antibody-dependent cell-mediated cytotoxicity (ADCC), in which natural killer cells recognize those cells coated with antibodies and kill them.

By blocking checkpoints, the cancer is less able to suppress the immune system, and the immune system can more effectively fight the cancer.

Monoclonal antibodies can have a chemotherapy drug, toxic agent, or radioactive material attached to them. Ado-trastuzumab emtansine (TDM-1; Kadcyla) received FDA approval in 2013 for the treatment of metastatic HER2-positive breast cancer in patients who failed prior therapy with trastuzumab and a taxane.[1] This antibody-drug conjugate adds the potent

microtubule-disrupting drug DM1 to trastuzumab—in other words, a targeted delivery of chemotherapy to cells that overexpress HER2.[6] Also in 2013, brentuximab vedotin (anti-CD30-MMAE [monomethyl auristatin E]; Adcetris) was approved by the FDA for the treatment of relapsed or refractory Hodgkin lymphoma or anaplastic large cell lymphoma.[1] This drug uses the brentuximab antibody to target CD30, which has limited expression in healthy tissue but is expressed by Hodgkin lymphoma and anaplastic large cell lymphoma. Brentuximab vedotin delivers MMAE, a cytotoxic agent that causes cell death by apoptosis.[7]

An example of a monoclonal antibody with a radioactive particle attached is ibritumomab tiuxetan (Zevalin). Ibritumomab tiuxetan is an antibody against CD20 with yttrium-90 attached. It is FDA-approved for the treatment of refractory non-Hodgkin lymphoma.[1] CD20 is expressed on the surface of lymphocytes, including the cancer cells of patients with non-Hodgkin lymphoma. The radiation enhances the killing effect of the antibody.

NONSPECIFIC IMMUNOTHERAPIES AND ADJUVANTS

Various immunotherapy strategies target cancer cells nonspecifically, stimulating the immune system in a more general way.[8] These include immunomodulatory drugs such as thalidomide (Thalomid), lenalidomide (Revlimid), pomalidomide (Pomalyst), and imiquimod (Aldara, Zyclara, generics). Another immunotherapy strategy is the live attenuated virus Bacille Calmette-Guerin; this virus is used in the treatment of the bladder.

All immune reactions involve cytokines, and several nonspecific cancer immunotherapy strategies use cytokines.[9] Cytokines interact in complex ways to provide homeostasis and immune control through positive and negative feedback mechanisms.

Interleukin-2 is a type of cytokine that leads to the growth of T lymphocytes. It was FDA-approved for the treatment of advanced renal cell carcinoma in 1992 and for metastatic melanoma in 1998; but its toxicity limits its use to patients with excellent organ function.[2] It had an objective response rate of 16% in 270 melanoma patients, and the 6% of patients who achieved complete response had a durable response. Its toxicities include fever, chills, myalgias, diarrhea, nausea, anemia, thrombocytopenia, hepatic dysfunction, myocarditis, confusion, and a predisposition to infection; but these effects are dose-dependent, largely predictable, and reversible. Interleukin-2 can only be used at well-established treatment centers with clinicians experienced in administering interleukin-2 therapy. At high doses, interleukin-2 is given in the inpatient setting.

Another type of cytokine is interferons, which were discovered in the 1950s.[2] Analyses of high-dose interferon-alfa use in melanoma cases found a consistent benefit for high-risk patients with melanoma, as it improved relapse-free survival by 13% to 18% and overall survival by 10% to 11%. Notably, interferon is difficult to tolerate, and its toxicity limits its use and often leads to treatment discontinuation. Predominant side effects include myelotoxicity, elevation of liver enzymes, nausea, vomiting, flulike symptoms, and neuropsychiatric symptoms. Interferon-alfa is only recommended for patients with a risk of relapse greater than 30%. It is FDA-approved for hairy cell leukemia, chronic myelogenous leukemia, follicular non-Hodgkin lymphoma, cutaneous T-cell lymphoma, kidney cancer, melanoma, and Kaposi sarcoma.

Granulocyte-macrophage colony-stimulating factor (GM-CFS) is another cytokine that stimulates the immune system. GM-CSF boosts white blood cells after chemotherapy, and is FDA-approved to help increase the number and function of white blood cells after bone marrow transplantation.[10] GM-CFS is indicated for cases of bone marrow transplantation failure or engraftment delay, before and after peripheral blood stem cell transplantation, and following induction chemotherapy in older patients with acute myelogenous leukemia. Patients taking GM-CSF have commonly experienced fever, liver-associated events, skin-associated events, infection, nausea, metabolic disturbances, and diarrhea.

TARGETING IMMUNE SYSTEM CHECKPOINTS

Much recent excitement in oncology has been generated by cancer immunotherapy approaches that target immune system checkpoints. When a T cell interacts with an antigen-presenting cell, the downstream T cell responses are affected by both costimulatory and coinhibitory signals. Coinhibitory signals include cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death receptor-1 (PD-1), along with programmed death receptor ligand-1 and -2 (PD-L1 and PD-L2). Strategies targeting these inhibitory signals are potentially very powerful because cancer exploits these checkpoints to grow unchecked. Blocking these checkpoints unblocks the immune system, and current results indicate that it is producing durable responses. An important challenge with these treatments is that the unchecked immune system results in immune-related adverse events (irAEs).

By blocking the checkpoints, the cancer is less able to suppress the immune system, and then the immune system can more effectively fight the cancer. Treatments targeting these immune checkpoints are being investigated for solid tumors, melanoma, renal cell cancer, non-small cell lung cancer, hepatocellular carcinoma, prostate cancer, glioma, glioblastoma multiforme, pancreatic cancer, triple-negative breast cancer, gastric cancer, urothelial cancer, head and neck cancers, and colorectal cancer.[11]

The first FDA-approved treatment that blocks immune checkpoints was ipilimumab (Yervoy). Ipilimumab is a monoclonal antibody to CTLA-4 indicated for the treatment of metastatic melanoma, based on a phase III trial in which ipilimumab increased median overall survival by 3.6 months, to 10.0 months

TABLE 1. Immunological reagents against cancer

Immunotherapy	Mechanism/target	Indications
Antibody-drug conjugates		
Brentuximab vedotin (Adcetris)	Targets CD30 with the cytotoxic agent MMAE	Anaplastic large cell lymphoma, Relapsed or refractory Hodgkin lymphoma
Trastuzumab emtansine (Kadcyla)	HER2 receptor	HER2+ metastatic breast cancer
Antibody-radioparticle conjugate		
Ibritumomab tiuxetan (Zevalin)	Targets CD20 with yttrium-90 attached	Refractory non-Hodgkin lymphoma
Cancer vaccine		
Sipuleucel-T (Provenge)	Culture dendritic cells to target the antigen prostatic acid phosphatase	Metastatic prostate cancer
Cytokines		
Granulocyte-macrophage colony-stimulating factor (Leukine)	Stimulates immune system	• Before and after peripheral blood stem cell transplantation • Bone marrow transplantation failure or engraftment delay • Following induction chemotherapy in older patients with acute myelogenous leukemia
Interferon-alfa	• Activates JAK-STAT pathway • Modulates function of natural killer cells and T cells • Activates distribution of cellular subsets • Induces pro-apoptosis genes	Chronic myelogenous leukemia, Cutaneous T-cell lymphoma, Follicular non-Hodgkin lymphoma, Hairy cell leukemia, Kaposi sarcoma, Kidney cancer, Melanoma
Interleukin-2	Increased T lymphocytes	Advanced renal cell carcinoma, Metastatic melanoma
Immunomodulatory drug		
Thalidomide (Thalomid)	Augment natural killer cell cytotoxicity Increase interleukin-2 secretions	Newly diagnosed multiple myeloma
Monoclonal antibodies		
Bevacizumab (Avastin)	Vascular endothelial growth factor	Breast cancer, Colorectal cancer, Non-small cell lung cancer
Cetuximab (Erbitux)	Epidermal growth factor receptor	Colorectal cancer, Head and neck cancer
Ipilimumab (Yervoy)	Blockades CTLA-4 for immune checkpoint blockade	Metastatic melanoma
Rituximab (Rituxan)	CD20 B-cell surface antigen	Chronic lymphocytic leukemia, Non-Hodgkin lymphoma
Trastuzumab (Herceptin)	HER2 receptor	HER2+ breast cancer, HER2+ metastatic gastric cancer

instead of the 6.4 months for patients who did not receive the agent.[12] Of interest with CTLA-4 blockades, complete tumor regression for a prolonged duration occurred in most of the few patients who achieved complete tumor regression.[13] However, 10% to 15% of patients treated with ipilimumab in the first phase III trial experienced severe or life-threatening toxicity. The irAEs most commonly experienced were diarrhea, enterocolitis, hepatitis, dermatitis, and endocrinopathies. These typically occurred several weeks into the course of treatment. Also, patients who experienced refractory or severe irAEs required immunosuppressants, increasing their risk for opportunistic infections.

Combining ipilimumab with GM-CSF resulted in improved overall survival in a recent phase II study with 245 patients with metastatic melanoma. The median overall survival was 17.5 months with the combination versus 12.7 months with ipilimumab alone.[14] The 1-year survival rates were 68.9% with the combination and 52.9% with ipilimumab alone. These results suggest synergy between the two treatments. The combination resulted in fewer grade 3-5 adverse events in the combination arm (45% of patients) than in the ipilimumab alone arm (58% of patients).

Recent reports have described combining ipilimumab with nivolumab, an antibody against the immune checkpoint PD-1. A small phase III trial of this combination in 53 patients with advanced melanoma resulted in a 2-year survival rate of 75%.[15] More than half (62%) of the patients experienced grade 3 or 4 adverse events, with the most common ones being elevated levels of lipase, aspartate aminotransferase, and alanine aminotransferase.[15,16] These rates of adverse events were higher than the rates with either treatment alone. Notably, the majority of the patients had durable responses.

Monoclonal antibodies targeting PD-L1 are also in development.[13] These, as with the other checkpoint inhibitors, are being tested against a variety of tumors, including non-small cell lung cancer, melanoma, colorectal cancer, renal cell carcinoma, ovarian cancer, pancreatic cancer, and breast cancer.

New approaches are being developed to measure response to checkpoint blockades because response measures that are appropriate for chemotherapeutic treatments, such as new lesions indicate progressive disease, are not appropriate for checkpoint blockades.[13] Checkpoint blockades are immunomodulatory antibodies that can cause an apparent worsening of the disease before the disease ultimately stabilizes or tumors regress. Responses can take a long time to become apparent; for example, the average time to achieve a complete response to ipilimumab in one long-term study was 30 months.[17] In addition, prolonged periods of stable disease can occur in patients who do not meet the criteria for an objective response. Efforts are ongoing to develop alternative response criteria, known as immune-related response criteria.[18]

ADOPTIVE CELLULAR THERAPY

Another area of active research is the use of adoptive T cell therapy.[3] T cells are stimulated outside the body and then, once activated, reinfused into patients. T cells used for this type of therapy can include tumor infiltrating lymphocytes (TILs), which are engineered to express a cancer-specific T cell receptor, and T cells engineered to express a chimeric antigen receptor (CAR). The CAR has both the extracellular portion of an antibody and the T cell receptor signaling machinery. Notably, TILs require high-dose interleukin-2, which comes with significant toxicity. The CAR approach also has potential toxicity, but offers promise, such as for chronic lymphoid leukemia, where the engineered cells stayed at high levels in the blood and bone marrow for 6 months and remission was ongoing at 10 months.[19]

THE FUTURE IN IMMUNOTHERAPY

Cancer immunotherapies such as the monoclonal antibodies rituximab and trastuzumab are now familiar in the clinic. New and emerging treatments that harness the immune system to fight cancer offer options where previous choices were poor until recently, particularly for melanoma. These therapies are being tested in many types of cancer, and they offer hope for durable responses. ■

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