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Commonly Reported Adverse Events Associated With Pediatric Immunotherapy: A Systematic Review From the Children's Oncology Group CE

Janice S. Withycombe, PhD, RN, MN[1,2], Aimee Carlson, MSN, CPNP, CPHON[3], Carly Coleman, MSN, PNP, RN, CPHON[4], Sharon L. Leslie, MSLS, AHIP[5], Micah Skeens, PhD, RN, PNP[6], Hanna Tseitlin, MN, PNP, CPHON[7], and Elizabeth A. Duffy, DNP, RN, CPNP[8]

Abstract

Background: Immunotherapy is a new and promising approach to treating pediatric cancers. These types of therapies have unique mechanisms of action for identifying and fighting cancer, as compared with traditional chemotherapy, and therefore are associated with different therapy-related adverse events (AEs). The purpose of this systematic review was to review available evidence to: (a) identify commonly reported AEs associated with immunotherapy agents frequently used in pediatric oncology and (b) generate recommendations for nursing practice. **Method:** A clinical question was developed and used to guide the systematic literature review. Five immunotherapy agents (dinutuximab, blinatumomab, rituximab, inotuzumab ozogamicin, brentuximab vedotin) were selected for inclusion secondary to their high relevance to pediatric oncology. A literature search was conducted to locate articles published between January 1, 2003 and October 31, 2018. **Results:** Seventeen articles met eligibility criteria for inclusion and were evaluated using the Grading of Recommendations Assessment, Development, and Evaluation criteria. The most commonly reported AEs for the selected immunotherapy agents were identified and summarized. Strong recommendations are made for nurses to become familiar with the unique AE profiles associated with individual immunotherapy agents. Agent-specific recommendations for nursing practice regarding AEs associated with dinutuximab and rituximab were generated. **Conclusions:** Immunotherapy is rapidly emerging as an effective therapy for pediatric cancers. Nurses need to be aware of the breadth of agent-specific, immunotherapy-related AEs to appropriately monitor and manage patients receiving these therapies. Additional work is needed to confidently profile immunotherapy-related AEs in pediatric oncology and to develop agent-specific educational materials for patients/families.

Keywords

adverse events, immunotherapy, pediatric oncology, toxicities

Introduction

Cancer immunotherapy is an emerging and promising approach to pediatric cancer treatment. Immunotherapy is defined as treatment strategies that aim to optimize the immune system's ability to target and fight cancer while minimizing autoimmune toxicity (Warren, 2018). Immunotherapy agents are commonly grouped into categories, such as, chimeric antigen receptors, immune checkpoint inhibitors, cancer vaccines, bispecific T-cell engagers (BiTEs), and monoclonal antibodies. Each of these therapies work differently but achieve a similar

[1]Clemson University, Clemson, SC, USA
[2]Bi-Lo Charities Children's Cancer Center, Greenville, SC, USA
[3]Cleveland Clinic Children's Hospital, Cleveland, OH, USA
[4]Cohen Children's Medical Center, New Hyde Park, NY, USA
[5]Emory University, Atlanta, GA, USA
[6]Nationwide Children's Hospital, Columbus, OH, USA
[7]McMaster Children's Hospital at Hamilton Health Sciences, Hamilton, Ontario, Canada
[8]University of Michigan School of Nursing, Ann Arbor, MI, USA

Corresponding Author:
Janice S. Withycombe, PhD, RN, MN, School of Nursing, Clemson University, 508 Edwards, Clemson, SC 29634, USA.
Email: jswithy@clemson.edu

response by using the patient's own immune system to fight cancer. Chimeric antigen receptor T-cell therapy uses the patient's own T-cells that have been genetically engineered to specifically target the cancer cells. In contrast, BiTE immunotherapy is composed of bispecific proteins that bind cell-surface molecules of T-cells to surface antigens of cancer cells, fostering cancer cell destruction (Huehls et al., 2015). Immune checkpoint inhibitors prevent cancer cells from evading the body's immune system by allowing the immune system to recognize tumor cells as foreign and target them for destruction. Cancer vaccines are another type of immunotherapy given to prevent or treat cancer through the formation of immunologic memory (Warren, 2018). Monoclonal antibodies are manufactured proteins that have several mechanisms of action. They can tag certain proteins on a tumor cell, alerting the immune system to find and destroy the tagged cells; additionally, some monoclonal antibodies can block abnormal proteins on or near cancer cells. Conjugated monoclonal antibodies can deliver toxic substances, such as chemotherapy or radioactive material, directly into cancer cells.

As immunotherapy agents have a different mechanism of action, compared with traditional chemotherapy, they hold promise for improving survival while potentially decreasing toxicity and/or late effects (Wedekind et al., 2018). While chemotherapy (e.g., alkylating agents, antimetabolites, etc.) affects all active cells in the body—most notably the rapidly dividing cells such as tumor cells, hair, bone marrow, and cells lining the digestive tract—immunotherapy strives to single out the body's own immune system to specifically target cancer cells. This is accomplished through several immune pathways such as innate immunity, B-cell antibody production, and T-cell antigen presentation, resulting in tumor cell lysis or through using conjugated immunotherapy agents (such as inotuzumab) that deliver toxins directly into cancer cells. Immunotherapy activates the immune system to recognize and/or develop memory of antigens specific to cancer cell lines (Abbott & Ustoyev, 2019; Capitini et al., 2014). As immunotherapy agents function differently from chemotherapy (Warren, 2018), it reasons that they may be associated with unique treatment-related adverse events (AEs).

Four monoclonal antibodies (brentuximab vedotin, rituximab, dinutuximab and inotuzumab ozogamicin) and one BiTE (bliniatumomab) are being studied with increased frequency in pediatric oncology clinical trials. Each of these agents work by identifying and acting on specific cell lines. For example, blinatumomab is specific to CD19 positive B-cell leukemias and lymphomas, as it targets only the CD19 positive cells. Inotuzumab ozogamicin, a conjugated anti-CD22 monoclonal antibody, is another immunotherapy agent that demonstrates activity in B-cell leukemias and lymphomas by binding to CD22 positive cells. Brentuximab vedotin is a conjugated monoclonal antibody with anti-CD30 activity, used in the treatment of Hodgkin lymphoma and anaplastic large cell lymphoma (Capitini et al., 2014). Rituximab, one of the first immunotherapy agents used in pediatric oncology, is an anti-CD20 monoclonal antibody used to treat Epstein Barr Virus associated posttransplant lymphoproliferative disorders, lymphocyte predominant Hodgkin lymphoma, diffuse large B-cell lymphoma and Burkitt lymphoma (Meinhardt et al., 2010). Dinutuximab is a chimeric monoclonal antibody that targets GD2 expressed in human neuroblastoma cells. This drug, in combination with traditional treatment modalities, has increased the 2-year event free survival for high-risk neuroblastoma, and is now included as standard of care in metastatic neuroblastoma following autologous stem cell transplant (Capitini et al., 2014; Meinhardt et al., 2010).

With the increased use of immunotherapy in pediatric oncology, and the varying mechanisms of action for each agent, it is important for nurses to be aware of the unique toxicity profiles associated with this therapeutic modality. Therefore, the purpose of this evidence-based practice (EBP) project was to complete a systematic review to: (a) identify commonly reported AEs associated with immunotherapy agents used in pediatric oncology and (b) generate recommendations for nursing care and management.

Method

In 2017, the Children's Oncology Group (COG) Nursing Discipline issued a call for nursing members to participate in a mentored EBP project. Four nurses (3 nurse practitioners and 1 nurse scientist with active clinical practice) were selected through a competitive review process to join an EBP team examining commonly reported AEs associated with selected immunotherapy agents. The team was led by a PhD-prepared nurse with experience in completing systematic reviews for EBP-related projects.

PICO Question Development

The topic for this systematic review was chosen to align with the COG Nursing Discipline's blueprint for nursing research (Landier et al., 2013). Addressing illness-related distress remains a current area of focus for COG Nursing that guided the development of the following Population, Intervention, Comparison, Outcome (PICO) question (Melnyk et al., 2010): "Among pediatric oncology patients receiving immunotherapy agents (dinutuximab, rituximab, brentuximab, inotuzumab, and blinatumomab), what therapy-associated toxicities are commonly reported?" The five agents included in this review were chosen based on

(a) their current or recent use in pediatric oncology clinical trials and (b) availability of published literature. For the purposes of this article, "commonly reported" toxicities were defined as the five most frequent Grades 3 to 5 AEs reported within each included study.

Literature Search Strategy

A health science informationist, with expertise in conducting systematic reviews, used the PICO question to construct and complete a literature search, with input from the clinical team. In October 2018, three databases were searched (PubMed, Embase, and Web of Science Core Collection) to identify relevant articles. The Cochrane Childhood Cancer review group website was hand searched. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations were used to guide the review process (Moher et al., 2009).

Articles were included if published in English between January 1, 2003 and October 31, 2018. The searches combined controlled vocabulary supplemented with keywords related to the concepts of childhood (e.g., pediatric, child, infant), oncology (e.g., neoplasm, cancer, carcinoma, malignancy), immunotherapy/antibody therapy (e.g., antineoplastic agents, monoclonal antibodies), and therapy-associated toxicities (e.g., drug-related side effects, toxicity, adverse effects). Inclusion criteria were as follows: age range of birth to 25 years old, humans, and studies involving single immunotherapy agents or studies with immunotherapy in combination with traditional chemotherapy. The date range of 15 years was chosen to capture the early immunotherapy studies conducted in pediatric oncology. Case reports and literature reviews were filtered out of the search strategy as they did not provide the level of detail (i.e., number or frequency) needed to determine the most commonly occurring AEs. "Nephrotic syndrome" was added as an exclusion criterion, as this condition may be treated with rituximab. Full search strategy details are provided in online supplementary materials.

A total of 635 articles were identified (629 through database searches and 6 additional articles through reference list reviews of open COG clinical trials). Duplicate articles (127) were excluded, leaving a total of 508 articles to undergo inclusion/exclusion evaluation. Twenty-five articles remainedeligible for full text review. Articles that included both pediatric and adult populations, but without distinguishing the AE reports by age, were excluded. Eight articles were excluded during the full text review phase, leaving 17 that met all eligibility criteria. See Figure 1 for the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

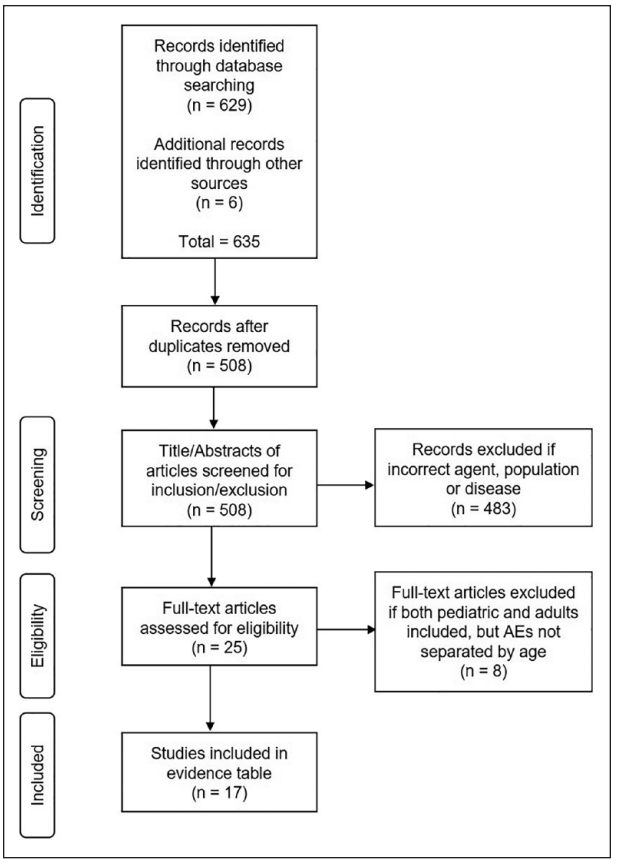

Figure 1. PRISMA flow diagram for the systematic review.
Note. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Evidence Review Method

Team members met in person at the start of the project, during an EBP workshop at Duke University, and again during an annual COG member meeting. Additionally, team conference calls were held 1 to 2 times per month for 18 months to discuss identified articles and resolve any conflicts related to article evaluations. Rayyan, a web-based systematic review tool, was used by team members to review the title and abstract for each citation and to clearly document review decisions related to inclusion/exclusion criteria (Ouzzani et al., 2016). To reduce bias, a minimum of two team members plus the project mentor reviewed each article. Matrix tables were completed independently, by each assigned reviewer, and discussed during team calls. The matrix tables were used to extract information related to the study design, number of participants, cancer treatment medications used within the study, reported AEs and their associated frequency and severity (if reported). The team also evaluated the quality of the articles based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool (Guyatt et al., 2011). The

criteria for the appraisal of the article's quality level included evaluations related to the study design, methodological flaws, inconsistency, indirectness, effect size, and publication bias. A quality rating (High, Moderate, Low, or Very Low) was generated for each article with the level being decreased when threats to quality were identified. Some, but not all, of the included studies were clinical trials that were categorized by phase (i.e., Phases 1, 2, or 3). This article describes the research design (not the study phase) for each included article, as the research design is used in evaluating the GRADE of each article. Therefore, quasi-experimental study designs refer to trials in which participants received an intervention (study drug) in a nonrandomized manner. The study mentor suggested edits and provided a final review of all developed matrix tables. Findings from all articles were used to generate practice recommendations which were scored for strength (strong vs. weak) per the GRADE criteria. The strength of the recommendation indicates the level of confidence that "adherence [to the recommendation] will do more good than harm" (Atkins et al., 2004). Discrepancies, among reviewers, were discussed with the full team until consensus was reached.

Results

Summary of Articles

The 17 articles retained in this review consisted of three randomized controlled trials (RCTs), 11 quasi-experimental studies and 3 retrospective studies. Five studies reported AEs in protocols that contained dinutuximab (Marachelian et al., 2016; Mody et al., 2017; Mueller et al., 2018; Ozkaynak et al., 2018; Yu et al., 2010), five included rituximab (Bilic et al., 2010; Goldman et al., 2014; Griffin et al., 2009; Meinhardt et al., 2010; Samochatova et al., 2014), four included brentuximab (Cole et al., 2018; Faulk et al., 2018; Flerlage et al., 2016; Locatelli et al., 2018), two included inotuzumab (Bhojwani et al., 2019; Rytting et al., 2014) and one included blinatumomab (von Stackelberg et al., 2016). The sample size, per study, ranged from 5 to 226 (mean 57; median 43). Most studies ($n = 15$) reported using the National Cancer Institute's Common Terminology Criteria for Adverse Events for grading AEs (National Cancer Institute, 2013).

Dinutuximab. Overall, a strong level of evidence was available across five studies to support AEs associated with dinutuximab in three RCTs and two quasi-experimental studies (Table 1). Pain and fever were reported across all studies as two of the most commonly occurring AEs associated with this immunotherapy agent. Regarding pain, two studies (Mueller et al., 2018; Yu et al., 2010) specified "neuropathic pain" in relationship to the graded AE. Of note, studies published prior to this agent obtaining Food and Drug Administration approval and designation as dinutuximab, use the term "Ch14.18" to refer to the study drug.

Rituximab. Overall, a moderate level of evidence was available across five quasi-experimental studies to support commonly occurring AEs with the use of rituximab in combination with chemotherapy (Table 2). One study (Meinhardt et al., 2010) utilized rituximab as a single agent for 5 days prior to chemotherapy, with the other four studies using rituximab combined with chemotherapy throughout treatment. Infection was reported as a frequently occurring AE in three out of the five studies pertaining to use of rituximab in children with cancer (Bilic et al., 2010; Goldman et al., 2014; Griffin et al., 2009). Another study (Samochatova et al., 2014) did not report infection as a frequently occurring AE but did report low serum Immunoglobin (Ig) levels in 55% of treated children. Low serum Ig levels have been associated with an increased risk for infection (Barmettler et al., 2018).

Hypersensitivity-related AEs were also reported in two of the five studies in children receiving rituximab (Griffin et al., 2009; Samochatova et al., 2014). Reported symptoms related to hypersensitivity included "urticarial," "broncho-obstruction," "fever," and "allergy/hypersensitivity reactions."

Brentuximab. Overall, a moderate level of evidence was available across four studies to support AEs occurring in three quasi-experimental and one retrospective study utilizing brentuximab (Table 3). Three studies used this drug in combination with chemotherapy, while one study (Locatelli et al., 2018) used the drug as a single agent in a dose escalation trial. There was a moderate level of evidence related to neutropenia as a commonly occurring AE associated with brentuximab (reported in 3 of the 4 included studies). An additional article reported a low level of evidence related to a unique AE—an increased risk for pulmonary toxicity—when brentuximab was administered in combination with chemotherapy (Faulk et al., 2018).

Inotuzumab. Two studies presented a low level of evidence for AEs commonly reported in studies utilizing inotuzumab (Table 4). Both were retrospective studies using inotuzumab as a single agent. Of note, both studies included patients that had been heavily pre-treated on prior protocols with one study (Bhojwani et al., 2019) including patients receiving inotuzumab through a compassionate use protocol. Secondary to the small number of subjects included in these studies, the low level of evidence, and the inconsistency in the most frequently reported AEs in each study, no conclusions could be confidently drawn related to the most commonly occurring AEs associated with this agent.

Table 1. Evidence Summary for Dinutuximab.

Author (year)	Study design (number of subjects)	Single agent or combination	Most frequently reported AEs	Evidence GRADE
Marachelian et al. (2016)	Randomized, cross over study (28)	Combination	Fever (46.3%), pain: reported as pain, pain in extremity, and abdominal pain (31.5%), anemia (27.8%), hypokalemia (25.9%), hyponatremia (18.5%)	Strong
Mody et al. (2017)	RCT (35)	Combination	Pain (44%), hypokalemia (38%), neutropenia (25%), thrombocytopenia (25%), anemia (25%), fever with infection (25%), and Hypoxia (25%)	Strong
Mueller et al. (2018)	Quasi-experimental (53)	Combination	Neuropathic pain (37.7%), pruritus (15.1%), cough (15.1%), capillary leak (13.2%), Fever (9.4%)	Moderate
Ozkaynak et al. (2018)	Quasi-experimental (105)	Combination	Pain (29.2%), allergic reactions (5.4%), capillary leak (1.4%), hypotension (10.6%), fever (24.6%)	Moderate
Yu et al .(2010)	RCT (226)	Combination	Neuropathic pain (52%), infection (39%), fever without neutropenia (39%), hypokalemia (35%), hypersensitivity reaction (25%)	Strong

Note. Terminology for the listed AEs came directly from the articles and were reported as Grades 3 or 4 events. GRADE = Grading of Recommendations Assessment, Development, and Evaluation; AEs = adverse events; RCT = randomized controlled trial.

Table 2. Evidence Summary for Rituximab.

Author (year)	Study design (number of subjects)	Single agent or combination	Most frequently reported AEs	Evidence GRADE
Bilic et al. (2010)[a]	Quasi-experimental (7)	Combination	Mucositis (100%), oral fungal infection (100%)	Low
Meinhardt et al. (2010)	Quasi-experimental (136)	Single agent for 5 days prior to combination therapy	Grades 3-4: Pain: included headache, myalgia, arthralgia, and "other" (25.1%); fatigue (18.4%); decreased hemoglobin (15.5%); ALT/AST elevation (11.8%); decreased platelets (8.1%)	Moderate
Griffin et al. (2009)	Quasi-experimental (20)	Combination	Grades 3-4: Vomiting (35%), infection (30%), nausea (25%), hypokalemia (25%), decreased platelets (25%), allergy/hypersensitivity (25%)	Moderate
Goldman et al. (2014)	Quasi-experimental (40)	Combination	Grades 3-4: Infection (49%), mucositis (19%), transaminitis (18%), anorexia (14.6%), and pain (13%)	Moderate
Samochatova et al. (2014)[a]	Quasi- experimental (83)	Combination	Serum Ig below 5g/L (55.4%), symptoms grouped together: headache, fever, nasal congestion and urticaria (30.1% during first cycle); Broncho-obstruction responsive to bronchodilators (6%), hypotension (1.2%)	Moderate

Note. AEs = adverse events; ALT = alanine aminotransferase; AST = aspartate transaminase; Ig = immunoglobin; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.
[a]Grade of AEs not reported. Terminology for the listed AEs came directly from the articles.

Blinatumomab. One single agent, dose escalation study provided a moderate level of evidence for AEs associated with blinatumomab (Table 5). In this study (von Stackelberg et al., 2016) anemia, thrombocytopenia, febrile neutropenia, hypokalemia, and neutropenia were the most frequently reported AEs. Only 8 of the 70 patients (11%) in the reviewed study experienced any grade of cytokine release syndrome, which did not meet our definition of a "commonly occurring" AE for the purposes of this review. Additional discussion on this important point occurs under study limitations.

Practice Recommendations

Recommendation 1. There is a strong recommendation, based on a strong level of evidence, to anticipate, assess, and manage pain and fever in children with neuroblastoma receiving therapy containing dinutuximab.

Table 3. Evidence Summary for Brentuximab.

Author (year)	Study design (number of subjects)	Single agent or combination	Most frequently reported AEs	Evidence GRADE
Cole et al. (2018)	Quasi-experimental (45)	Combination	Grades 3-4: Decreased neutrophil count (44.5%), transaminitis (27.5%), decreased white blood cell count (24.5%), decreased platelets (18%), rash (7%)	Moderate
Faulk et al. (2018)[a]	Retrospective study (19)	Combination	Odds of pulmonary toxicity four times higher in pts receiving brentuximab in addition to chemo	Low
Flerlage et al. (2016)	Quasi-experimental (16)	Combination	Grades 3-4: Neutropenia (81.3%), leukopenia (75%), stomatitis (6.3%), and anemia (6.3%)	Moderate
Locatelli et al. (2018)	Dose escalation (36)	Single	Grades 3-4: Neutropenia (11%), increased transpeptidase (6%), pyrexia (6%)	Moderate

Note. AEs = adverse events; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.
[a]Grade of AEs not reported.

Table 4. Evidence Summary for Inotuzumab.

Author (year)	Study design (number of subjects)	Single agent or combination	Most frequently reported AEs	Evidence GRADE
Bhojwani et al. (2019)	Retrospective study (51)	Single	Grades 3-4: Infection (19.6%), febrile neutropenia (11.8%), electrolyte disturbances (5.9%), ALT increase (5.9%), infusion reaction (3.9%)	Low
Rytting et al. (2014)	Retrospective study (5)	Single	One patient experienced Grade 5 sepsis. One patient experienced a perianal fissure[a]	Very low

Note. AEs = adverse events; ALT = alanine aminotransferase; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.
[a]Grade of AE not reported.

Table 5. Evidence Summary for Blinatumomab.

Author (year)	Study design (number of subjects)	Single agent or combination	Most frequently reported AEs	Evidence GRADE
von Stackelberg et al. (2016)	Dose escalation (70)	Single	Grades 3-4: Anemia (36%), thrombocytopenia (21%), febrile neutropenia (17%), hypokalemia (17%), neutropenia (17%)	Moderate

Note. AEs = adverse events; GRADE = Grading of Recommendations Assessment, Development, and Evaluation.

Recommendation 2. There is a strong recommendation, based on a moderate level of evidence, for awareness of increased infection risks in children receiving rituximab as treatment for cancer. Infection risks should be anticipated for children receiving rituximab, including rituximab in combination with chemotherapy, and preventative actions should be taken per local institutional practices and/or clinical trial protocols.

Recommendation 3. There is a strong recommendation, based on a moderate level of evidence, to anticipate and monitor hypersensitivity-related reactions in children receiving rituximab during cancer therapy. Familiarity with local institutional or clinical trial-specified use of prophylactic medications, such as administration of acetaminophen or diphenhydramine pre-rituximab infusion, is warranted.

Recommendation 4. There is a strong recommendation, based on a moderate level of evidence, for nurses to be aware of the differing AE profiles associated with individual immunotherapy agents.

Discussion

The primary objective of this review was to describe therapy-associated toxicities commonly reported for immunotherapy agents frequently used in pediatric oncology.

Our systematic review encompassed 17 articles that detailed information related to the five agents selected for inclusion in our search. Two agents, dinutuximab and rituximab, had stronger levels of evidence available to answer the PICO question, perhaps secondary to the fact that these agents have been utilized longer in pediatric oncology.

Fever and pain are well-documented toxicities occurring with dinutuximab. As such, clinicians should anticipate their occurrence and have plans in place for assessment and management. Protocol-related care to minimize and manage fever and pain may be dictated in a clinical trial using dinutuximab. Institutions using dinutuximab outside of a clinical trial setting should have policies in place to optimize evidence-based care directed toward anticipating and minimizing pain and fever in children receiving this agent.

This review identified infections as commonly reported AEs in children receiving rituximab as part of their cancer therapy. This finding is consistent with studies in adult oncology where 4% of patients receiving rituximab as monotherapy, and 30% to 50% of patients receiving rituximab in combination with chemotherapy, developed bacterial, or viral infections (Salles et al., 2017). The increased risk of infection associated with rituximab is secondary to B-cell depletion which may persist for multiple weeks following administration (Abulayha et al., 2010; Grillo-Lopez et al., 2002). Clinicians should be aware of the increased risk for infections when rituximab is included in a treatment regimen and follow local institutional or protocol-specific guidelines for prophylactic management, which may include monitoring of B-cell and Immunoglobulin G (IgG) levels and administration of intravenous immunoglobulin (IVIG) or prophylactic antibiotics when rituximab is given in combination with chemotherapy.

For the rituximab studies included in this review, AEs related to infection were reported to occur more commonly than hypersensitivity reactions. This finding differs somewhat from the adult literature, which reports infusion-related reactions as the most commonly occurring AE associated with rituximab (Salles et al., 2017). It is possible that hypersensitivity reactions during infusion were of lesser severity and/or frequency in children who participated in the included studies, secondary to the implementation of pre-medication regimens which included acetaminophen or paracetamol and diphenhydramine prior to administering rituximab. Premedications were detailed in four of the five studies, with the remaining study (Samochatova et al., 2014), noting "supportive care" pre-rituximab infusion. Hypersensitivity reactions are well documented with this agent, and thus warrant awareness and consideration for management (Guan et al., 2015).

Brentuximab, inotuzumab, and blinatumomab are newer agents and therefore less evidence was available to address the PICO question. This review provides preliminary evidence of commonly occurring AEs associated with immunotherapy agents frequently utilized in pediatric oncology. The literature suggests that there are unique toxicity profiles associated with different immunotherapy agents, with variations present even within subcategories such as monoclonal antibodies. Secondary to the identified agent specific toxicities noted in this review, a strong recommendation was made for nurses to become familiar with individual toxicity profiles associated with the immunotherapy agents commonly utilized in their practice settings. Of note, toxicity profiles may change over time with increased use of the agents.

Immunotherapy is rapidly emerging as an effective therapeutic approach in oncology (Boyiadzis et al., 2016). The growing adoption of immunotherapy is partly due to the reduction in toxic side effects when compared with chemotherapy (Landau, 2019). Even so, these therapies, as demonstrated in this review, have significant toxicities. It has recently been suggested that institutions and practice sites using these agents should work to establish multidisciplinary teams with the purpose of identifying and managing AEs related to immunotherapy agents (The ASCO Post, 2019). Nurses would be important members of teams developed for this purpose, as they are often the frontline caregivers for patients and as they are tasked with providing anticipatory guidance during patient/family education (Rodgers et al., 2016), which includes topics such as commonly occurring treatment-related AEs.

This review had several limitations. First, many of the included articles only reported higher level toxicities (Grades 3-5) and three articles reported toxicities without including specific grading for the events. This limited our ability to comment on the most commonly occurring toxicities overall as it is possible that lower grade toxicities (Grades 1-2) occurred with greater frequency. There are also additional immunotherapy-related toxicities that the nurse should be aware of, such as cytokine release syndrome associated with blinatumomab, that were noted in our review but did not occur with sufficient frequency to be listed as a commonly occurring toxicity. Cytokine release syndrome, associated with immunotherapy agents, is a significant and potentially life-threatening AE (Lee et al., 2014). Although not a frequently occurring AE, nurses should be aware of the association between cytokine release syndrome and specific immunotherapy agents so that appropriate monitoring/intervention can occur.

Additionally, this review found only a small number of published manuscripts in pediatric oncology, which detailed AEs associated with dinutuximab, blinatumomab, rituximab, inotuzumab ozogamicin, and brentuximab vedotin. Within the 17 included studies, 10

contained sample sizes of fewer than 50 patients and only three studies were RCTs. The remaining studies were quasi-experimental or retrospective studies that yielded a moderate to low level of evidence. Secondary to these limitations, it is possible that future studies will yield more robust information that could change the reported AEs commonly associated with these agents. Even with these identified limitations, this review provides evidence for distinct toxicity profiles associated with frequently used monoclonal antibody immunotherapy agents in pediatric oncology.

Conclusion

Nurses provide direct care to patients receiving immunotherapy across inpatient and outpatient treatment settings and are therefore well positioned to be among the first to identify and respond to treatment-associated AEs specific to these agents. Awareness of commonly occurring AEs can ultimately lead to reduced illness-related distress in children receiving immunotherapy. Knowledge of immunotherapy-specific AEs is also warranted in order to provide safe, effective, and evidence-based care to patients receiving these newer and innovative therapies (Bayer et al., 2017). As more evidence becomes available, it will be important for clinicians to work toward developing and refining toxicity profile information specific to individual immunotherapy agents. This type of drug-specific information will hold great value in educating new team members working with patients receiving these agents. Equally important, this information would be useful for developing patient/family educational resources to assist families with anticipating and/or identifying commonly occurring AEs related to immunotherapy.

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ORCID iDs

Janice S. Withycombe https://orcid.org/0000-0002-3042-9049
Aimee Carlson https://orcid.org/0000-0003-3634-4094
Sharon Leslie https://orcid.org/0000-0002-6597-977X
Micah Skeens https://orcid.org/0000-0001-6786-8128
Elizabeth A. Duffy https://orcid.org/0000-0001-5038-803X

Supplemental Material

Supplemental material for this article is available online.

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Author Biographies

Janice S. Withycombe, PhD, RN, MN, is an associate professor in the School of Nursing at Clemson University and a researcher at Bi-Lo Charities Children's Cancer Center, PRISMA Health. She is the Chair of the Nursing Research Subcommittee within the Children's Oncology Group.

Aimee Carlson, MSN, CPNP, CPHON, is a pediatric nurse practitioner at Cleveland Clinic Children's Hospital in the Department of Pediatric Hematology, Oncology, and Transplant.

Carly Coleman, MSN, PNP, RN, CPHON, is a registered nurse on a pediatric oncology bone marrow transplant unit at Cohen Children's Medical Center.

Sharon L. Leslie, MSLS, AHIP, is the nursing informationist at the Woodruff Health Sciences Center Library at Emory University.

Micah Skeens, PhD, RN, PNP, is a nurse scientist at Nationwide Children's Hospital. She currently serves as the Chair of the Nursing Clinical Trials Subcommittee for the Children's Oncology Group.

Hanna Tseitlin, MN, PNP, CPHON, is a pediatric nurse practitioner at McMaster Children's Hospital in the Department of Pediatric Hematology/Oncology.

Elizabeth A. Duffy, DNP, RN, CPNP, is a clinical assistant professor at The University of Michigan School of Nursing. She is chair of the Nursing Evidence-Based Practice Subcommittee for the Children's Oncology Group.