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Risk Factors and Outcomes Related to Pediatric Intensive Care Unit Admission after Hematopoietic Stem Cell Transplantation: A Single-Center Experience

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A B S T R A C T

To describe incidence, causes, and outcomes related to pediatric intensive care unit (PICU) admission for patients undergoing hematopoietic stem cell transplantation (HSCT), we investigated the risk factors predisposing to PICU admission and prognostic factors in terms of patient survival. From October 1998 to April 2015, 496 children and young adults (0 to 23 years) underwent transplantation in the HSCT unit. Among them, 70 (14.1%) were admitted to PICU. The 3-year cumulative incidence of PICU admission was 14.3%. The main causes of PICU admission were respiratory failure (36%), multiple organ failure (16%), and septic shock (13%). The overall 90-day cumulative probability of survival after PICU admission was 34.3% (95% confidence interval, 24.8% to 47.4%). In multivariate analysis, risk factors predisposing to PICU admission were allogeneic HSCT (versus autologous HSCT, $P = .030$) and second or third HSCT ($P = .018$). Characteristics significantly associated with mortality were mismatched HSCT ($P = .011$), relapse of underlying disease before PICU admission ($P < .001$), acute respiratory distress syndrome at admission ($P = .012$), hepatic failure at admission ($P = .021$), and need for invasive ventilation during PICU course ($P < .001$). Our data indicate which patients have a high risk for PICU admission after HSCT and for dismal outcomes after PICU stay. These findings may provide support for the clinical decision-making process on the opportunity of PICU admission for severely compromised patients after HSCT.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) represents the only viable treatment option for selected children with malignant and nonmalignant disorders, even though this procedure may lead to severe complications often requiring admission to the pediatric intensive care unit (PICU). However, undergoing HSCT is confirmed to be a risk factor for mortality among this subset of patients [1,2]. Recent studies have reported that outcomes for these patients have improved over the course of years because of PICU technical advances (eg, noninvasive ventilation [NIV] and high-flow oxygen therapy [HFOT]) and improvements in supportive treatment during HSCT [1,3-6]. Nevertheless, the mortality rate is still high, especially when invasive ventilation (IV) and continuous renal replacement therapy are needed. Many ethical and end-of-life challenges regarding the appropriateness of using intensive care resources for this population exist [5-8]. Data regarding outcomes and risk factors associated with mortality in PICU are needed to establish the optimal clinical management of severely compromised patients after HSCT.

The aim of our study was to describe incidence, causes, and outcomes related to PICU admission of patients undergoing transplantation in the HSCT unit of University-Hospital of Padua. We investigated risk factors predisposing to PICU admission and prognostic factors associated with mortality in patients transferred to PICU.

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MATERIALS AND METHODS

Design of the Study and Population

We retrospectively reviewed the clinical records of all patients affected by oncologic and hematologic disorders undergoing HSCT in the pediatric HSCT unit of University-Hospital of Padua, between October 1998 and April

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2015. According to our institutional protocol, the following initial intensive supportive measures were established in the HSCT unit: noninvasive monitoring (pulse oximetry and electrocardiogram), 6-hour fluid balance monitoring, central venous pressure determination, HFOT, inotropic treatment with dopamine, and continuous morphine infusion. PICU admission criteria were the need for invasive or more frequent monitoring (such as continuous invasive arterial pressure monitoring), positive pressure ventilation, or a second inotropic drug. We considered all of the patients admitted to our departmental PICU after the initiation of conditioning for HSCT, with the following exclusion criteria: PICU admission for postoperative monitoring or procedural sedation and planned PICU admission for stem cell infusion in patients at risk (ie, age less than 1 year or severe congenital immunodeficiency). In accordance with the Declaration of Helsinki, parents and children/adolescents, when able to understand, were asked to sign the informed consent for transplantation procedure, data collection, and analysis.

Data Collection

Data were collected from the HSCT unit database and from the TIPnet database (http://tipnet.cineca.it) of our PICU. For each patient, we considered sex, age at HSCT, underlying disease, date and number of HSCT, status of disease at HSCT, total body irradiation, type of donor, relapse, and date of death or of last follow-up.

For children admitted to PICU, we gathered further data about HSCT, including donor/recipient HLA matching, occurrence of acute graft-versus-host disease (GVHD) [9] or chronic GVHD, engraftment for polymorphonuclears and platelets, and veno-occlusive disease [10]. In addition, data collected at PICU admission were date and cause of PICU admission, Pediatric Index of Mortality score 3 [11], partial oxygen pressure/fraction of O2 ratio, presence of fluid overload [12], presence of infections or viral reactivations, use of HFOT, and dopamine administration before PICU admission. Data collected at admission or anytime during PICU stay included the presence of pediatric acute respiratory distress syndrome (PARDS) [13], septic shock [14], acute kidney injury with Kidney Disease Improving Global Outcomes staging [15], hepatic failure, or *multiple organ failure*, defined as the involvement of >2 organs. Regarding PICU stay, the following data were recorded: need for NIV, HFOT, IV, high-frequency oscillatory ventilation, inhaled nitric oxide, external cardiac massage, or continuous renal replacement therapy; maximum number of vasoactive amines simultaneously administered; occurrence of aspergillosis; date of discharge; and cause of death.

Definitions

We classified the underlying disease in 2 groups: hematological disorders (acute lymphoblastic or myeloid leukemia, lymphoma, other hematological malignancies, nonmalignant disorders) and solid tumors. The status of disease at the time of stem cells infusion was classified as *complete remission* (CR) when the disease was in morphologic, instrumental, or molecular CR, or as *presence of disease* in the other cases. Donor/recipient were considered *HLA mismatched* if < 5/6 for bone marrow transplantations and peripheral blood stem cell transplantations and < 4/6 for cord blood transplantations; the HLA analysis was based on high-resolution genotyping. The day of the stem cells infusion was conventionally considered day 0. *Neutrophil engraftment* was defined as a neutrophil count $\geq .5 \times 10^9$/L for 3 consecutive days, and *platelet engraftment* was defined as a platelet count $\geq 50 \times 10^9$/L for 7 consecutive days independently of platelet transfusions. The definition of organ failure was based on the criteria of the TIPnet database, approved by a national consensus conference (available at www.tipnet.cineca.it).

Statistical Analysis

All statistical analyses were performed using the R statistical software, release 3.2.3 [16]. First, characteristics of patients requiring and not requiring PICU admission were compared. All patients entered the study at the first day of the conditioning regimen for their first HSCT. Univariate analysis of risk factors for PICU admission was conducted using Pearson chi-square test, Fisher exact test, or Mann Whitney U test. Gray's test was applied to compare the 3-year cumulative incidence of PICU admission in allogeneic and autologous HSCT. The competing risks regression model of Fine and Gray was applied in the multivariate analysis [17]. Then, survival probability and risk factors for patients admitted to PICU were investigated: the Kaplan-Meier estimate of the 90-day cumulative probability of survival after PICU admission was calculated and the 95% confidence intervals (CI) were computed using the Greenwood formula. The log-rank test was used to assess differences in the characteristics of patients before or at the time of PICU admission. The risk factors were then included in a multivariate analysis using the Cox proportional hazards model. The independence between parameters collected during PICU course and the state (dead/alive) of patients 90 days after PICU admission was evaluated through the Pearson chi-square test and Fisher exact test. A logistic regression model was used for the multivariate analysis of these variables. A P value <.05 was considered statistically significant.

RESULTS

Incidence and Causes of PICU Admission

Four hundred ninety-six patients were included in this study: 284 males (57.3%) and 212 females (42.7%). Among them, 465 received 1 HSCT, 29 patients underwent 2 HSCT, and 2 patients underwent 3 HSCT, for a total of 529 HSCT procedures. The median age at first transplantation was 8.3 years (range, .2 to 23.6 years). Overall, 70 patients were admitted to PICU: 60 of 465 (12.9%) after their first HSCT, 8 of 29 (27.6%) after their second HSCT, and 2 of 2 (100%) after their third HSCT. The 3-year cumulative incidence of admission was 14.3% (95% CI, 11.1% to 17.4%). Regarding patients admitted to PICU, 56 of 70 (80%) were admitted once and 14 of 70 (20%) patients required 2 or more admissions, for a total number of 92 PICU admissions. The number of HSCT performed and the number of PICU admissions per year are shown in Figure 1. Forty-six out of 70 patients (65.7%) were admitted to PICU within 3 months of their last HSCT. Median time from stem cell infusion to the first admission was 49 days, ranging from -6 days (2 patients admitted during conditioning) to 3 years. All of the 7 children admitted later than 12 months after the HSCT were affected by chronic GVHD. The causes for the 92 PICU admissions are reported in Table 1. The median length of PICU stay was 7 days (range, 1 to 81 days).

Table 1
Causes of PICU Admission*

Cause	n	%	Time of PICU admission, median (range), days from last HSCT
Respiratory failure	33	36	61 (6-1546)
Viral pneumonia (CMV, EBV, adenovirus, parainfluenza virus, or combined)	9		39 (15-92)
Lobar pneumonia	5		15 (11-409)
Aspergillosis	5		185 (97-583)
PARDS	4		117.5 (76-228)
Interstitial pneumonia	4		16.5 (16-61)
Bronchiolitis obliterans due to cGVHD	2		972 (398-1546)
Pulmonary edema	1		463
Pneumothorax	1		270
Epiglottitis	1		6
Cellulitis	1		45
Organ failure	15	16	15 (3-403)
MOF	13		16 (3-403)
VOD	2		14.5 (14-15)
Septic shock	12	13	87.5 (1-494)
Neurological dysfunction	11	12	106 (-6-1132)
Coma	6		121.5 (43-1132)
Status epilepticus	4		69 (-6-134)
Posterior reversible encephalopathy syndrome	1		409
Acute kidney injury	9	10	23 (0-1102)
Hypovolemic shock	6	7	78.5 (39-208)
Heart failure	5	5	166 (29-267)
Cardiogenic shock	2		201 (166-236)
Pericardial effusion	2		167 (67-267)
Ventricular arrhythmia with hypokalemia	1		29
Adverse drug reaction	1	1	47

CMV indicates cytomegalovirus; EBV, Epstein-Barr virus; cGVHD, chronic graft-versus-host disease; MOF, multiple organ failure; VOD, veno-occlusive disease.

* Includes 92 admissions