Immunotherapy in Pediatric Oncology

An overview of therapy types and nursing implications

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BACKGROUND: By using the body's own protective system to fight cancer, immunotherapy is not only effective but also is associated with fewer side effects than chemotherapy.

OBJECTIVES: This article provides an overview of four types of immunotherapy (monoclonal antibodies, chimeric antigen receptors, immune checkpoint inhibitors, and cancer vaccines) and discusses the critical role assumed by nurses in the care of patients receiving immunotherapy.

METHODS: A review of the literature was undertaken to identify, describe, and compare the types of immunotherapy used and studied for use in pediatric oncology.

FINDINGS: Nurses caring for pediatric patients with cancer may have little experience with immunotherapy. However, they should become knowledgeable about it, particularly as it becomes further integrated into pediatric cancer treatments.

KEYWORDS
neoplasm; pediatric nursing; molecular targeted therapy; immunotherapy

DIGITAL OBJECT IDENTIFIER
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ONE OF THE EARLIEST DOCUMENTED USES OF IMMUNOTHERAPY was in 1891, after American cancer surgeon and researcher William B. Coley observed disease regression in a young man with sarcoma following a strep infection (Ginex, Brassil, & Ely, 2017). Coley then devoted the rest of his career to the study of immunotherapy, specifically whether intentionally infecting the body with bacteria could stimulate the immune system to treat cancer (Ginex et al., 2017). Much of today's research on immunotherapy is devoted to its use in adults. However, interest in immunotherapy in pediatric patients has grown exponentially, particularly when it is used as an adjuvant therapy with standard cancer treatments (Shah & Goldberg, 2015). Immunotherapy was listed as one of the seven next great achievements in pediatric research (Cheng, Bogue, & Dover, 2017). In addition, the U.S. Food and Drug Administration (FDA) has approved a number of immunotherapy drugs for pediatric use (Shah & Goldberg, 2015).

Cancer immunotherapy can be defined as several treatment strategies that aim to optimize the immune system to fight disease while minimizing autoimmune toxicity (Shah & Goldberg, 2015). Unlike chemotherapy, immunotherapy targets specific cells and spares healthy cells, resulting in substantially fewer side effects. Immunotherapy offers a promising approach for many pediatric malignancies, particularly those no longer responsive to standard cytotoxic therapies (Wayne, Capitini, & Mackall, 2010). This article offers an overview of four immunotherapies in use or being studied for use among pediatric patients with cancer (i.e., monoclonal antibodies [MABs], chimeric antigen receptors, immune checkpoint inhibitors, and cancer vaccines), as well as discusses the significant role nurses play when caring for pediatric patients with cancer undergoing immunotherapy.

Monoclonal Antibodies

MABs are manufactured proteins that have the capability to act as endogenous antibodies and target a specific antigen on a tumor cell (Bayer et al., 2017). MABs can be derived from various types of cells, including murine

(mouse), chimeric (mice/human), humanized (mostly human), or human (fully human) (Bayer et al., 2017). Ideally, the antigen recognized by MABs is highly expressed on the tumor cell but not on healthy cells, reducing the amount of side effects. Because of their relatively low maintenance complexity (they can be readily stored in hospital pharmacies) and their limited production requirements, MABs offer efficacy and convenience (Ceppi, Beck-Popovic, Bourquin, & Renella, 2017).

Mechanism of Action

MABs can act in a variety of ways, but their actions lead to the same result: The immune system recognizes and targets a specific antigen of a tumor cell to induce cell destruction. For MABs to be successful, a specific interaction between the targeted tumor antigen and the expressed antibody on the MAB must be formed (Shah & Goldberg, 2015). This interaction will then result in the death of tumor cells through either a direct or an indirect pathway (Wayne et al., 2010). Indirect mechanisms, including antibody-dependent cell-mediated cytotoxicity and complement-mediated cytotoxicity, work by acting as an alarm system and recruiting the aid of the immune system to the site of the tumor (see Figure 1). However, the use of this indirect pathway for killing requires functional immune effector cells (e.g., cytokines), which are often defective in patients with cancer because of their immunocompromised state (Wayne et al., 2010). MABs that work via direct T-cell–mediated cytotoxicity address this issue by removing the need to rely on a patient's operating immune system (see Figure 2).

A primary example of direct T-cell–mediated cytotoxicity is the use of a biphasic antibody; the biphasic (two-armed) structure allows for simultaneous engagement with cytotoxic T cells and antigens of the target tumor cells (Shah & Goldberg, 2015). In contrast to indirect cytotoxicity, which results in tumor cells being tagged as foreign for destruction by the immune system, direct T-cell–mediated cytotoxicity instantly links the tumor cells to the destructive immune cells. Another example of direct T-cell–mediated cytotoxicity is a conjugated MAB, which is comprised of a MAB and an endogenic antibiotic or toxin that exerts a destructive action directly against a targeted antigen (Shah & Goldberg, 2015).

Clinical Application

MABs are being used as an adjunct therapy in a variety of pediatric cancers. Although only a few have been approved by the FDA, many are in the final stages of clinical trials, and it is anticipated that the uses of MABs in pediatric cancer treatment will only continue to grow as more information about tumor genetics and molecular biology is learned (Wayne et al., 2010).

Denosumab is a human MAB that targets the receptor activator of nuclear factor-kB ligand (RANKL), the signaling process responsible for motility and anchorage-independent growth of osteosarcoma cells (Bishop, Janeway, & Gorlick, 2016).

> **"Immunotherapy offers a promising approach for many pediatric malignancies."**

Dinutuximab is an anti-disialoganglioside 2 (GD2) chimeric antibody that has also shown some success in targeting receptors found on osteosarcoma cells and has revolutionized the treatment for neuroblastoma. GD2 is a molecule on the surface of nearly all neuroblastoma cells, making it an ideal target for immunotherapy (Bartholomew et al., 2016). Dinutuximab has become the poster drug for immunotherapy in treating neuroblastoma via antibody-dependent cell-mediated cytotoxicity. Immunotherapy has also shown great success in treating leukemia and lymphoma with drugs like rituximab, a chimeric anti–B-lymphocyte antigen CD20 MAB, and blinatumomab, a biphasic cluster of differentiation 3 and anti–B-lymphocyte antigen CD19 MAB, which transiently docks T cells with target tumor B cells to promote direct cytotoxicity (Shah & Goldberg, 2015).

Chimeric Antigen Receptors

Chimeric antigen receptor (CAR) T-cell therapy uses purposely altered T cells to more specifically target cancer cells (Bayer et al., 2017). A CAR is an engineered receptor that provides antigen binding and T-cell–activating functions. When a T cell is modified to express a CAR that antagonizes a specific antigen on a tumor cell, the immune system is activated to induce direct cytotoxicity against the malignant tumor cells (Wayne et al., 2010).

Mechanism of Action

T cells are collected from the patient and genetically engineered, with the use of a viral vector, to express a CAR that is specific to an antigen expressed on a tumor cell (Callahan, Baniewicz, & Ely, 2017). Then, the modified T cells are reinfused into the patient with the intention of targeting and destroying all cells that express the tumor marker and proliferating to act as surveillance for any cancer cells that may try to return.

Clinical Application

One type of CAR T-cell therapy targets antigen CD19 (CART-19) and is approved by the FDA for treating relapsed and refractory B-cell leukemia that is positive for the CD19 antigen (Callahan et al., 2017). Because most acute lymphoblastic leukemia is positive

for the CD19 antigen, this treatment offers an improved prognosis for patients. However, with relapse, occasionally leukemia cells will become negative for the CD19 antigen, similar to when bacteria mutates in resistance to antibiotics. In these cases, another tumor marker on B cells (possibly the CD22 antigen) must be targeted instead (Bayer et al., 2017).

Prior to CAR T-cell therapy, bone marrow transplantation was the gold standard of treatment for patients with relapsed or refractory leukemia. Although CAR T-cell therapy is often used as a bridge to a stem cell transplantation, it is increasingly being used as monotherapy because of its highly successfully outcomes. Tisagenlecleucel, also known as CTL019, is the chimeric version of CART-19 that has been approved by the FDA.

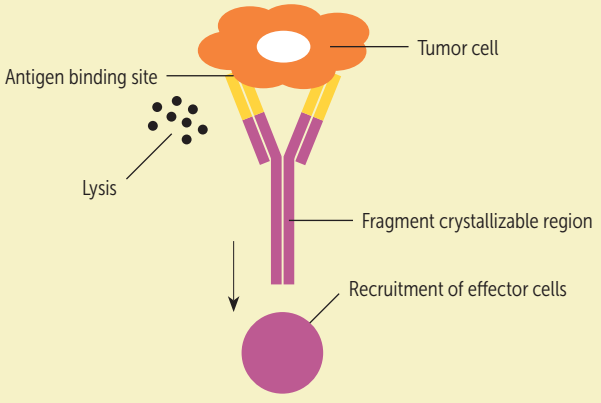
Immune Checkpoint Inhibitors

One reason that cancer is so difficult to treat is because of the ability of cancer cells to employ mechanisms that permit their bypassing of the immune system. In other words, the cancer "hides" from the body and escapes an attack. Immune checkpoint inhibitors are targeted drugs used to block these mechanisms that otherwise allow cancer to remain invisible (Ceppi et al., 2017). More specifically, they prevent T-cell suppression by blocking the cytotoxic T-lymphocyte antigen 4 (CTLA-4), the programmed cell death protein 1 (PD-1), and the PD-1–ligand 1 (PD-L1) pathways, resulting in enhanced antitumor response (Bishop et al., 2016).

Mechanism of Action

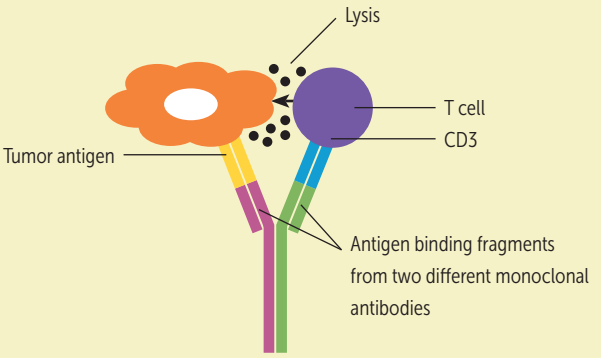
The immune system consists of internal regulatory mechanisms that provide alerts when abnormal cells are detected and need to be attacked (Bayer at al., 2017). Tumor cells can evade these mechanisms, which enables them to survive and multiply. Immune checkpoint inhibitors are drugs that prevent tumor cells from hiding from the immune system. The immune system is then able to recognize tumor cells and flag them for destruction.

FIGURE 1.
ANTIBODY-DEPENDENT T-CELL–MEDIATED CYTOTOXICITY



Note. Monoclonal antibodies that work via indirect pathways rely on a specific interaction to occur between the tumor antigen and the antibody expressed on the monoclonal antibody, leading to the recruitment and activation of immune effector cells.

FIGURE 2.
DIRECT CELL-MEDIATED CYTOTOXICITY



Note. Monoclonal antibodies that work via a direct pathway are able to bypass reliance on the immune system to effectively respond to and link the tumor directly with a T cell to immediately initiate cell death.

Clinical Application

There is still much to learn about this type of immunotherapy, but numerous phase 1 and 2 trials are underway (Lucchesi, Sardi, Puppo, Chella, & Favre, 2017). Immune checkpoint inhibitors may be particularly useful in treating pediatric cancers with a high number of mutations and, consequently, high expression of neoantigens. Single-drug therapy options include nivolumab and pembrolizumab, anti-PD-1 antibodies; ipilimumab, an anti-CTLA-4 antibody, and atezolizumab, an anti-PD-L1 antibody. Nivolumab, pembrolizumab, and ipilimumab are approved by the FDA only for use in adults. However, evidence to support their use in pediatric patients with cancer, specifically those with Hodgkin lymphoma and various brain and solid tumors, is rapidly growing (Ceppi et al., 2017). Combination drug therapy, which couples CTLA-4 and PD-1 blockade agents, also has shown potential in pediatric patients with cancer. However, such therapy may create unintentional autoimmunity in addition to other unknown consequences. This immunotherapy is not yet approved for use in pediatric cancer and requires extensive testing in clinical trials before being approved for use in pediatric patients with cancer (Mahoney, Rennert, & Freeman, 2015).

Cancer Vaccines

A cancer vaccine is an intramuscular vaccine that aims to treat an existing cancer or prevent development of a cancer.

Mechanism of Action

Cancer vaccines are examples of active immunotherapy. They are used to (a) elicit specific antitumor cellular responses by activating T cells (CD4 and CD8) against specific tumor antigens (Shah & Goldberg, 2015) and (b) generate sustained responses to a specific antigen through the formation of immunologic memory (Wayne et al., 2010). However, in pediatric cancers, a patient's ability to mount an active response through his or her immune system may be particularly difficult because of underlying immunosuppression (Rousseau & Brenner, 2005).

Clinical Application

Cancer vaccines are likely to work best as adjuvant therapy in the minimal residual disease setting (when the tumor cell burden is at its lowest) (Rousseau & Brenner, 2005) and are not successful as monotherapy (Shah & Goldberg, 2015). Vaccines in clinical trials include T-cell chemokine lymphotactin and interleukin 2 for neuroblastoma, and irradiated autologous leukemic blasts admixed with fibroblasts expressing the ligand for CD40 or interleukin 2 for high-risk acute lymphoblastic leukemia or acute myeloid leukemia (Rousseau & Brenner, 2005). Although promising, cancer vaccines have a long way to go before FDA approval; limitations surrounding the use of cancer vaccines in pediatrics include a lack of available research, an inability to draw conclusions from clinical trials because of small sample sizes, and the rapid progression of most cancers that would occur if left untreated while a course of vaccination was trialed (Rousseau & Brenner, 2005).

Implications for Nursing

Immunotherapy is an evolving treatment for various pediatric cancers that represents the foundation of individualized care. In addition, immunotherapy has unique toxicities that differ from those of traditional chemotherapies, which most nurses are used to administering.

Monoclonal Antibodies

In general, most MABs are well tolerated and have much less risk of organ toxicity than radiation therapy and chemotherapy.

FIGURE 3.
IMMUNOTHERAPY DRUGS USED OR STUDIED FOR USE IN PEDIATRIC ONCOLOGY

BLINATUMOMAB[a]
- Bispecific MAB, chimeric; CD3 and anti-CD19
- Used to treat leukemia and lymphoma in pediatric patients
- Monitor patient for severe side effects, including CRS, seizures and encephalopathy, tumor lysis syndrome, and transaminitis.

CART-19[b]
- CAR; anti-CD19
- Used to treat CD19-positive relapsed leukemia in pediatric patients
- Instruct patient and family to call about any fever. Monitor patient for signs of CRS. Patients with B-cell aplasia will require monthly immunoglobulin via IV.

DINUTUXIMAB[b]
- MAB, chimeric; anti-GD2
- Used to treat neuroblastoma and osteosarcoma in pediatric patients
- Monitor patient for pain (narcotic bolus prior to infusion with continuous infusion, with or without patient-controlled analgesia), fever (continue acetaminophen every 4–6 hours until the infusion is complete), hypersensitivity reactions (keep hydrocortisone and epinephrine at bedside, and continue with diphenhydramine every 4–6 hours), and capillary leak syndrome (assess for early signs, including peripheral/facial edema, weight gain, respiratory distress, and/or crackles). Intervene with albumin followed by furosemide; obtain daily weights.

IPILIMUMAB[a]
- Immune checkpoint inhibitor; anti-CTLA-4
- Used to treat solid tumors in pediatric patients
- Monitor patient for additional immune-related side effects (neurotoxicity, hematologic toxicity, and progressive multifocal leukoencephalopathy).

NIVOLUMAB[a]
- Immune checkpoint inhibitor; anti-PD-1
- Used to treat Hodgkin lymphoma in pediatric patients
- Monitor patient for additional immune-related side effects (cardiac toxicity, hypertension, and progressive multifocal leukoencephalopathy).

PEMBROLIZUMAB[a]
- Immune checkpoint inhibitor; anti-PD-1
- Used to treat glioblastoma, medulloblastoma, and atypical teratoid rhabdoid tumor in pediatric patients; used off label after CAR T-cell therapy (with evidence of B cells in periphery)
- Monitor patient for additional immune-related side effects (vitiligo).

RITUXIMAB[b]
- MAB, chimeric; anti-CD20
- Used to treat leukemia and lymphoma in pediatric patients
- Monitor patient for B-cell aplasia (which may require long-term immunoglobulin via IV) and viral infections.

TOCILIZUMAB[b]
- MAB, human; anti-interleukin 6
- Used to treat CRS after CAR T-cell therapy
- Monitor patient for transaminitis and neutropenia.

[a] Not approved for use in pediatric oncology
[b] Approved for use in pediatric oncology
CAR—chimeric antigen receptor; CRS—cytokine release syndrome; CTLA-4—cytotoxic T-lymphocyte antigen 4; GD2—disialoganglioside 2; MAB—monoclonal antibody; PD-1—programmed cell death protein 1
Note. Based on information from Bartholomew et al., 2016; Bayer et al., 2017; Ceppi et al., 2017; Wayne et al., 2010.

The most common side effects that nurses should assess for are infusion-related reactions, including fever, headache, and nausea; these are usually mild and self-limiting. MABs that are derived from mice tend to induce more acute reactions compared to those that are more humanized. Most MABs require premedication with acetaminophen and diphenhydramine. Although rare, anaphylaxis is also a possibility, particularly in treatment-naive patients (Bayer et al., 2017). Side effects specific to common MABs are listed in Figure 3.

Chimeric Antigen Receptor T-Cell Therapy

The most important side effect that nurses should assess for when a patient is receiving CAR T-cell therapy is cytokine release syndrome, a systemic inflammatory response produced by elevated levels of cytokines (Smith & Venella, 2017). Cytokine release syndrome occurs when CAR T cells begin to proliferate in the body, and it may be life-threatening. Nurses should be aware of the signs and symptoms of cytokine release syndrome (see Figure 4). Nonspecific markers of inflammation that often correlate with cytokine release syndrome include elevated lactate dehydrogenase, C-reactive protein, and ferritin. Severity can range from mild (a low-grade fever) to severe (pulmonary edema and severe hypotension).

The risk for cytokine release syndrome remains high in the first 10–14 days after CAR T-cell therapy, until inflammation subsides. Cytokine release syndrome severity often correlates with the amount of disease burden prior to CAR T-cell therapy. For example, the higher the minimal residual disease prior to CAR T-cell therapy, the more likely it is that the patient will experience cytokine release syndrome because of the large amount of tumor cell lysis that will occur. However, patients respond to CAR T cells differently; patients with low minimal residual disease may experience severe cytokine release syndrome, whereas patients with high minimal residual disease may experience no symptoms of cytokine release syndrome. In addition, the absence of cytokine release syndrome in a patient does not mean that the CAR T-cell therapy is not working; this information should be shared with the patient and his or her family to reduce any unnecessary stress related to thinking that the therapy has failed.

Although cytokine release syndrome is treatable, close attention must be paid to balance the benefits of treating it with the risk of certain drugs interfering with the efficacy of the CAR T-cell therapy. For example, once patients receive CAR T-cell therapy, they are instructed to avoid steroids because they can decrease (and even destroy) the function of the circulating CAR T cells. However, in the instance of life-threatening cytokine release syndrome, methylprednisolone may be given as a last resort to reduce severe inflammation (Smith & Venella, 2017).

In August 2017, when the FDA approved the chimeric version of CART-19, the use of tocilizumab was also approved for management of severe cases of cytokine release syndrome. Increased interleukin 6 production plays a significant role in the debilitating side effects of cytokine release syndrome. Tocilizumab acts as an interleukin 6 antagonist to block inflammation while sparing the integrity of the CAR T cells. The administration of tocilizumab should be considered if the patient is experiencing severe hypotension (requiring the addition of a second blood pressure medication) or a decline in respiratory status (hypoxia, shortness of breath, tachypnea) that could lead to intubation (Smith & Venella, 2017).

Another common but treatable side effect of CART-19 is B-cell aplasia. Following CAR T-cell therapy and for several years afterward, measuring the patient's peripheral blood for the presence of B cells is used as a pharmacodynamic measure of CART-19 persistence and function (Maude et al., 2014). As long as a patient lacks B cells, he or she will require monthly immunoglobulin via IV; patients may transition from IV administration to subcutaneous immunoglobulin, which can be administered at home biweekly. Subcutaneous immunoglobulin has led to improvements in overall quality of life for patients who are immunoglobulin dependent and has a decreased

FIGURE 4.
SYMPTOMS OF CYTOKINE RELEASE SYNDROME AND THEIR TREATMENT

CAPILLARY LEAKAGE SYNDROME AND PULMONARY EDEMA
- Methylprednisolone
- Oxygen
- Intubation

COAGULOPATHY
- Fresh frozen plasma
- Cryoprecipitate
- Platelets

FEVER, MYALGIA, HEADACHE, ANOREXIA, NAUSEA, AND VOMITING
- Acetaminophen
- Narcotics
- Total parenteral nutrition
- Antiemetics

HYPOTENSION
- IV fluid
- Vasoactives
- Tocilizumab

RENAL DYSFUNCTION
- Renal dosing of medications
- Dialysis

Note. Nursing assessment for all symptoms should consist of daily obtaining of weights, frequent taking of vital signs, daily obtaining of laboratory values (electrolytes, hepatic function, coagulation factors, C-reactive protein, lactate dehydrogenase, and ferritin), and monitoring for tumor lysis syndrome.
Note. Based on information from Smith & Venella, 2017.

IMPLICATIONS FOR PRACTICE

- Become familiar with immunotherapy for use in pediatric oncology as an emerging therapy that offers a novel alternative to chemotherapy.
- Understand the various types of immunotherapy and their unique mechanisms of actions.
- Be prepared to administer commonly used immunotherapy drugs, assess and treat for side effects, and provide patients and families with valuable education.

incidence of serious adverse effects compared to immunoglobulin administered via IV (Kobrynski, 2012).

Immune Checkpoint Inhibitors

Because immune checkpoint inhibitors are not yet approved for use in pediatric patients, information about the potential side effects is primarily drawn from the adult literature. General side effects of immune checkpoint inhibitors result from an increase in the amplitude of the inflammatory response. The most common immune-related adverse events include dermatitis (rash, pruritis), colitis (diarrhea), hepatotoxicity (elevated aspartate aminotransferase and alanine transaminase), and endocrinopathies (Bayer et al., 2017). Most immune-related adverse events are mild and easily treatable with topical corticosteroid creams and oral antihistamines, hydration, or steroids. However, some immune-related adverse events are so severe that they require hospitalization, treatment with steroids administered via IV, and tumor necrosis factor-alpha inhibitors (Bayer et al., 2017).

The effects of endocrine manifestations are often irreversible (Sznol et al., 2017). The most common endocrine immune-related adverse events are hypothyroidism and hypophysitis, which require immediate treatment with high-dose steroids and often long-term hormone replacement. All patients who present with endocrinopathies require referral to an endocrinologist.

The potential for immune checkpoint inhibitors to cause such immune-related adverse events requires nurses to be detailed in their physical assessments and obtain frequent blood draws (thyroid panel, pituitary function test, and liver function test) to detect the onset of any gland or organ toxicity (Bayer et al., 2017). In addition, nurses must conduct psychiatric assessments to monitor for atypical symptoms, including mood changes and alterations in sleep patterns. For patients who present with a preexisting autoimmune disorder, the benefits of immune checkpoint inhibitor therapy must be carefully weighed against the increased risk for severe immune-related adverse events.

Cancer Vaccines

Although much more research is required, the few phase 1 and 2 studies that have been done show that cancer vaccines appear to be well tolerated in pediatric patients (Rousseau & Brenner, 2005). Common side effects of cancer vaccines include minor injection site pain, erythema, and induration (Wayne et al., 2010). The biggest potential for harm is risk for autoimmunity.

Conclusion

The use of targeted therapy to attack specific molecules expressed on different tumor cells allows providers to offer treatment for some pediatric cancers with increased efficacy and decreased side effects. As MABs, CAR T-cell therapy, immune checkpoint inhibitors, and cancer vaccines continue to show potential in clinical practice, as well as in trials, they will likely become integrated into standard pediatric cancer treatments. As a result, nurses have a responsibility to be knowledgeable about the diverse categories and classes of immunotherapy so that they are ready to provide safe, effective, and evidence-based care for their patients.

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