Cancer Immunotherapy

An evidence-based overview and implications for practice

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BACKGROUND: Significant research progress has been made in immunotherapies since the mid-1990s, and this rapid evolution necessitates evidence-based education on immunotherapies, their pathophysiology, and their toxicities to provide safe, effective care.

OBJECTIVES: The aim of this article is to provide an evidence-based overview, with implications for practice, of checkpoint inhibitors, monoclonal antibodies, oncolytic viral therapies, and chimeric antigen receptor T-cell therapies.

METHODS: Each immunotherapy category is presented according to the pathophysiology of its immune modulation, the classes of agents within each category, evidence-based toxicities associated with each class, and implications for practice.

FINDINGS: Immunotherapies vary in their pathophysiology and offer potential to be highly effective for the management of a wide array of cancer types. Understanding the unique pathophysiology and toxicities is necessary to assess, manage, and provide safe, effective patient-focused care.

KEYWORDS
immunotherapy; monoclonal antibodies; pathophysiology; toxicities

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IMMUNOTHERAPY IS AN APPROACH TO CANCER TREATMENT, management, and cure developed on the pathophysiologic foundations of harnessing a patient's own immune system to fight diverse cancer types (Farkona, Diamandis, & Blasutig, 2016). Although the concept of immunotherapy has been researched for more than a century, discoveries have more recently led to the development of new classes of agents. This article presents the pathophysiology, target cancer types, and toxicities of four major categories of immunotherapies: checkpoint inhibitors, chimeric antigen receptor (CAR) T-cell therapy, monoclonal antibodies, and oncolytic viral therapies (Farkona et al., 2016). As clinical trials provide insight into the efficacy of these agents and broader populations of patients have access to immunotherapy-based treatments, an urgent need exists for comprehensive education for nurses on this content to empower safe, evidence-based care of patients undergoing these treatment modalities.

Checkpoint Inhibitors

Pathophysiology

In a healthy body, the immune system has internal regulatory mechanisms that enable immune cells to identify abnormal cells that need to be attacked while protecting normal tissue. Cancer cells take advantage of abnormalities that cause decreased expression of checkpoint proteins that would otherwise keep tumors from developing (Trivedi et al., 2015). Malignant cells learn to evade these mechanisms, enabling them to multiply, like cloaking themselves in a disguise. Drugs that prevent cancer cells from using these pathways are called checkpoint inhibitors and are among the newest agents used to treat cancer (Trivedi et al., 2015).

These drugs prevent the abnormal cells from bypassing the immune response, removing their disguise, and flagging them for destruction by activated T cells. So far, three known checkpoint pathways have been identified and can be acted upon with targeted treatments (Collin, 2016). These checkpoints maintain a balance, making the immune system able to fight infections and malignancies, while concurrently preventing tissue injury (Bockorny & Pectasides, 2016). The U.S. Food and Drug Administration (FDA) has approved four different checkpoint inhibitors (see Table 1),

specifically ipilimumab (Yervoy®), nivolumab (Opdivo®), pembrolizumab (Keytruda®), and atezolizumab (Tecentriq®), each of which uses a different mechanism to inhibit different checkpoints. Known immune checkpoints that can be targeted by these drugs are cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1) (Peterson & Steele-Moses, 2016).

CTLA-4 pathways suppress T-cell activation by binding to *ligands*, molecules that bind to other molecules. When this pathway is blocked, an increase of T-cell formation occurs that has an antitumor effect. PD-1 has a controlling effect on the T cells in the peripheral tissues. When PD-1 is bound to its ligands, PD-L1 and programmed death-ligand 2 inhibit pathways that produce an effective defense against tumors. Blocking these pathways enhances the antitumor response (Carlo, Voss, & Motzer, 2016). Introducing a checkpoint inhibitor drug boosts the immune system to attack these cells before they reach a certain point in response (Becze, 2016; Peterson & Steele-Moses, 2016). These new therapies have been shown to be effective in fighting cancer and offer new treatment options for patients (Peterson & Steele-Moses, 2016).

Targeted Cancer Types and Toxicities

Checkpoint inhibitors have been tested in the treatment of diverse, primarily solid tumor cancer types. The wide range of diseases affected is because of the general T-cell impact of the agents. When activated, healthy cells can be affected, leading to side effects in various organ systems related to exacerbation of the inflammatory response caused by the immune system. Some common toxicities include fatigue, colitis, pneumonitis, dermatitis, and hepatitis. Although most toxicities are mild and can be managed easily with a course of steroids, some can require emergent management and hospitalization. For toxicities that are refractory to initial steroid treatment, antitumor necrosis factor agents may be required (Friedman, Proverbs-Singh, & Postow, 2016; Peterson & Steel-Moses, 2016). These patients may require specialist consultations to assist with the management of these toxicities (Friedman et al., 2016).

"The understanding of how antibodies target cancer cells has helped to revolutionize the methods used to treat cancer."

Implications for Nursing Practice and Patient Education

Checkpoint inhibitors have presented a new challenge to oncology nurses caring for patients receiving these treatments. The ability of these treatments to cause immune-related adverse events emphasizes the need for focused assessments, including laboratory tests and physical or psychiatric assessments (Peterson & Steel-Moses, 2016). Careful monitoring of laboratory tests at intervals deemed appropriate by the clinician, including thyroid panel, pituitary function test, liver function test, and pancreatic enzymes, is needed for early detection of potential gland and organ toxicity.

Patients may present with atypical symptoms attributed to checkpoint inhibitor therapy. For example, psychiatric assessments should include questions about mood changes and alteration in sleep patterns secondary to drug-induced hypothyroidism

TABLE 1.
CHECKPOINT INHIBITORS BY CLASS

CHECKPOINT	FDA-APPROVED AGENTS	USED TO TREAT	IMMUNE-RELATED ADVERSE EVENTS
CTLA-4	Ipilimumab (Yervoy®)	Melanoma	Rash, pruritus, diarrhea (colitis), hepatitis, endocrinopathies, neurotoxicity, pancreatitis, hematologic toxicity
PD-1	Nivolumab (Opdivo®)	Non-small cell lung cancer, melanoma, renal cell carcinoma, Hodgkin lymphoma	Diarrhea (colitis), hepatitis, endocrinopathies, pneumonitis, pancreatitis
PD-1	Pembrolizumab (Keytruda®)	Non-small cell lung cancer, melanoma, squamous cell carcinoma of the head and neck	Vitiligo, hepatitis, endocrinopathies, pneumonitis, pancreatitis, diarrhea (colitis)
PD-L1	Atezolizumab (Tecentriq®)	Bladder cancer, non-small cell lung cancer	Fatigue, nausea, loss of appetite, pruritus, rash, diarrhea (colitis), endocrinopathies

CTLA—cytotoxic T-lymphocyte-associated; FDA—U.S. Food and Drug Administration; PD—programmed death; PD-L—programmed death-ligand
Note. Based on information from Becze, 2016; Friedman et al., 2016; Peterson & Steele-Moses, 2016; Rosenberg et al., 2016.

or hyperthyroidism. Physical assessments should include additional monitoring for changes in weight, fatigue, and pain.

When patients are preparing to initiate treatment with any checkpoint inhibitor, they should be educated, in detail, about potential toxicities, how to care for themselves, and when and how to contact their treating physician about exacerbation of baseline symptoms and development of new ones. Education should include standards of best practice for patients receiving antineoplastic treatments, including infection control, good hand hygiene, hydration, safe sexual practices, and intact skin integrity. Patients should be aware of food and beverages that can exacerbate gastrointestinal symptoms and avoid those irritants. The patient should notify the treating physician of any new medications or dietary supplements before staring checkpoint inhibitor therapy.

Chimeric Antigen Receptor T-Cell Therapy

Pathophysiology

CARs are synthetic, genetically engineered receptors consisting of signal domains and an extracellular recognition domain derived from murine or humanized monoclonal antibodies (Maus, Grupp, Porter, & June, 2014). The first CAR was conceived and developed in 1989, leading to increased interest in adoptive cellular therapies and advancement in the field (Gross, Waks, & Eshhar, 1989; Tasian & Gardner, 2015). CARs are customized receptors composed of an extracellular antigen-binding domain targeting antigens expressed on malignant cells (Shalabi, Angiolillo, & Fry, 2015). The engagement of a CAR with the target antigen leads to intracellular signaling and resultant proliferation of the CAR T cells through a costimulatory domain (Tasian & Gardner, 2015). Trials with successful CARs contain a costimulatory domain that results in improved T-cell proliferation and persistence (Maude, Teachey, Porter, & Grupp, 2015). Phase 1 and 2 CAR T-cell trials are ongoing, with the goal of obtaining FDA approval in 2017.

CAR T-cell therapy is a form of targeted immunotherapy that uses tumor-specific antigen recognition. The principle advantage of this therapy is the ability of the T cells to expand and go after target cells, along with the potential for surveillance through T-cell memory (Singh, Frey, Grupp, & Maude, 2016). With CART-19 therapy, cluster of differentiation (CD) 19 is the target antigen. This antigen is expressed on the majority of acute lymphoblastic leukemia cases and is highly expressed throughout B-cell development, from the early pro-B cell stage through mature B cells, and is not expressed on stem cells (Maude, Barrett, Teachey, & Grupp, 2014). For these reasons, the CD19 antigen is an excellent target for relapsed and refractory acute lymphoblastic leukemia (ALL). CART-19 cells are T cells that express genetically engineered CARs that allow the T cells to attack cells expressing the CD19 antigen (Maude, Shpall, & Grupp, 2014). CART-19 therapy is a novel targeted immunotherapy with the benefits of targeting a specific antigen on a tumor cell, potential for proliferating in the patient, and potential for long-term persistence for disease surveillance.

Because CD19 is expressed on the normal B cell, CART-19 therapy eradicates nonmalignant B cells in addition to the leukemic cells, resulting in the expected side effect of B-cell aplasia. Unfortunately, CARs cannot distinguish between a normal cell expressing the antigen and a malignant cell. B-cell aplasia results in hypogammaglobulinemia, which is treatable with immunoglobulin replacement therapy (Grupp, 2014).

Once the T lymphocytes are collected from the patient, they undergo the manufacturing process. This includes genetic modifications of the T cells using a lentiviral vector, which leads to the T cells expressing the CAR that recognizes the B-cell antigen CD19. Following genetic modification, the CAR T cells are expanded in the laboratory. Once the CAR T cells are infused into the patient, they engage with cells expressing the CD19 antigen, leading to activation of the T cell and resulting in T-cell proliferation and expansion, tumor killing, and T-cell persistence (Maude, Shpall, & Grupp, 2014).

Another targeted antigen for B-cell ALL is CD22. A clinical trial for this target is open and accruing patients (https://clinicaltrials.gov/show/NCT02315612). Ongoing research continues for future targeted immunotherapies for leukemia and other malignant diseases.

Indication

CART-19 therapy is being evaluated in clinical trials for individuals with relapsed and refractory CD19 positive B-cell malignancies, including ALL and B-cell lymphoma. Cytokine release syndrome (CRS) is the most common toxicity of CAR T-cell therapy and is experienced to some degree by the majority of all patients receiving therapy (Maude, Shpall, & Grupp, 2014). The range of symptoms accompanying this inflammatory process (CRS) may be mild to moderate, with fever, myalgias, fatigue, nausea, and headache, to more severe CRS, with hypotension and capillary leak. Neurotoxicities, including seizures and encephalopathy, are also possible (Maude, Shpall, & Grupp, 2014).

Implications for Nursing Practice and Patient Education

CAR T-cell therapy has the potential to offer treatment for patients who have relapsed or refractory ALL, who would otherwise have limited options. Because of the growing popularity of this therapy, nurses will require education so that they can provide the best possible care to patients. Nursing interventions and assessment of therapy complications are profound responsibilities with this new therapy. Nursing interventions during CAR T-cell infusions include administering premedications, monitoring vital signs pre- and post-CAR T-cell infusions, and monitoring for allergic reactions. Post-CAR T-cell infusion nursing assessment of complications can range from routine outpatient nursing management to more complex management in the inpatient and

TABLE 2.
MONOCLONAL ANTIBODIES BY CLASS

DISEASE PRIMARILY TREATED	FDA-APPROVED AGENTS FOR CANCER	SIDE EFFECT PROFILE (MOST COMMON)	DRUG CLASS
Adenocarcinoma of the stomach or gastroesophageal junction	Ramucirumab (Cyramza®)	Hypertension, neutropenia, fatigue, stomatitis	Human monoclonal antibody
Bone metastasis	Denosumab (Xgeva®)	Hypocalcemia, osteonecrosis (jaw)	Human monoclonal antibody
Breast cancer	Trastuzumab (Herceptin®)[1,2], ado-trastuzumab emtansine (Kadcyla®)[1,2], bevacizumab (Avastin®)[3,4,5], pertuzumab (Perjeta®)	Cardiac toxicity[1], pulmonary toxicity[2], arterial/venous thromboembolus[3], hypertension[4], progressive multifocal leukoencephalopathy[5], endocrinopathies, acute infusion reactions, skin reactions, neutropenia, diarrhea, fatigue	Humanized monoclonal antibody
Cervical, ovarian, or fallopian cancer	Bevacizumab[1,2,3]	Cardiac toxicity, pulmonary toxicity, arterial/venous thromboembolus[1], hypertension[2], progressive multifocal leukoencephalopathy[3], endocrinopathies, acute infusion reactions, skin reactions, neutropenia, diarrhea, fatigue	Humanized monoclonal antibody
Colorectal cancer	Bevacizumab[2,3,4], cetuximab (Erbitux®)[1], panitumumab (Vectibix®), ramucirumab (Cyramza®)	Cardiac toxicity, pulmonary toxicity[1], arterial/venous thromboembolus[2], hypertension[3], progressive multifocal leukoencephalopathy[4], endocrinopathies, acute infusion reactions, skin reactions, neutropenia, diarrhea, fatigue	Includes human, humanized, and chimeric monoclonal antibodies
Glioblastoma	Bevacizumab	Arterial/venous thromboembolus, hypertension, progressive multifocal leukoencephalopathy, acute infusion reactions, skin reactions, neutropenia, diarrhea, fatigue	Humanized monoclonal antibody
Head and neck cancer	Cetuximab[1]	Cardiac toxicity, pulmonary toxicity[1], arterial/venous thromboembolus, hypertension, progressive multifocal leukoencephalopathy, endocrinopathies, acute infusion reactions, skin reactions, neutropenia, diarrhea, fatigue	Chimeric monoclonal antibody
Head and neck squamous cell cancer	Nivolumab (Opdivo®)[1], pembrolizumab (Keytruda®)	Cardiac toxicity, pulmonary toxicity, arterial/venous thromboembolus, hypertension, progressive multifocal leukoencephalopathy, endocrinopathies[1], acute infusion reactions, skin reactions, neutropenia, diarrhea, fatigue	Includes human and humanized monoclonal antibody
Kidney cancer	Bevacizumab[1,2,3], nivolumab[4]	Arterial/venous thromboembolus[1], hypertension[2], progressive multifocal leukoencephalopathy[3], endocrinopathies[4], acute infusion reactions, neutropenia, diarrhea, fatigue	Includes human and humanized monoclonal antibody
Leukemia	Rituximab (Rituxan®)[1,2], blinatumomab (Blincyto®)[1,2,3], alemtuzumab (Campath®)[1,2], obinutuzumab (Gazyva®), ofatumumab (Arzerra®), gemtuzumab (Mylotarg®)	Cytokine release syndrome[1], tumor lysis syndrome[2], neurotoxicities[3], mucositis, hepatitis B reactivation, immunosuppression, fatigue, nausea, diarrhea, shortness of breath, neutropenia, dermatitis, peripheral edema	Includes human, humanized, murine, and chimeric monoclonal antibodies
Lymphoma	Rituximab[1,2], alemtuzumab (Lemtrada®)[1,2], nivolumab[3], obinotuzumab (Gazyva®), tositumomab (Bexxar®), brentuximab vedotin (Adcetris®), ibritumomab tiuxetan (Zevalin®)	Cytokine release syndrome[1], tumor lysis syndrome[2], neurotoxicities[3], mucositis, hepatitis B reactivation, immunosuppression, fatigue, nausea, diarrhea, shortness of breath, neutropenia, dermatitis, peripheral edema	Includes human, humanized, murine, and chimeric monoclonal antibodies
Melanoma	Ipilimumab (Yervoy®)[1,2], nivolumab[2], pembrolizumab	Enterocolitis[1], endocrinopathies[2], acute infusion reactions, skin reactions, neutropenia, diarrhea, fatigue	Includes human and humanized monoclonal antibodies

Continued on the next page

TABLE 2. *(CONTINUED)*
MONOCLONAL ANTIBODIES BY CLASS

DISEASE PRIMARILY TREATED	FDA-APPROVED AGENTS FOR CANCER	SIDE EFFECT PROFILE (MOST COMMON)	DRUG CLASS
Multiple myeloma	Daratumumab (Darzalex®), elotuzumab (Empliciti™)	Cytokine release syndrome, tumor lysis syndrome, neurotoxicities, mucositis, hepatitis B reactivation, immunosuppression, fatigue, nausea, diarrhea, shortness of breath, neutropenia, dermatitis, peripheral edema	Includes human and humanized monoclonal antibodies
Neuroblastoma	Dinutuximab (Unituxin®)	Capillary leak syndrome, sepsis, severe hypotension, infusion-related reaction, severe thrombocytopenia	Chimeric monoclonal antibody
Non-small cell lung cancer	Bevacizumab[1,2,3], nivolumab[4], pembrolizumab, atezolizumab (Tecentriq®), ramucirumab, necitumumab (Portrazza®)	Cardiac toxicity, pulmonary toxicity, arterial/venous thromboembolus[1], hypertension[2], progressive multifocal leukoencephalopathy[3], endocrinopathies[4], acute infusion reactions, skin reactions, neutropenia, diarrhea, fatigue	Includes human and humanized monoclonal antibodies
Sarcoma	Olaratumab (Lartruvo™)	Nausea/vomiting, diarrhea, fatigue, musculoskeletal pain, mucositis, lymphopenia, neutropenia	Human monoclonal antibody
Urothelial carcinoma	Atezolizumab	Acute infusion reactions, skin reactions, neutropenia, diarrhea, fatigue	Humanized monoclonal antibody

FDA—U.S. Food and Drug Administration
Note. Toxicities that were primarily associated with particular agents are indicated by numbered superscripts within the row. The remaining toxicities may occur with any agents in the row.
Note. Based on information from El Miedany, 2015; FDA, 2016; Pandey & Mahadevan, 2014.

intensive care unit (ICU) settings. Outpatient nursing management includes physical assessments and monitoring for fever, infection, pain, nausea, fatigue, and other adverse effects. Laboratory assessment includes monitoring for cytopenia and organ toxicities.

Nursing care for inpatients can be more complex and range from nursing management of patients with febrile neutropenia or neurotoxicities to management of patients with severe CRS requiring ICU-level care. Nurses are well positioned to notice a critical change in patient status and can collaborate with the multidisciplinary team to manage acute and chronic complications of CAR T-cell therapy. This includes appropriate supportive care interventions and ongoing patient and family education. In some settings, CART-19 infusions may be performed in an outpatient setting rather than in a hospital. Best clinical practice includes requiring patients to reside within proximity to the hospital and to come to the clinic for frequent monitoring. The need for surveillance for treatment side effects is a shared responsibility between the healthcare providers and patients and their caregivers. Building a trusting relationship with the caregivers and providing education, support, and a method for communication is essential to ensure patient safety and successful treatment.

Monoclonal Antibodies

Pathophysiology

The idea that scientists would be able to provide a "magic bullet" to eliminate cancer by using antibodies has existed for more than a century (Pandey & Mahadevan, 2014). Because of the various targets of antibodies, several mechanisms of action help to destroy the cancer cells. Those mechanisms include inhibiting tumor cell survival cascades, inhibiting tumor growth by interfering with tumor angiogenesis, evading programmed cell death, and evading immune checkpoints, thereby inhibiting tumor growth. The body's natural response to antigens helped lead to the "creation of cell lines capable of producing a single antibody class, the monoclonal antibody" (El Miedany, 2015, p. S5). Monoclonal antibodies are substances that have the capability to act as a naturally made antibody within the human body but are created to target a specific antigen. Some monoclonal antibodies are being used in combination with radiation in the targeting of specific cancer cells, and others use inflammatory cytokine and tumor invasion to destroy cancer tumors (Pandey & Mahadevan, 2014). The understanding of how antibodies target cancer cells has helped to revolutionize the methods used to treat cancer and resulted in a more tolerable toxicity profile than standard chemotherapy.

Targeted Cancer Types and Toxicities

The different classes of monoclonal antibodies are derived from various types of cells: murine (derived from mice) and chimeric (derived from mice and a human immunoglobulin). Humanized monoclonal antibodies are mostly human antibodies with only small loops derived from mice; the human monoclonal antibodies are wholly human-derived antibodies (El Miedany, 2015). A list of monoclonal antibodies, FDA-approved agents, commonly treated malignancies, and frequently reported toxicities is in Table 2.

Implications for Nursing Practice and Patient Education

Adverse reactions to monoclonal antibodies are most often experienced by treatment-naive patients. Although an acute infusion reaction is rare, when it does occur, its severity can range from a fever to anaphylaxis. That is why patient education is important for nurses caring for patients being treated with a monoclonal antibody. The symptoms should be reported by the patient and treated promptly, often requiring the use of steroids (Pandey & Mahadevan, 2014). Many of the side effects reported are seen throughout most of these agents, and others are specific for a

TABLE 3.
ONCOLYTIC VIRAL IMMUNOTHERAPIES BY CATEGORY

CATEGORY	FDA-APPROVED AGENTS	USED TO TREAT[a]	SIDE EFFECT PROFILE
Pathogenic genetically modified double-stranded DNA virus: herpes simplex virus	Talimogene laherparepvec (Imlygic®)	Metastatic melanoma, squamous cell carcinoma, breast cancer, rectal cancer, head and neck cancer	Immune-mediated: fever, malaise, chills, nausea, vomiting, headache, elevated liver enzymes, injection site pain, autoimmune vitiligo
Pathogenic genetically modified double-stranded DNA virus: adenovirus	Under development in early animal and human trials	Glioblastoma, ovarian cancer, hepatocellular carcinoma, pancreatic cancer, colorectal cancer, neuroendocrine cancer, squamous cell carcinoma, melanoma, leiomyosarcoma, salivary cancer	Immune-mediated: fever, malaise, injection site pain
Nonpathogenic negative-stranded RNA virus: Newcastle disease virus	Under development in early animal and human trials	Cervical cancer, melanoma, breast cancer, colon cancer, squamous cell carcinoma	Immune-mediated: fever, myalgia, hypotension
Pathogenic double-stranded RNA virus: reovirus	Under development in early animal and human trials	Ovarian cancer, breast cancer, lung cancer, colon cancer, osteosarcoma, malignant gliomas, head and neck cancer	Well tolerated, side effects no different than chemotherapeutic toxicities with taxols alone
Nonpathogenic picornavirus: Seneca Valley virus	Under development in early animal and human trials	Neuroendocrine cancer, neuroblastoma, rhabdomyosarcoma, small-cell lung cancer	Well tolerated
Pathogenic genetically modified double-stranded DNA virus: vaccinia	Under development in early animal and human trials	Melanoma, prostate	Immune-mediated: fever, malaise, chills
Pathogenic genetically modified single-stranded RNA virus: polio	Under development in early animal and human trials	Glioblastoma	Unknown
Pathogenic genetically modified negative-stranded RNA virus: measles	Under development in early animal and human trials	Glioblastoma, thyroid cancer, head and neck cancer, multiple myeloma, lymphoma, ovarian cancer, prostate cancer	Well tolerated
Pathogenic genetically modified negative-stranded RNA virus: vesicular stomatitis virus	Under development in early animal and human trials	Glioblastoma, pancreatic cancer, melanoma, prostate cancer, colorectal cancer, breast cancer, liver cancer	Neurotoxicity
Nonpathogenic single-stranded DNA virus: parvovirus	Under development in early animal and human trials	Glioblastoma	Unknown
Nonpathogenic poxviridae virus: myxoma virus	Under development in early animal and human trials	Glioblastoma	Unknown
Pathogenic genetically modified positive-stranded RNA virus: Sindbis virus	Under development in early animal and human trials	Glioblastoma	Unknown
Nonpathogenic pig alphaherpesvirus: pseudorabies	Under development in early animal and human trials	Glioblastoma	Unknown

[a] All are investigational, except talimogene laherparepvec for metastatic melanoma, which is FDA-approved.
FDA—U.S. Food and Drug Administration; OVI—oncolytic viral immunotherapy
Note. Based on information from Eager & Nemunaitis, 2011; Masouel et al., 2013; Murphy et al., 2012; Wollman et al., 2012.

particular monoclonal antibody. Because these toxicities differ from what is experienced with traditional chemotherapy, patients should know that these reactions can be masked as common symptoms that they may not associate with treatment (e.g., diarrhea with monoclonal antibodies may be related to monoclonal antibody–induced colitis). These symptoms should not be ignored; effective, prompt communication between the patients and their healthcare providers is imperative. Most of the symptoms will not self-resolve and must be treated quickly to prevent more severe side effects. Lastly, the patients should be reminded that good hand hygiene and infection prevention are important because the immune system may easily become compromised, depending on the mechanism of action of the monoclonal antibody (Pandey & Mahadevan, 2014).

Insufficient data exist that discuss the safety risks for healthcare professionals administering monoclonal antibodies. However, nurses who are involved in the administration of monoclonal antibodies are potentially exposed to these agents through direct contact, such as exposure to contaminated body fluids (King et al., 2016). In addition, many of the monoclonal antibodies are expected to be licensed for administration by subcutaneous administration, which will increase the risk of exposure to nurses. Unlike traditional chemotherapies, monoclonal antibodies do not have direct cytotoxic activity; however, they can exert cytotoxic effects (King et al., 2016). Regulators disagree on proper handling of these agents because much remains to be discovered in their mechanism of action and long-time exposure effects. In the interim, healthcare professionals should wear at least single gloves when handling monoclonal antibodies (Meade, 2015).

Oncolytic Viral Immunotherapy

Pathophysiology

Oncolytic viral immunotherapy (OVI) is a viral targeted therapy that directly kills cancer cells by causing tumor death, producing tumor-toxic cytokines or antitumor host immune responses (see Table 3). Two types of OVIs are nonpathogenic (harmless to humans) and pathogenic (requiring genetic modification for use) (Prestwich et al., 2008).

Four mechanisms of action are thought to exist with OVIs: viral cell receptor response, cytokine release, nuclear replication, and extracellular immune responses. Viral cell receptor responses target viral-specific cell surface receptors that are overexpressed in cancer cells. Cytokine release is seen with double-stranded RNA viruses that cause antiviral cellular activation of cytokines that promote apoptosis. Nuclear replication of cancer cells can be disrupted by certain double-stranded DNA viruses that have been genetically modified to target tumor DNA synthesis. Extracellular immune responses or antitumor host immune responses are activated with the introduction of specific viruses working "synergistically" to kill cancer cells (Wollmann, Ozduman, & van den Pol, 2012).

IMPLICATIONS FOR PRACTICE

- Recognize that immunotherapy is a current and evolving treatment for diverse cancer types and is a part of personalizing cancer care.
- Be aware that immunotherapies differ by their pathophysiology and have unique toxicities that differ from traditional chemotherapies that are used more commonly in oncology practices.
- Understand the different categories of immunotherapeutic agents, as well as their common toxicities, to inform safe, evidence-based nursing practice when caring for patients undergoing these treatments.

Targeted Cancer Types and Toxicities

Oncolytic viral immunotherapies are being investigated in clinical trials across a wide array of cancer types. The only FDA-approved agent is talimogene laherparepvec (TVEC) (Imlygic®) for intralesional injection of metastatic melanoma. Hoffner, Iodice, and Gasal (2016) provide additional information about TVEC administration and mechanisms of action.

Implications for Nursing Practice and Patient Education

Nursing considerations for safe handling of oncolytic viruses begin with administration. Typically, physicians or advanced practice practitioners will administer OVIs in the clinical setting. However, a case can be made for nurses to administer superficial intralesional injections adhering to safe infection-control administration guidelines. Some institutions in which OVIs are administered may recommend that patients who receive OVIs be placed on contact isolation postinjection to minimize the risk for passing viral infection to others. Pregnant healthcare providers should not administer OVIs, and patients should avoid immunocompromised populations, such as small children and older adults (Hoffner et al., 2016). Antiviral medication should be avoided during treatment, unless an uncontrolled infection exists.

If dressing changes are required near a site of OVI injections, strict infection-control precautions should be used. Standard personal protective equipment (PPE), such as gloves and gowns, should be used. All used and soiled dressings should be discarded in a biohazard container. Special consideration should be given to patient and caregiver education to minimize the risk for infection. PPE should be provided or ordered, and, if a biohazard container is not available, discarded dressings should be bagged, sealed, and thrown out per usual.

Be sure to maintain material safety data sheets or drug information in patient care areas. If an accidental spill occurs, use hospital-grade virucidals to clean the area. If splashback occurs, flush or wash the exposed area with water for 15 minutes and watch for signs and symptoms of viral infection, which can include common cold symptoms, gastrointestinal upset, rash, and redness to exposed areas. Patients, caregivers, and healthcare providers should be assessed for exposure and followed up with for possible viral transmission via polymerase chain reaction testing if symptomatic (Lion, 2014).

Conclusion

As immunotherapies continue to transition from clinical trials to the standard of care for some cancers, nurses must be knowledgeable about the diverse categories and classes of agents in this field and deliver safe, effective, and evidence-based care to their patients. Nurses' most important roles in the immunotherapy evolution are safe administration of these agents and patient education. Nurses should also be a voice for high-quality cancer care and play an active role in policy decisions surrounding this novel therapy (Kennedy Sheldon, 2016). The articles in this supplement will present evidence-based and clinically informed approaches to the management of patients across the lifespan, including strategies for nursing education, preparation of clinical settings to provide immunotherapy and deliver focused care to patients receiving these therapies, algorithms to guide toxicity management, and guidelines for safe handling and administration of these agents to protect patients and healthcare providers.

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