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Evidence-Based Recommendations for Nurse Monitoring and Management of Immunotherapy-Induced Cytokine Release Syndrome: A Systematic Review from the Children's Oncology Group CE

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Abstract

Children with B-precursor acute lymphoblastic leukemia and B-cell lymphoma, particularly those with relapsed or refractory disease, are increasingly enrolled on phase II and phase III clinical trials studying immunotherapies. These therapeutic agents may be associated with a high risk of cytokine release syndrome (CRS), and nurses lack standardized guidelines for monitoring and managing patients with CRS. Six studies and one clinical practice guideline were included in this systematic review that examined the evidence of CRS following administration of chimeric antigen receptor T-cell therapy or the bi-specific T-cell engager antibody, blinatumomab. Six nursing practice recommendations (five strong, one weak) were developed based on low or very low-quality evidence: three reflect preinfusion monitoring, one focuses on monitoring during and postinfusion, and three pertain to the nurse's role in CRS management.

Keywords

cytokines, immunotherapy, guidelines, chimeric antigen receptor T-cell therapy

Introduction

Contemporary, risk-adapted therapeutic regimens for B-precursor acute lymphoblastic leukemia (B-ALL), the most common malignancy in children, have demonstrated a 5-year survival rate >90% (Pui et al., 2015). However, patients with B-ALL in the first relapse have poor event-free survival of 35% to 50%, and survival rates decrease further for refractory and multiply relapsed disease (Sun et al., 2018). The outcomes for these patients have only slightly improved over the past two decades (Sun et al., 2018). Promising results in refractory or relapsed B-ALL from early phase trials of T-cell-engaging immunotherapies, such as blinatumomab, a bi-specific T-cell engager (BiTE) antibody, and chimeric antigen receptor (CAR) T-cell therapy (CAR T), have led to expanded use of targeted immunotherapy in multicenter trials for relapsed/refractory B-ALL and B-cell lymphoma (Frey & Porter, 2016). It is essential for nurses to understand the unique side effect profile of these newer agents to recognize early signs and symptoms of cytokine release syndrome (CRS) and to respond to severe and life-threatening toxicities.

CRS is the most common and potentially life-threatening toxicity associated with T-cell-engaging immunotherapies (Brudno & Kochenderfer, 2016; Maude et al., 2014a; Neelapu et al., 2018). CRS can range in severity from low-grade constitutional symptoms to a high-grade syndrome associated with life-threatening multisystem

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organ failure (Neelapu et al., 2018). Multiple review articles describe single-institutional experiences or general strategies for monitoring and managing CRS, however, evidence-based guidelines for nursing practice are lacking. The purpose of this systematic review was to identify evidence-based monitoring and management recommendations for pediatric oncology nurses caring for patients with B-ALL and B-cell lymphoma who are at risk for CRS secondary to treatment with blinatumomab or CAR T.

Background

CAR T refers to cellular immunotherapy with autologous or allogeneic T-cells that are genetically engineered to express CARs to redirect their cytotoxic specificity toward targets such as CD19, which is expressed in both early and mature B-cells and has "near-universal" expression on malignant cells (Maude et al., 2014a, 2014b; Frey & Porter, 2016). The BiTE antibody, blinatumomab, specifically targets CD3 T-cell antigens and CD19 on B-cell lymphoblasts and is being used in patients with relapsed and refractory ALL and in those with persistent minimal residual disease (MRD; Wilke & Gökbuget, 2017). Both immunotherapies have CRS as their most common adverse reaction (Maude et al., 2014a). While BiTE antibody infusions can be interrupted or discontinued in the setting of severe CRS (Folan et al., 2016), CAR T activation and expansion cannot be reliably suppressed without dampening the antitumor efficacy of the engineered cells (Bonifant et al., 2016). Future CAR T clinical trials will likely study enhanced safety mechanisms such as the design of cellular "emergency off switches" (Bonifant et al., 2016; Frey & Porter, 2016).

CRS is a systemic inflammatory response syndrome related to the engaged T-cell proliferation with the release of high levels of inflammatory cytokines (such as interleukin [IL]-6, IL-10, and interferon-gamma [IFNγ]) produced by monocytes and macrophages (Fitzgerald et al., 2017; Lee et al., 2014; Maude et al., 2014a, 2014b). Constitutional "flu-like" symptoms of CRS include fever, malaise, anorexia, and myalgia; however, CRS can affect any organ system, manifesting as hypotension, tachycardia, capillary leak, respiratory distress, and/or disseminated intravascular coagulation (Brudno & Kochenderfer, 2016). Unfortunately, these symptoms can quickly progress to shock, multisystem organ failure, and even death (Brudno & Kochenderfer, 2016). Accurate nursing assessment and early identification of CRS and initiation of appropriate therapy can mitigate the risk of CRS-related morbidity and mortality (Halton et al., 2017).

Neurotoxicity or CAR T-related encephalopathy syndrome (CRES) can occur following immunotherapy administration and may coexist with and persist after resolution of CRS symptoms (Brudno & Kochenderfer, 2016; Neelapu et al., 2018). While nursing assessment and management of neurotoxicity/CRES are essential components of care for patients receiving immunotherapy (Smith & Venella, 2017; Wang & Han, 2018; Wilke & Gökbuget, 2017), it is beyond the scope of this review.

CRS Toxicity Grading

Intensive monitoring and early recognition of toxicities are essential to initiate CRS management strategies. All patients who receive CAR T and BiTE are at risk for some degree of CRS. Severe CRS has been reported in 27% to 43% of patients receiving CAR T and CRS of any grade in 3% to 16% of patients receiving blinatumomab, although institutions vary in their use of grading methods and definitions (Frey & Porter, 2016; Stein et al., 2019). The severity of CRS often triggers specific actions in monitoring and management algorithms, therefore the ability to grade CRS is critical to the nurse's ability to provide optimal patient care (Neelapu et al., 2018). Consistent use of grading scales also allows for the comparison of results across multiple studies.

Organ toxicities are typically graded using the Common Terminology Criteria for Adverse Events v. 4.03 (CTCAE) (National Cancer Institute, 2010), however, many do not consider the CTCAE system adequate to define and differentiate levels of CRS, as it lacks reference to specific symptoms (e.g., fever, hypoxia, and hypotension) commonly seen with immunotherapy (Frey & Porter, 2016). Researchers have thus developed their own grading systems or made modifications from previously published versions. A total of five grading scales were utilized by the seven publications included in this review (Table 1), thus limiting the ability to compare results between studies (Fitzgerald et al., 2017; Hu et al., 2017; Lee et al., 2015; Maude et al., 2018; Neelapu et al., 2018; Teachey et al., 2016; von Stackelberg et al., 2016).

Methods

Question Development

The topic of immunotherapy-induced CRS was chosen to align with the Children's Oncology Group (COG) Nursing Discipline's blueprint and organizing framework (Kelly et al., 2014; Landier et al., 2013) and guided the development of the following clinical PICO question (Melnyk et al., 2010): (P) among pediatric oncology patients (I) receiving immunotherapy/antibody therapy, what (C) nursing interventions are needed for (O) prevention, monitoring, and management of cytokine release syndrome?

Table 1. Comparison of CRS Grading Scales.

Grading scale	Citation	Scale description	Used for CRS grading by
CTCAE	National Cancer Institute (2010)	Interventions range from none to ventilatory/vasopressor support and are divided between short-term and prolonged duration.	von Stackelberg et al. (2016)
"Lee" CRS grading scale	Lee et al. (2014)	CRS grade based on the presence or absence of fever, hypotension, hypoxia; need for vasopressors; degree of oxygen support; and presence of other organ toxicities.	Hu et al. (2017), Neelapu et al. (2018), and Teachey et al. (2016) (cited for comparison purposes)
"Davila" Severe CRS diagnostic criteria secondary to CAR T-cells	Davila et al. (2014)	Defines criteria for "severe" CRS as having prolonged fevers, cytokine changes, and evidence of at least one other clinical toxicity.	Teachey et al. (2016) (cited for comparison purposes)
"Revised" CRS grading system	Lee et al. (2015)	Levels of severity are defined by whether infusion interruption is required, duration of supportive medications, presence of other organ dysfunctions.	Lee et al. (2015)
"University of Pennsylvania/ Children's Hospital of Philadelphia" CRS grading scale	Porter et al. (2015)	Differentiates mild, moderate, severe, and life-threatening by the amount of supportive care required and types of therapies administered.	Fitzgerald et al. (2017), Maude et al. (2018), and Teachey et al. (2016)

Note. CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; CAR T = chimeric antigen receptor-modified T-cells.

Evidence-Based Practice Review Team

The COG Nursing Discipline chose the team members (three pediatric oncology nurse practitioners [United States] and one pediatric oncology nurse educator [Australia]), who had an interest in and experience with CRS, through a competitive process for participation in the systematic review development. Team members were mentored by two doctorally prepared pediatric nurse practitioners with experience in systematic reviews. All team members attended a two-day training workshop regarding the evidence-based practice process, including PICO question development, literature search, data analysis, and manuscript writing.

Literature Search and Appraisal

A literature search was conducted in March 2018 with the assistance of a medical librarian. Five databases were searched: MEDLINE, Cumulative Index of Nursing and Allied Health Literature Plus, Web of Science, SCOPUS, and Turning Research Into Practice (Trip). Search terms included multiple combinations of terms, including *cytokine release syndrome, cytokine storm, cytokine-associated toxicit*, cell-mediated immune response, immune mediated toxic*, immune-related adverse effect, monoclonal antibodies, immunotherapy*, immuno-oncology, antibody therap*, immune-based biotherapy*, blinatumomab, bi-specific T-cell engage*, brentuximab, rituximab, alemtuzumab, chimeric antigen receptor, chimeric t-cell receptor, CAR-T cell, ipilimumab, nivolumab, anti-CD40, agonistic CD40, tocilizumab, anti-IL-6, anti-interleukin-6, interven*, manag*, monitor*, assess*, control, approach*, prevent*, and nurs.** Mesh terms included *nursing assessment, patient reported outcome measures, patient acuity, oncology nursing, pediatric nursing, monitoring-physiologic, neoplasms/nursing, and adverse reactions/nursing*. English was the only search limit used. See Supplemental Table 1 for the detailed search strategy.

Studies were included if at least one human participant was <18 years of age with a diagnosis of cancer and immunotherapy-induced CRS, published in English, with available full-text, and a publication date since 2000. Studies were also required to present evidence relevant to an aspect of CRS prevention, monitoring, or management. Studies were excluded if they were preclinical, only available as a conference abstract, or were nonresearch (review articles, case studies, and single-institutional experience). Clinical practice guidelines were eligible if they reflected multiinstitutional contributors. The websites of the Oncology Nursing Society and the Association of Pediatric Hematology/Oncology Nurses were searched for guidelines and additional studies, but none were identified.

Evidence Review

The systematic search of the literature was performed according to the preferred reporting items for systematic

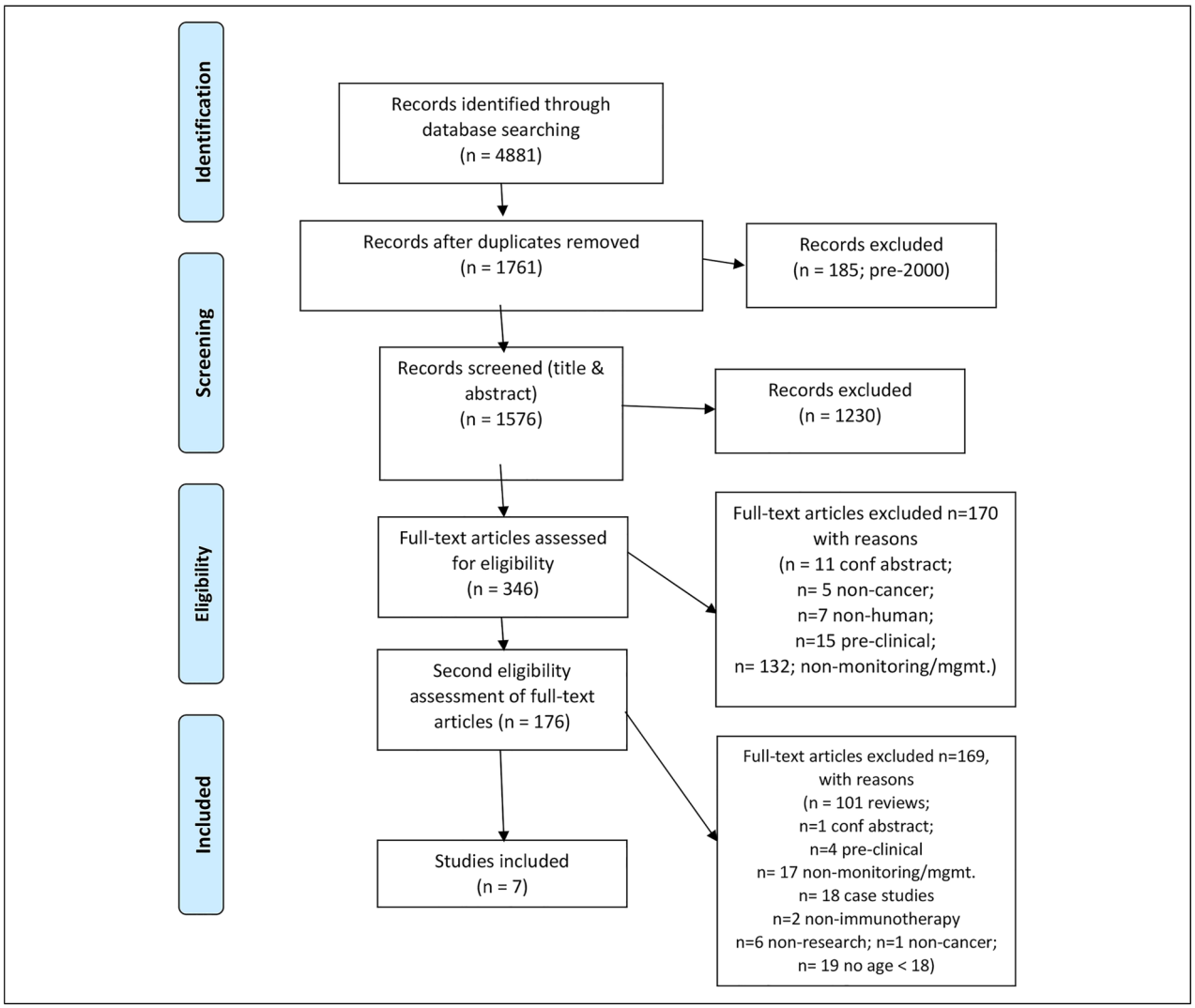

Figure 1. Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram.

reviews and meta-analysis (PRISMA) criteria (Moher et al., 2009) and 4,881 sources of evidence were identified (Figure 1). After duplicates and articles published prior to 2000 were removed, the titles and abstracts of the remaining 1,576 were reviewed by EKB. Two team members performed a full-text assessment of the remaining 346 articles to determine whether they met the specified inclusion criteria, with EKB breaking any ties. The remaining 176 articles were reviewed by two team members to make a final decision regarding inclusion, and 7 articles were ultimately included: quasi-experimental (5), retrospective cohort (1), and clinical practice guideline (1).

Each of the final studies was appraised by a pair of team members using the Grading of Recommendations Assessment, Development and Evaluation system (Neumann et al., 2016), and findings were recorded in an electronic evidence table and presented to the entire team for discussion. The single clinical practice guideline was appraised by all team members using the Appraisal of Guidelines for Research and Evaluation II instrument (Brouwers et al., 2010). A level of evidence quality (high, moderate, low, or very low) was determined for the body of evidence and recommendation statements (strong or weak) were developed.

Results

Table 2 shows characteristics of the CAR T ($n = 5$) and blinatumomab ($n = 1$) studies included in the review. All were conducted in the United States, except for the research by Hu et al. (2017), which was performed in China. While all studies included patients <18 years, five studies also included adults 18–30 years, and two studies included adults >30 years. The seventh evidence source, the clinical practice guideline, was published by the CAR-T-Cell-therapy-associated TOXicity (CARTOX)

Table 2. Characteristics of Included Studies.

Author (date)	Study design (no. of subjects) (age range)	Immunotherapy disease	Incidence of CRS, *N* (%)
Fitzgerald et al. (2017)	Retrospective cohort study (39) (5–22 years)	CAR T R/R ALL	36 (92%)
Hu et al. (2017)	Quasi-experimental (15) (7–57 years)	CAR T R/R ALL	10 (66%)
Lee et al. (2015)	Quasi-experimental (21) (5–27 years)	CAR T R/R ALL or NHL	16 (76%) 94 (93%)
Maude et al. (2018)	Quasi-experimental (75) (3–23 years)	CART CB19 + R/R B-cell ALL	58 (77%)
Teachey et al. (2016)	Quasi-experimental (63) (5–72 years)	CART R/R ALL	51 (94%)
von Stackelberg et al. (2016)	Quasi-experimental Phase I (49) Phase II (44) (<2–17 years)	Blinatumomab R/R B-cell precursor ALL	8 (11%)

Note. ALL = acute lymphoblastic leukemia; CAR T = chimeric antigen receptor-modified T-cells; CRS = cytokine release syndrome; NHL = non-Hodgkin lymphoma; R/R = refractory/relapsed.

Working Group. Members represented multiple disciplines and institutions who reviewed the available adult and pediatric literature and proposed CRS monitoring, grading, and management recommendations.

CRS Prevention

Several strategies were identified to prevent or decrease the severity of CRS: administration of prephase chemotherapy to reduce tumor burden, administration of premedications, and modification of immunotherapy dose or infusion rate. Nurses should be aware of the goal and potential impact of these strategies.

Three studies addressed the use of lymphodepleting chemotherapy prior to the administration of CAR T. All patients in two of the studies received a prephase of fludarabine and cyclophosphamide (Hu et al., 2017; Lee et al., 2015) with the goal of tumor burden reduction, and 96% of participants in the third study received some form of prephase lymphodepleting chemotherapy (Maude et al., 2018). With the first cycle of blinatumomab in a phase II dose-escalation trial (von Stackelberg et al., 2016), dexamethasone or hydroxyurea was administered for CRS prevention in patients with high tumor burden (baseline bone marrow blasts >50%). All patients received premedication with dexamethasone prior to each blinatumomab dose. To further reduce CRS risk in this same phase II study of blinatumomab, the final recommendation was a "stepwise" dosing strategy of 7 days at a lower dose of blinatumomab, followed by an increased dose on day 8 to the maximum tolerated dose for the remainder of the course (von Stackelberg et al., 2016).

CRS Monitoring: Preimmunotherapy Infusion

Practice Recommendation #1: Nurses Recognize Patients with Higher Disease Burden as Being at Risk for More Severe CRS. Several studies correlated higher disease burden prior to CAR T initiation with a higher risk of CRS development and greater CRS severity (Hu et al., 2017; Lee et al., 2015; Teachey et al., 2016). Hu et al. (2017) showed that higher levels of MRD following a pre-CAR T lymphodepleting conditioning regimen were associated with a greater risk of grade 3 CRS. A similar pattern was noted by Lee et al. (2015), who found that those with a higher pre-CAR T-cell disease burden had more severe CRS. However, Teachey et al. (2016) found that disease burden alone, although important, was insufficient to yield the most accurate predictions of CAR T CRS risk. Their models of pediatric patients at high risk of CRS development relied on measures of certain peak cytokine levels (Teachey et al., 2016). Low disease burden was helpful in identifying patients at a lower risk of CRS development and severity (strong negative predictive value), as only 7% of patients with bone marrow blasts <5% prior to CAR T developed severe CRS (Teachey et al., 2016).

Other identified risk factors for severe CRS include comorbidities, the development of CRS within 3 days of CAR T infusion (Neelapu et al., 2018), a higher number of previous relapses (Fitzgerald et al., 2017), and higher levels of circulating CAR T-cells (Lee et al., 2015), though these factors were not analyzed by the other studies in the review.

The included blinatumomab study required patients to have >25% bone marrow blasts at baseline, so could not draw conclusions between those with and without high

tumor burden (von Stackelberg et al., 2016). However, authors noted their study to have a higher risk of CRS than a similar study of patients whose tumor burden was detectable only at the MRD level (von Stackelberg et al., 2016). They also recommended future studies to investigate higher starting doses in children who have already received other agents to decrease tumor burden (von Stackelberg et al., 2016).

Nurses caring for patients known to have higher levels of disease burden or other risk factors should be prepared to more closely monitor these patients for evidence of CRS and initiate aggressive supportive care as indicated. However, given the lack of ability to predict the severity of CRS with any degree of certainty, all patients who will receive CAR T or blinatumomab should be considered at risk for CRS and receive close nursing monitoring.

CRS Monitoring: During and Postimmunotherapy Infusion

Practice Recommendation #2: Nurses Recognize the Time Period for Which Patients are at the Greatest Risk of CRS Development. A critical component of effective CRS monitoring and management is the nurse's awareness of the time period during which to expect CRS development. Four of the five CAR T studies reported time to CRS onset (median of ~3 days; range 1–22 days) and duration (range 2–36 days) (Hu et al., 2017; Lee et al., 2015; Maude et al., 2018; Teachey et al., 2016), which aligns with the CARTOX guideline recommendation to anticipate onset within the first week post CAR T infusion, with a peak in symptoms within the first 1 to 2 weeks postinfusion (Neelapu et al., 2018). Several studies reported on critical care utilization, with a median time to intensive care unit (ICU) admission of 5.6 days (Fitzgerald et al., 2017) and a median duration of 7 days (range 1–34) (Maude et al., 2018). Hemodynamic instability and mechanical ventilation onset mirrored the time to ICU admission (Fitzgerald et al., 2017). For CAR T recipients receiving the IL-6 receptor antagonist, tocilizumab, Teachey et al. (2016) report the time to administration of the first dose as a median of 5 days (range 2–12 days).

In addition to the steroid and hydroxyurea premedications given for the first four days of cycle one, study patients were hospitalized for close monitoring during blinatumomab administration during the first week of the first cycle and first two days of the second cycle (von Stackelberg et al., 2016). The authors noted the first three days of cycle one to be "critical" for managing potential fever and hypotension.

Nurses should recognize the first two weeks following CAR T administration and the first four days of the first blinatumomab cycle as the most likely time for CRS symptom development and escalation.

Practice Recommendation #3: Nurses Closely Monitor Vital Signs of Febrile Patients and Those at Increased Risk of Developing Severe CRS. Nurses are well positioned to mitigate the risk of CRS-related morbidity and mortality through early recognition of CRS signs such as fever, hypotension, tachycardia, and hypoxia. The CARTOX working group recommended that vital signs be measured a minimum of every 4 h in hospitalized patients who are at risk of developing CRS (Neelapu et al., 2018). Vital signs are also critical for the accurate classification of patients according to CRS grading scales (Neelapu et al., 2018). Across studies, fever definitions varied or were not included, but fever thresholds ranged from ≥ 38°C to ≥ 38.3°C (Maude et al., 2018; Neelapu et al., 2018; Teachey et al., 2016). The incidence of fever in patients with CRS was reported in two studies and ranged from 92% to 100% (Hu et al., 2017, Teachey et al., 2016), with patients with grades 3 to 4 CRS having fevers of a longer duration than those with grades 1 and 2 (Fitzgerald et al., 2017; Hu et al., 2017). Fitzgerald et al. (2017) found that fever preceded the onset of hypotension in all cases of CRS, but this was not analyzed in other studies. Febrile patients remain at risk for infection, so it is important to evaluate these patients for infectious organisms even if the fever is suspected to be CRS-related (Neelapu et al., 2018; Teachey et al., 2016).

Biomarker Utility in Predicting CRS Risk and Severity. Multiple studies examined biomarkers in hopes of identifying patterns that could be used to develop models to predict the timing of CRS onset and/or severity. To be clinically relevant, biomarkers must have a short turnaround time and be performed in a Clinical Laboratory Improvement Amendments-approved lab (Teachey et al., 2016). In the seven articles reviewed, C-reactive protein (CRP), ferritin, cytokines (such as IL-6, IL-10, and IFNγ) were among the biomarkers most frequently examined.

C-Reactive Protein. While Maude et al. (2018) noted great variability in levels of this inflammatory marker among patients with CRS, several studies found statistically significant differences in peak CRP levels when comparing patients with grade 3 CRS versus grades 0 to 2 (Hu et al., 2017; Lee et al., 2015) and grades 4 to 5 versus grades 0 to 3 (Teachey et al., 2016). It is not thought that these peak levels are predictive in real-time (Teachey et al., 2016), but the CARTOX working group suggested that CRP could be used clinically to signify that CRS is no longer a risk, with the return to baseline levels (Neelapu et al., 2018).

Ferritin. Peak levels of ferritin were higher in grade 3 CRS versus grades 0 to 2 (Hu et al., 2017) and when grades 4 and 5 were compared with grades 0 to 3 (Teachey et al., 2016; Maude et al., 2018). Fitzgerald et al. (2017) noted prolonged organ dysfunction in patients with grades 3 and 4 CRS whose peak ferritin levels were >11,200 pmol/L.

Interleukin 6. High levels of IL-6, a proinflammatory effector cytokine thought to be predominantly released by blood vessel endothelial cells, have been consistently reported in patients with CRS (Wang & Han, 2018). Three studies found significantly higher peak IL-6 levels in patients with more severe versus less severe/no CRS, however, different severity cutoffs were used: grade ≥3 CRS versus grades 0–2 (Hu et al., 2017; Lee et al., 2015); grades 4 and 5 CRS versus grades 0–3 CRS (Teachey et al., 2016). Two additional studies only noted a "more pronounced" effect in those with grade 4 CRS versus grades 0 to 3 (Maude et al., 2018) and those with CRS versus those without (von Stackelberg et al., 2016). Peak IL-6 also showed a strong correlation when paired with peak CRP (Hu et al., 2017; Lee et al., 2015), ferritin (Hu et al., 2017), and D-dimer levels (Hu et al., 2017).

Interleukin 10. In contrast to IL-6, IL-10 is an antiinflammatory cytokine produced by monocytes and macrophages (Wang & Han, 2018), yet similar patterns of peak levels were observed. IL-10 levels were noted to be higher in CRS than non-CRS (von Stackelberg et al., 2016) and in those with grade 4 CRS versus grades 0 to 3 (Maude et al., 2018), and reached statistical significance in patients with more severe CRS (grade ≥3 CRS vs. grades 0–2 [Hu et al., 2017]; grades 4 and 5 vs. grades 0–3 [Teachey et al., 2016]).

Interferon γ. Variability among studies was also noted for IFNγ, a proinflammatory cytokine. Several studies found statistically higher peak levels of IFNγ in patients with more severe CRS (grade ≥3 vs. grades 0–2 [Hu et al., 2017; Lee et al., 2015]; grades 4 and 5 vs. grades 0–3 [Teachey et al., 2016]), with others noting only data trends (higher in those with any CRS vs. none [von Stackelberg et al., 2016] and grade 4 vs. grades 0–3 [Maude et al., 2018]).

Other Biomarkers and Predictive Modeling. Many additional biomarkers have been studied to identify clinically relevant measures that might offer a CRS predictive value. For example, peak D-dimer levels differed significantly between those with grade 3 CRS and those grades 0 to 2 (Hu et al., 2017). Teachey et al. (2016) performed serial cytokine assessments in the first month after CAR T and prior to CRS development and found levels of 24 of the 43 measured cytokines to be statistically higher in patients with severe CRS (grades 4 and 5) versus grades 0 to 3. They then developed predictive modeling based on logistic regression for mixed (adult and pediatric) and pediatric-only cohorts. When limited to pediatric patients, levels of IFNγ, IL-13, and MIP1α within the first three days after CAR T infusion had high sensitivity (100%) and specificity (96%) for predicting patients who were at a higher risk for development of severe CRS (Teachey et al., 2016).

Nurses should be aware of the ongoing research to identify clinically relevant biomarkers to increase their understanding of CRS pathology, the mechanism of action for some treatments (e.g., tocilizumab), as well as explain the rationale for laboratory testing to patients and families. Additional research is necessary before recommending specific biomarker testing at specific time points in the CRS trajectory.

CRS Management

Practice Recommendation #4: Nurses Anticipate the Need to Quickly Escalate the Level of Care in Patients with CRS. CRS grading definitions and criteria for ICU admission vary, but ~40% of patients across three CAR T studies required ICU-level support such as vasopressors and mechanical ventilation related to CRS and its associated multisystem organ dysfunction (Fitzgerald et al., 2017; Maude et al., 2018; Teachey et al., 2016). Maude et al. (2018) reported a median ICU stay of 7 days for patients with CRS post CAR T (range 1–34). The CARTOX working group recommends treating all patients with grades 3 and 4 CRS in the ICU, as well as the early escalation of care for those with persistent hypotension (Neelapu et al., 2018). The guideline also recommends additional education for nurses caring for patients with potential CRS to promote early recognition of CRS signs and symptoms, respond to rapid changes in clinical status, and facilitate escalation in the level of care (Neelapu et al., 2018). Critical care teams should also be aware of all existing patients with potential for CRS development (Neelapu et al., 2018). Efforts to design predictive models of CRS risk could result in early initiation of ICU transfer for more aggressive monitoring and symptom management (Teachey et al., 2016).

Patients developing severe CRS during blinatumomab administration may also require critical care support. In the study by Von Stackleberg et al. (2016), 6% of patients who developed grade 3 or grade 4 CRS required either infusion interruption and/or discontinuation.

Practice Recommendation #5: Nurses Anticipate the use of Tocilizumab or Other IL-6 Inhibitors to Mitigate CRS Symptoms. The monoclonal antibody, tocilizumab, is an IL-6 receptor antagonist originally indicated for rheumatoid and other forms of arthritis and arteritis (Genentech, Inc., 2017). In 2017, the Food and Drug

Administration approved tocilizumab as a treatment for severe CAR T-induced CRS in children and adults (Neelapu et al., 2018). Nurses should anticipate the use of tocilizumab or other IL-6 blockers in patients who develop symptoms consistent with grades 3 and 4 CRS following CAR T (Fitzgerald et al., 2017; Hu et al., 2017; Lee et al., 2015; Maude et al., 2018; Teachey et al., 2016); the CARTOX working group has recommended administration beginning with persistent grade 1 symptom (Neelapu et al., 2018). Some patients may require multiple doses of IL-6 inhibitors for persistent CRS signs and symptoms (Fitzgerald et al., 2017; Neelapu et al., 2018; Teachey et al., 2016). Off-label usage of IL-6 antagonists for pediatric patients with CRS receiving other immunotherapy agents, such as blinatumomab, has also been reported (von Stackelberg et al., 2016). Patients receiving an IL-6 antagonist were noted to defervesce and show signs of clinical improvement within hours of administration (Fitzgerald et al., 2017; Teachey et al., 2016), but nurses should be aware that improvements in hemodynamic instability took several days to improve and resolve (Fitzgerald et al., 2017; Teachey et al., 2016).

Practice Recommendation #6: Nurses Clarify Orders for Corticosteroids for Patients with CRS who Have Received CAR T Therapy. Through the mechanism of inflammatory response suppression, corticosteroids are a viable option for the treatment of CRS. Four of the five CAR T studies reviewed (Fitzgerald et al., 2017; Hu et al., 2017; Lee et al., 2015; Teachey et al., 2016) report the use of steroids alone or in combination with tocilizumab. However, several studies (Fitzgerald et al., 2017; Lee et al., 2015; Maude et al., 2018) and the guideline (Neelapu et al., 2018) cite the potential for corticosteroid inhibition of CAR T efficacy and therefore recommend that steroids be limited to CAR T-induced hypotension or shock that is refractory to at least one dose of tocilizumab. The long-term effects and safety of corticosteroid usage following CAR T require additional investigation (Neelapu et al., 2018). Until more evidence is generated, nurses should be knowledgeable about the rationale and limitations of utilizing steroids in this population and be prepared to clarify any order for steroids in patients who have received CAR T therapy but are without evidence of moderate to severe CRS.

Discussion

CRS is a frequent and potentially life-threatening consequence of T-cell-engaging immunotherapies, yet recommendations for nursing practice are often based on single-institution experiences or are lacking altogether. The purpose of this systematic review was to identify evidence-based recommendations for the nursing care of patients at risk for CRS, or who have developed CRS following immunotherapy administration. These recommendations (Table 3), categorized as preinfusion monitoring, monitoring during and postinfusion, and CRS management, are intended to guide nurses at the bedside who can recognize complications and intervene quickly.

The strengths of this review include a team of clinical nurses with experience caring for patients with CRS, a carefully developed literature search strategy, and strict adherence to inclusion and exclusion criteria. There were several limitations to this review. This is a rapidly emerging field and new evidence continues to be published, however, evidence in this review is limited to that which was published prior to the March 2018 literature search. There were varying definitions of "increased tumor burden," CRS, and CRS severity across studies, as well as usage of multiple CRS grading tools. These variations limited the ability to provide direct comparisons of CRS symptoms and treatment trajectories. There was

Table 3. Nurse Monitoring & Management of CSR Practice Recommendations.

Preinfusion monitoring	Monitoring during and postinfusion	CRS management
Strong recommendation with a low level of evidence that nurses recognize patients with higher disease burden as being at risk for more severe CRS. *Strong recommendation* with a low level of evidence that nurses recognize the time period for which patients are at the greatest risk of CRS development	*Strong recommendation* with a low level of evidence that nurses closely monitor vital signs (temperature, blood pressure, respiratory rate, and oxygen saturation) of febrile patients and those at increased risk of developing severe CRS.	*Strong recommendation* with a low level of evidence that nurses anticipate the need to quickly escalate the level of care in patients with CRS. *Strong recommendation* with a low level of evidence that nurses anticipate the use of tocilizumab or other IL-6 inhibitors to mitigate CRS symptoms. *Weak recommendation* with a very low level of evidence that nurses clarify orders for corticosteroids for patients with CRS who have received CAR T therapy

Note. CRS = cytokine release syndrome; CAR T = chimeric antigen receptor-modified T-cells; IL = interleukin.

evidence of indirectness as several of the included studies had a mix of pediatric, young adult, and/or adult patients and a limited number of studies solely enrolled children and adolescents. The proportion of patients who experienced CRS within each study led to smaller sample sizes, and thus quality downgrades for imprecision. And finally, there was inconsistency in the results of studies examining the predictive role of biomarkers.

Despite these limitations, six evidence-based recommendations for nursing practice were developed that can be used by individuals and organizations to guide clinical care for patients with or at risk for immunotherapy-induced CRS. Most of the included research studies (five of six) focused on CAR T, while only one article dealt with a monoclonal antibody (blinatumomab). Additional research is needed to discern if there are nuances of CRS, its monitoring, and its management based on the type of immunotherapy administered.

Summary

Treatment is evolving for children with cancer, and many protocols now include immunotherapy as first-line agents. Immunotherapies may offer additional options for treating childhood cancer, but some carry a higher risk of developing CRS, which can result in rapid clinical deterioration and even death. Nurses are well positioned to play a critical role in monitoring for signs and symptoms of CRS and ensuring that appropriate management strategies are utilized. Future research is needed to standardize CRS grading methodology, develop models to identify high-risk patients, and expand on current CRS management strategies.

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Supplemental Material

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