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Outcomes of Critically-Ill Children with Acute Lymphoblastic Leukemia and Cytokine Release Syndrome due to Chimeric Antigen Receptor T Cells Therapy: United States, multicenter PICU, cohort database study

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Abstract

Objective: Cytokine release syndrome (CRS) is a potentially lethal toxicity associated with chimeric antigen receptor T cell (CAR-T) therapy for pediatric acute lymphoblastic leukemia (ALL). Outcomes after critical illness due to severe CRS are poorly described. Our aim is to characterize critical illness outcomes across a multicenter cohort of pediatric intensive care unit (PICU) patients with ALL and CRS.

Design: Multicenter retrospective cohort study.

Setting: 21 PICUs contributing data to Virtual Pediatric Systems, LLC (January 2020 – December 2021).

Patients: PICU patients with ALL or unclassified leukemia and CRS.

Interventions: None

Measurements and Main Results: We identified 55 patients; 34 (62%) were 12 years or older, 48 (87%) were admitted from a hospital inpatient ward, and 23 (42%) received advanced organ failure support or monitoring. Fifty-one (93%) survived to PICU discharge including 19 of 23 (83%) who received advanced organ failure support or monitoring defined as receipt of non-invasive or invasive ventilation, cardiopulmonary resuscitation, extracorporeal membrane

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oxygenation, continuous renal replacement therapy, or placement of a tracheostomy, arterial catheter, hemodialysis catheter, or intracranial catheter. Twelve (22%) patients received invasive ventilation, nine of whom survived to PICU discharge. Two of four patients who received continuous renal replacement therapy and one of three patients who required cardiopulmonary resuscitation survived to PICU discharge. Lengths of PICU stay were median 3.0 days (IQR 1.4, 7.8) amongst PICU survivors, 7.8 (5.4, 11.1) amongst those receiving advanced organ failure support or monitoring, and 7.2 days (IQR 2.9, 14.7) amongst non-survivors. Of the 51 patients who survived to PICU discharge, 48 (94%) survived the hospitalization.

Conclusions: PICU patients with CRS frequently received a high level of support, and the majority survived their PICU stay and hospitalization. Additional multicenter investigations of severe CRS are necessary to inform evidence-based practice.

Keywords

critical care outcomes; intensive care units; pediatric; adoptive cellular immunotherapy; CAR-T cell therapies; acute lymphoblastic leukemia; extracorporeal membrane oxygenation

Introduction

Chimeric antigen receptor T cell (CAR-T) therapy is a novel immunotherapy that has rapidly transitioned from an experimental to standard treatment for multiply-relapsed or refractory acute lymphoblastic leukemia (ALL) [1–6]. The therapy's mechanism relies on the activation of hundreds of millions of T cells directed against leukemic cells. This immunologic activation can result in a significant inflammatory response and may progress to Cytokine Release Syndrome (CRS), a potentially life-threatening toxicity [6, 7]. CRS severity scales (grades 1 to 5) define grades ≥ 3 as severe CRS, manifesting as cardiovascular and respiratory failure [8, 9]. Neurologic dysfunction, termed immune-effector cell associated neurotoxicity syndrome, is another potentially fatal immune-mediated complication of CAR-T therapy that can occur coincidentally or independently of CRS [9]. Risk factors for development of severe CRS include high leukemic burden, exposure to specific lymphodepletion agents, high levels of inflammation at time of CAR-T infusion, recent or concurrent infection, and product-specific CAR-T factors [10]. Treatment of severe CRS includes supportive care and therapeutic immunosuppressive agents including tocilizumab and off-label prescription of glucocorticoids, siltuximab, and anakinra [9, 11].

Data delineating characteristics and outcomes of children who become critically-ill due to CAR-T-induced CRS are limited. Publications primarily describe outcomes in the context of clinical trials, which report incidence of severe CRS in 14–77% of patients [5, 6, 9, 12, 13]. In a pooled analysis of two phase 2, single-arm multicenter studies including 137 children and young adults who received Tisagenlecleucel CAR-T therapy for relapsed/refractory B-cell ALL, 42% experienced grade 3 or 4 toxicities including one-quarter who developed hypotension and one-third who required intubation [13]. The largest pediatric observational safety and efficacy analysis included 255 children with ALL in whom 16% developed severe CRS [3]. In this report, we aim to characterize the critical care support and outcomes across a multicenter cohort of children and young adults with ALL and CAR-T-induced CRS.

Materials and Methods

Colorado's Multiple Institutional Review Board waived the need for study approval (#21–3632). Data were obtained from the Virtual Pediatric Systems (VPS, LLC) Database, a multi-institutional registry of PICU-specific data available for quality improvement and research [14]. We identified patients with a diagnosis of ALL or unspecified leukemia and "Cytokine Release Syndrome/Cytokine Storm/Hyperinflammatory State related to CAR-T and other biologic/immunotherapy." We evaluated PICU admissions from January 1, 2020 (when CRS diagnosis was introduced in VPS, LLC) through December 31, 2021. We extracted patient characteristics including demographic information, admission source, and severity of illness scores (Pediatric Risk of Mortality [PRISM] III and Pediatric Index of Mortality [PIM] 3) [15, 16]. We evaluated clinical interventions including placement of support devices (tracheostomy, arterial catheter, hemodialysis catheter, intracranial catheter), cardiopulmonary resuscitation (CPR), extracorporeal membrane oxygenation (ECMO), respiratory support, and continuous renal replacement therapy (CRRT). The VPS, LLC Database contains optional data elements that were excluded if unavailable for more than 50% of patients (e.g., vasopressor support, organ dysfunction scores, and Functional Status Scale score) [17]. Our primary outcome was PICU mortality and secondary outcomes were PICU length of stay and in-hospital mortality. We characterized patients who received advanced organ failure support or monitoring including non-invasive or invasive ventilation support, CPR, ECMO, CRRT, or placement of a tracheostomy, arterial catheter, hemodialysis catheter, or intracranial catheter. Durations were calculated as end time minus start time. Analyses were conducted using R Statistical Software (version 4.0.2, Vienna).

Results

Of the 220,615 PICU admissions in the database, we identified 55 patients across 21 centers who had leukemia and CRS. Patients were most commonly 12 years or older (n=34; 62%) including 14 (25%) patients 18 years or older (Table 1). Patients were most frequently admitted from an inpatient hospital ward (n=48, 87%) and PRISM-III risk of mortality was median 5.3% (IQR 1.6%, 9.6%). Fifty-one (93%) patients survived to PICU discharge. Amongst survivors, PICU length of stay was median 3.0 days (IQR 1.4, 7.8). Of the 51 patients who survived to PICU discharge, 48 (94%) survived to hospital discharge.

Twenty-three (42%) patients required advanced organ failure support or monitoring (Table 2). Of these patients, 19 (83%) were supported with invasive or non-invasive mechanical ventilation initiated almost immediately after PICU admission. Of the 12 patients supported with invasive ventilation, 9 (75%) survived to PICU discharge. Fourteen (61%) patients underwent arterial catheter placement most commonly within two days of PICU admission and 4 (17%) were supported with CRRT a median 7.6 days (IQR 5.4, 11.1) after PICU admission. Two of four patients supported with CRRT and one of three patients who received CPR survived to PICU discharge. Median PICU length of stay was 7.8 days (IQR 5.4, 11.1). Nineteen (83%) patients survived to PICU discharge and 17 (74%) survived to hospital discharge.

Four (7%) patients died in the PICU. PRISM III risk of mortality was median 10.6% (IQR 1.0, 20.7) amongst those who died compared with 5.3% (IQR 1.7%, 9.6%) amongst PICU survivors. While in the PICU, these patients were supported with high levels of support including invasive ventilation (n=3), arterial catheter placement (n=3), CRRT (n=2), CPR (n=2), and ECMO (n=1). The duration of PICU stay amongst these four patients was variable with a median of 7.2 days (IQR 2.9, 14.7).

Discussion

In this multicenter cohort of critically-ill PICU patients in the VPS, LLC Database (2020–2021) with leukemia and CRS, nearly half required advanced organ failure support or monitoring. Despite high levels of support, most patients with critical illness due to CRS in this cohort survived their PICU stay and hospitalization. However, four patients died during their PICU admission, and these patients received significant interventions.

As PICU practitioners gain experience managing children with critical illness due to CRS, our ability to risk-stratify patients and identify those likely to benefit from advanced life support will improve. Specifically, the consideration to initiate ECMO is a complex clinical decision informed by incomplete evidence [18]. Recent publications have emphasized the importance of instituting robust decision-making processes to determine ECMO candidacy and, specifically for patients who have had a hematopoietic cell transplantation, candidacy should be considered in the context of patient and family preferences, comorbidities, and reversibility of underlying organ failure(s) [19, 20]. To better delineate the risks and benefits of advanced life support such as ECMO, multicenter cohorts of critically-ill children with CRS are necessary to inform our understanding of factors associated with favorable outcomes. This iterative knowledge will improve clinical decision-making for the oncologist, intensivist, patient, and family.

Limitations of this report include missing data elements related to patient and clinical factors that are not obligatorily reported within the VPS, LLC Database. These include organ dysfunction scores, leukemic disease burden, comorbidities, detailed characterization of infections and sepsis, timing of CRS onset and rapidity of progression, vasoactive support, and immunosuppressive treatments. It is also possible that some patients received alternative immunotherapies, such as Blinatumomab, resulting in CRS [21]. Additionally, the lack of key data elements and small cohort prohibits identification of risk factors associated with mortality.

Conclusions

As the use of novel immunotherapies in pediatric oncology becomes more common and broadens in scope, toxicity syndromes may become more prevalent. Pediatric intensive care practitioners must employ systematic evaluation of our combined experiences to build upon the knowledge derived from clinical trials to optimize the care we provide. Multicenter analyses and longitudinal investigations are needed to guide appropriate critical care support and optimize survival and long-term recovery.

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Table 1.

Characteristics and outcomes of patients based on survival to pediatric intensive care unit discharge

Characteristics and Outcomes	All (n=55)[a]	Survived to PICU Discharge (n=51)	Died prior to PICU Discharge (n=4)
Age, n (%)			
≥ 29 days and < 2 years	5 (9)	5 (10)	0 (0)
≥ 2 and < 12 years	16 (29)	13 (26)	3 (75)
≥ 12 and < 18 years	20 (37)	19 (37)	1 (25)
≥ 18 years	14 (25)	14 (27)	0 (0)
Female sex, n (%)	29 (53)	28 (55)	1 (25)
Patient origin, n (%)			
Home or Emergency Department	5 (9)	5 (10)	0 (0)
Transfer from In-Patient Floor	48 (87)	45 (88)	3 (75)
Inpatient Procedure Suite/Procedure Room	1 (2)	1 (2)	0 (0)
Transfer from another PICU	1 (2)	0 (0)	1 (25)
Severity of illness scores, median (IQR)			
PIM-3 percent risk of mortality (%)	5.0 (3.9, 6.8)	5.0 (3.9, 6.8)	5.8 (3.7, 7.2)
PRISM-III percent risk of mortality (%)	5.3 (1.6, 9.6)	5.3 (1.7, 9.6)	10.6 (1.0, 20.7)
Temperature > 38.3°C at time of PICU admission, n (%)[b]	35 (64)	33 (65)	2 (50)
Documented or suspected infection, n (%)[c]	22 (40)	20 (39)	2 (50)
Maximal respiratory support, n (%)			
Invasive mechanical ventilation[c]	12 (22)	9 (18)	3 (75)
Non-invasive ventilation	7 (13)	7 (14)	0 (0)
High flow nasal canula	4 (7)	3 (6)	1 (25)
None or Supplemental oxygen	32 (58)	32 (62)	0 (0)
Duration of invasive ventilation (days), median (IQR)	3.9 (2.6, 5.7)	4.7 (3.5, 6.5)	2.2 (2.1, 2.5)
Pediatric Intensive Care Unit Interventions			
Tracheostomy, n (%)	1 (2)	1 (2)	0 (0)
Arterial catheter placement, n (%)	14 (25)	11 (22)	3 (75)

Characteristics and Outcomes	All (n=55)[a]	Survived to PICU Discharge (n=51)	Died prior to PICU Discharge (n=4)
Hemodialysis or plasmapheresis catheter placement, n (%)	7 (13)	6 (12)	1 (25)
Continuous renal replacement therapy, n (%)[e]	4/52 (8)	2/48 (4)	2/4 (50)
Cardiopulmonary resuscitation, n (%)[e]	3/40 (8)	1/37 (3)	2/3 (67)
Extracorporeal membrane oxygenation, n (%)	1 (2)	0 (0)	1 (25)
Intracranial catheter placement, n (%)[e, f]	1/47 (2)	1/44 (2)	0/3 (0)
PICU length of stay (days), median (IQR)	3.1 (1.5, 8.0)	3.0 (1.4, 7.8)	7.2 (2.9, 14.7)
Survived to hospital discharge, n (%)	48 (87)	48 (94)	0 (0)

[a] Oncologic diagnoses were ALL (n=54) or unclassified leukemia (n=1).

[b] Highest temperature extracted from data available between 2 hours prior to PICU admission and 4 hours after PICU admission.

[c] Patients with a documented or suspected infection had an infectious diagnosis or a diagnosis of sepsis. 20/22 were present on admission and 2 developed during the PICU stay.

[d] No patients supported with high-frequency oscillatory ventilation

[e] When procedure data were not reported for entire cohort, denominator represents patients for whom each procedure was reported.

[f] One patient underwent intracranial catheter placement, which represented either an ICP monitor, external ventricular drain, or a brain tissue oxygen monitor (not otherwise specified in the data).

PICU: pediatric intensive care unit; IQR: interquartile range.

Table 2.

Characteristics and outcomes of patients who received advanced organ failure support or monitoring

Characteristics and Outcomes	Received Advanced Organ Failure Support or Monitoring (n=23)
Age, n (%)	
≥ 29 days and < 2 years	3 (13)
≥ 2 and < 12 years	5 (22)
≥ 12 and < 18 years	10 (43)
≥ 18 years	5 (22)
Female sex, n (%)	10 (43)
Patient origin, n (%)	
Home or Emergency Department	1 (4)
Transfer from In-Patient Hospital Ward	20 (87)
Inpatient Procedure Suite/Procedure Room	1 (4)
Transfer from another PICU	1 (4)
Severity of illness scores, median (IQR)	
PIM-3 percent risk of mortality	6.4 (4.4, 11.2)
PRISM-III percent risk of mortality	7.9 (3.5, 15)
Temperature > 38.3°C, n (%)[a]	14 (61)
Documented or suspected infection, n (%)[b]	10 (43)
Maximal respiratory support, n (%)	
Invasive mechanical ventilation[c]	12 (52)
Non-invasive ventilation	7 (31)
High flow nasal canula	1 (4)
None or Supplemental oxygen	3 (13)
Duration of invasive ventilation (days), median (IQR)	3.9 (2.6, 5.7)
Pediatric Intensive Care Unit Interventions, n (%)	
Tracheostomy placement	1 (4)
Arterial catheter placement	14 (61)
Hemodialysis or plasmapheresis catheter placement	7 (30)
Continuous renal replacement therapy	4 (17)
Cardiopulmonary resuscitation[d]	3/15 (20)
Extracorporeal membrane oxygenation	1 (4)
Intracranial catheter placement[d, e]	1/21 (5)
Time from PICU Admission to PICU Intervention (days), median (IQR)	
Non-invasive or invasive mechanical ventilation	0.1 (0, 0.9)
Arterial catheter placement	1.0 (0.5, 1.9)
Continuous renal replacement therapy	7.6 (4.6, 10.0)
PICU length of stay (days), median (IQR)	7.8 (5.4, 11.1)

Characteristics and Outcomes	Received Advanced Organ Failure Support or Monitoring (n=23)
Survived to PICU discharge, n (%)	19 (83)
Survived to hospital discharge, n (%)	17 (74)

[a]Highest temperature extracted from data available between 2 hours prior to PICU admission and 4 hours after PICU admission.

[b]Patients with a documented or suspected infection had an infectious diagnosis or a diagnosis of sepsis. All were present at the time of PICU admission.

[c]No patients supported with high-frequency oscillatory ventilation

[d]When procedure data were not reported for entire cohort, denominator represents patients for whom each procedure was reported.

[e]One patient underwent intracranial catheter placement, which represented either an ICP monitor, external ventricular drain, or a brain tissue oxygen monitor (not otherwise specified in the data).

PICU: pediatric intensive care unit; IQR: interquartile range.