Reduced-Intensity Conditioning Allogeneic Stem Cell Transplantation in Pediatric Patients and Subsequent Supportive Care

Catherine Barrell, RN, MSN, PNP-BC, Danielle Dietzen, RN, MSN, CPNP, Zhezhen Jin, PhD, Sharon Pinchefsky, RN, MSN, CPNP, Kristen Petrillo, RN, BSN, and Prakash Satwani, MD

Myeloablative conditioning (MAC) followed by allogeneic hematopoietic stem cell transplantation (AlloHSCT) is a well-established treatment for a variety of malignant and nonmalignant diseases in children and adults (Thomas, 1983). The backbone of these regimens consists of cytotoxic high-dose chemotherapy and/or total body irradiation, which are associated with a 20%–40% incidence of transplantation-related mortality (TRM). The majority of transplantation-related deaths tend to occur in the first 100 days following MAC-AlloHSCT (Satwani et al., 2008). Along with high rates of mortality, MAC-AlloHSCT also is associated with a high incidence of acute morbidities. These regimen-related toxicities include severe mucositis (requiring opioid patient-controlled analgesia [PCA] and total parenteral nutrition [TPN]), infections, and veno-occlusive disease, all of which can require transfer to a pediatric intensive care unit (PICU) (DeLeve, Shulman, & McDonald, 2002). Avritscher, Cooksley, and Elting (2004) reported that patients with mucositis are more likely to develop infections, require PCA, and experience significant weight loss. A study by Socie et al. (1999) revealed the consequences of these toxicities when the authors reported that, although 6,691 patients achieved long-term survival two years after MAC-AlloHSCT, 375 patients died of secondary complications such as graft-versus-host disease (GVHD), infections, secondary malignancy, and organ failure 6–10 years post-treatment.

The development of nonmyeloablative conditioning was initially designed to treat patients aged 60 years and older with poor performance status, organ dysfunction, or extensive prior therapy (Barker et al., 2003). Nonmyeloablative conditioning regimens are defined

Purpose/Objectives: To determine if children undergoing reduced-intensity conditioning allogeneic hematopoietic stem cell transplantation (RIC-AlloHSCT) have lower incidence of acute toxicities and, subsequently, require less supportive care than is required with myeloablative conditioning (MAC)-AlloHSCT. An additional purpose is to examine later outcomes by comparing 100-day transplantation-related mortality (TRM).

Design: Retrospective chart and electronic medical records review.

Setting: A pediatric care center in the northeastern United States.

Sample: 86 patients who underwent AlloHSCT from January 2004 through March 2008.

Methods: Charts were retrospectively reviewed. The comparison between groups was done by t test (continuous variables) and chi-square test (categorical variables). The logistic regressions, Kaplan-Meier product-limit estimator, log rank test, and Cox proportional hazards model were used.

Main Research Variables: Days requiring total parenteral nutrition (TPN), patient-controlled analgesia (PCA), incidence of mucositis, days with fevers, number of infections, transfers to pediatric intensive care unit (PICU), blood product infusions, and 100-day TRM, all for 30 days post-transplantation.

Findings: When comparing pediatric patients undergoing RIC-AlloHSCT (n = 43) versus MAC-AlloHSCT (n = 43) in the first 30 days post-transplantation, a statistically significant decreased incidence was noted for mucositis, infections, transfers to PICU, days on TPN and PCA, and days with fever, as well as 100-day TRM.

Conclusions: For pediatric patients, RIC-AlloHSCT is associated with significantly lower acute post-transplantation toxicities and TRM than MAC-AlloHSCT.

Implications for Nursing: For nurses to correctly educate their patients and family members, and to aid nurses in anticipating patient's needs, an understanding of the potential different acute toxicities and supportive care between pediatric patients undergoing RIC- versus MAC-AlloHSCT is vital.

as those that should not eradicate host hematopoiesis and should allow relatively prompt hematopoietic recovery (in less than 28 days) without a transplantation (Champlin et al., 2000). However, the nonmyeloablative conditioning regimens were associated with higher risk of graft failure. Subsequently, reduced-intensity conditioning (RIC) regimens were developed with more intense chemotherapy and/or radiotherapy to promote engraftment. RIC regimens differ from nonmyeloablative conditioning regimens because RIC regimens require an AlloHSCT for hematologic recovery and, if the graft is rejected, prolonged aplasia typically occurs.

RIC regimens have been adopted in pediatric patients to achieve the goal of long-term overall survival with the hope of decreased acute and long-term toxicities. In children, particularly with nonmalignant diseases, the goal of AlloHSCT should not only focus on cure but also prevent short- and long-term toxicities. Because myeloablation is not required to establish donor cell engraftment, RIC-AlloHSCT has been shown to provide enough immunosuppression to promote engraftment and correct underlying defects of nonmalignant conditions. In malignant disease, RIC-AlloHSCT has shown to be effective by eradicating malignant cells through a graft-versus-malignancy effect provided by alloreactive donor T-lymphocytes and/or natural killer cells (Satwani et al., 2008).

The limited published data on RIC-AlloHSCT have primarily focused on acute toxicities and TRM in adults. Unfortunately, even less has been published on the pediatric population (ages 3 months to 21 years) (Bradley et al., 2007; Del Toro et al., 2004; Pulsipher et al., 2009; Satwani et al., 2008). No studies have specifically looked at acute post-transplantation toxicities and the need for supportive care. In particular, no data exist related to blood and platelet transfusions requirements, days requiring PCA and TPN, and PICU transfers. Because of this lack of published data, the authors' goal was to determine if pediatric patients undergoing RIC-AlloHSCT have lower incidence of acute toxicities and, subsequently, require less supportive care than what is required with MAC-AlloHSCT. The working hypothesis was that patients receiving RIC-AlloHSCT would have a lower incidence of acute toxicities and require less supportive care than patients undergoing MAC-AlloHSCT. A retrospective review was conducted comparing all pediatric patients who underwent RIC-AlloHSCT with patients who received MAC-AlloHSCT at the New York-Presbyterian Morgan Stanley Children's Hospital in New York, NY, part of the Columbia University Medical Center. The differences in specific complications, incidence of acute post-transplantation toxicities, need for additional supportive care, and, ultimately, differences in TRM between the two groups were reviewed.

Methods

Design, Setting, and Participants

The retrospective study compared the occurrence of acute post-transplantation toxicities including mucositis, infection, neutropenia, and thrombocytopenia and subsequent supportive care treatments indicated for these toxicities. The supportive care measures examined were days on TPN and PCA and number of transfusions in patients undergoing RIC- versus MAC-AlloHSCT. All patients receiving RIC- or MAC-AlloHSCT at the Morgan Stanley Children's Hospital from January 2004 to March 2008 were included in this study. The date to start the review was chosen when the Children's Hospital of New York-Presbyterian moved to a newly constructed building, so that the environment where the pediatric patients were hospitalized would not be a confounding factor (the new building had a more efficient air purification center and electronic medical records were available). Data collection was started in July 2008; therefore, March was selected as an endpoint so all patients would be evaluable at the 100-day post-transplantation mark. Indications for transplantation included both malignant and nonmalignant conditions. Allogeneic sources of stem cells included bone marrow (BM), peripheral blood stem cells (PBSCs), and umbilical cord blood (UCB). Data were collected from paper and electronic

Fever: axillary or oral temperature of 100.5°F or greater two times at least one hour apart or one temperature reading of 101°F or greater

Infection: positive blood culture, positive culture from sterile sites, persistent positive viral polymerase chain reaction with or without evidence of systemic disease

Myeloid engraftment: the first day of two consecutive absolute neutrophil counts (ANCs) greater than 500 x 10^9/L

Poor risk malignant patients: patients with chemotherapy-resistant malignant disease, third complete remission or greater, induction failure, progressive disease, and/or receiving second allograft

Primary graft failure (PGF): a failure to achieve a donor-derived ANC of 500 x 10^9/L or greater by day +42 and/or 50% or less whole blood donor chimerism by day +60 in all except patients with immune deficiency. In patients with T-cell or combined immune deficiency, PGF was defined as 50% or less T-cell (CD3) donor chimerism by day +180. Patients who received a second stem cell infusion before day +42 for impending graft failures also were considered to have PGF.

Time to platelet engraftment: the first day post-nadir when platelets were greater than 20 x 10^9/L without transfusions during the previous seven days

Treatment-related mortality: death from any cause related to transplantation process other than disease relapse

Figure 1. Definitions of Main Research Variables

medical records. Four members of the pediatric HSCT team—three nurse practitioners and one quality control nurse—collected the data. A worksheet was developed by the first author of this article to ensure all members were collecting accurate data. At the start of data collection, each member of the team separately reviewed two patients' charts using the worksheet to test for reliability. All four team members' data collected on the worksheet were the same for the two patients' charts; therefore, the worksheet was validated as a reliable tool for accurate data collection. The only exclusion criterion was patients whose paper charts were not available for review in the medical records department (n = 4).

All patients were on clinical protocols for AlloHSCT approved by the institutional review board at Columbia University Medical Center, and all research protocols were in compliance with the Declaration of Helsinki. Separate institutional review board approval was received for the current study.

Conditioning Regimens

Specific conditioning regimens were protocol- and disease-specific. All patients and their parents were educated on the differences between RIC- and MAC-AlloHSCT regimens. A recommendation to each patient and parent on the type of regimen to use was made by the HSCT physician based on availability of open clinical trials and an evaluation of the patient's disease type and status. No randomization was done between types of regimen. An option for standard MAC-AlloHSCT was provided to all the patients and their parents. Parents of patients younger than age 18 signed informed consent, and patients aged 8–18 years signed informed assent.

The RIC regimen included patients who received busulfan (6.4–8 mg/kg), fludarabine (150–180 mg/m^2) with or without rabbit antithymocyte globulin (R-ATG) or busulfan (12.8–16 mg/kg), or fludarabine (150–180 mg/m^2) with or without alemtuzumab (54 mg/m^2). The MAC regimen included total body irradiation (12 GY with or without cyclophosphamide 120 mg/kg or melphalan 135 mg/m^2) or busulfan (12.8–16 mg/kg), with cyclophosphamide (120 mg/kg) or melphalan (135 mg/m^2) with or without R-ATG (only given to patients receiving unrelated donor cells) or cyclophosphamide (200 mg/kg) with fludarabine (180 mg/m^2) plus R-ATG.

Infection Prophylaxis and Supportive Care

Supportive care HSCT protocols used by the authors' program have been previously reported and include prophylaxis for GVHD (Bhatia et al., 2010), fungi, *Pneumocystis jiroveci*, herpes simplex virus, and cytomegalovirus (Roman et al., 2008; Shereck, Cooney, van de Ven, Della-Lotta, & Cairo, 2007).

Data Analysis

The continuous variables were summarized as mean and standard deviation, and categorical variables were summarized as percentages. The comparison between two groups was done by t test for continuous variables and chi-square test for categorical variables. The logistic regression models were used to identify risk factors for the incidences of grade 2 or higher mucositis, two or more infections, six or more platelet transfusions, four or more packed red blood cell transfusions, and seven days or more of fever (see Figure 1). The Kaplan-Meier product limit estimator was used for the estimation of the probabilities of acute GVHD, neutrophil and platelet recovery, and TRM. The estimated probabilities were summarized along with standard errors. The log rank test was used to assess the difference in these probabilities among different groups, and Cox proportional hazards models were used for multivariate analysis. Factors included in univariate analysis were age, gender, malignant versus nonmalignant diseases, RIC- versus

Table 1. Demographic and Clinical Characteristics of Pediatric Recipients of AlloHSCT

	RIC (N = 43)		MAC (N = 43)		
Characteristic	$\bar{X}$	**SD**	$\bar{X}$	**SD**	**p**
Age (years)	10.5	6.66	10.34	6.4	0.929
Characteristic	**n**		**n**		**p**
Gender					
Male	28		27		0.82
Female	15		16		
Disease type[a]					
Malignant	23		32		0.043
Nonmalignant	20		11		
Risk type					
Average risk	40		29		0.003
Poor risk	3		14		
Donor source					
Cord	17		21		0.056
Unrelated	6		12		
Related	20		10		
HLA match					
Full match	18		22		0.387
Mismatched	25		21		

[a] For malignant, disease types include acute myeloid leukemia, acute lymphoblastic leukemia, chronic myeloid leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma, brain tumor, myelodysplastic syndrome, and neuroblastoma. For nonmalignant, disease types include severe aplastic anemia, sickle cell disease, hemophagocytic lymphohistiocytosis, Thalassemia major, Fanconi's anemia, and leukodystrophy.

AlloHSCT—allogeneic hematopoietic stem cell transplantation; HLA—human leukocyte antigen; MAC—myeloablative conditioning; RIC—reduced-intensity conditioning

MAC-AlloHSCT, average versus poor risk disease status, fully human leukocyte antigen (HLA) matched versus HLA mismatched donor, and donor sources. Factors with p value less than 0.2 were included in multivariate analysis. A p value of less than 0.05 was considered significant on multivariate analysis. All statistical analyses were performed using SAS®, version 9.2.

Results

Demographics

The sample size consisted of 86 pediatric patients. The mean age was similar in the RIC- (10.5 years) and the MAC-AlloHSCT (10.34 years) groups. No significant differences were noted between the RIC and MAC groups with regard to gender or disease type (malignant versus nonmalignant). The MAC-AlloHSCT group did, however, have a significantly higher number of patients with poor risk disease compared to RIC-AlloHSCT (14 versus 3, p = 0.003). The authors included patients who received their stem cells from different donor sources, such as UCB, unrelated donors (BM and PBSCs), and related (sibling or maternal) donors (BM and PBSCs). The only marginally significant difference in donor source was a higher number of related donors in the RIC-AlloHSCT group (p = 0.056). No difference was noted when comparing both groups' HLA disparity (full matched versus mismatched). Demographic details are listed in Table 1.

Table 2. Incidence of Mucositis, Infections, PICU Transfers, and Transfusion Requirements on Day +30 in Pediatric Recipients of AlloHSCT

	RIC (N = 43)	MAC (N = 43)	
Characteristic	**n**	**n**	**p**
Mucositis grade			
0–1	28	12	0.0005
Greater than 1	15	31	
Number of infections			
0–1	36	23	0.003
Greater than 1	7	20	
Patients with line removed	2	5	0.237
PICU transfers	3	15	0.002
Platelet			
0–5	21	4	<0.001
6 or greater	22	39	
Packed red blood cells			
0–3	24	19	0.281
Greater than 3	19	24	

AlloHSCT—allogeneic hematopoietic stem cell transplantation; MAC—myeloablative conditioning; PICU—pediatric intensive care unit; RIC—reduced-intensity conditioning

Note. Day +30 includes all incidences that occurred in the first 30 days post-HSCT.

Hematopoietic Reconstitution and Graft-Versus-Host Disease

Although graft failure is a common concern in RIC regimens, no statistically significant difference was found between the RIC- and MAC-AlloHSCT groups. The incidence of primary graft failure was three patients (7%) in the RIC-AlloHSCT group and four patients (9%) in the MAC-AlloHSCT group (p = 0.69). The probability of neutrophil recovery during the first 42 days following AlloHSCT was 93% (standard error of mean [SEM] 3.88%) for RIC-AlloHSCT and 86% (SEM 5.28%) for MAC-AlloHSCT (p = 0.196). However, the probability of platelet engraftment during the first 100 days was 84% (SEM 5.63%) for RIC-AlloHSCT and 63% (SEM 7.37%) for MAC-AlloHSCT (p = 0.022).

The probability of acute grade 2–4 GVHD during the first 100 days was 40% (SEM 7.46%) for RIC-AlloHSCT and 54% (SEM 7.6%) for MAC-AlloHSCT (p = 0.16). Although the likelihood of acute GVHD in the first 100 days post-AlloHSCT was lower in the RIC group, it was not statistically significant.

Veno-Occlusive Disease and Renal Dysfunction

Renal and hepatic dysfunction often are observed in patients following AlloHSCT. A review of the data did not demonstrate a significant disparity between the RIC- and MAC-AlloHSCT groups with regard to renal function post-AlloHSCT. No incidence of veno-occlusive disease was noted in patients undergoing RIC, whereas three patients in the MAC-AlloHSCT group developed veno-occlusive disease. That was not found to be statistically significant.

Infections

The numbers of infections in the first 30 days following AlloHSCT were recorded. The types of infections included bacterial, viral, and fungal infections in the blood, gastrointestinal, respiratory, and urinary tract. A significantly higher incidence (p = 0.004) of three or more documented infections were noted in the MAC-AlloHSCT group (n = 9) compared to the RIC-AlloHSCT group (n = 0). Although not statistically significant, the authors found that five patients in the MAC-AlloHSCT group required central venous line removal because of infection in contrast to only two patients in the RIC-AlloHSCT group (see Table 2).

Mucositis

The review showed that a statistically higher (p = 0.001) number of patients in the MAC group (n = 23) compared to the RIC group (n = 9) developed severe grade 3 or higher mucositis.

Supportive Care

The probability of fever during the first 30 days was 81% (SEM 5.93%) for RIC-AlloHSCT and 88% (SEM 4.89%) for MAC-AlloHSCT (p = 0.817). The authors examined the incidence of days with fever during the first 30 days following AlloHSCT. For the RIC-AlloHSCT group, 11 patients (26%) had fever for more than seven days; for the MAC-AlloHSCT group, 23 patients (54%) had fever more than seven days (p = 0.008).

The probability of TPN requirement during the first 30 days was 47% (SEM 7.61%) for RIC-AlloHSCT and 70% (SEM 7%) for MAC-AlloHSCT (p = 0.0013). The probability of PCA requirement during the first 30 days was 33% (SEM 7.15%) for RIC-AlloHSCT and 81% (SEM 5.93%) for MAC-AlloHSCT (p < 0.0001) (see Figure 2).

The probability of platelet transfusion requirement during the first 100 days was 84% (SEM 5.63%) for RIC-AlloHSCT and 63% (SEM 7.37%) for MAC-AlloHSCT (p = 0.022). The review also found that half of the patients in the MAC-AlloHSCT group (n = 22) required more than 15 platelet transfusions within the first 30 days post-transplantation. That figure was significantly higher (p = 0.001) than the RIC group (n = 4). The authors did not note a significant difference for red blood cell transfusion requirements between the two groups.

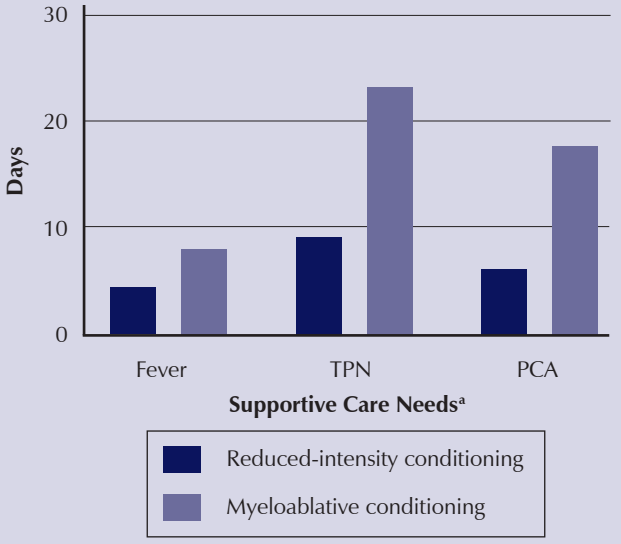
A comparison of the number of transfers to the PICU between the two groups was performed. A substantially higher (p = 0.003) number of patients from the MAC-AlloHSCT group (n = 15) compared to the RIC-AlloHSCT group (n = 3) were transferred to the PICU for various reasons.

Transplantation-Related Mortality

The review found that the incidence of TRM at 100 days was 16% in the MAC-AlloHSCT group and only 2% in the RIC-AlloHSCT group, which was statistically significant (p < 0.029).

Univariate and Multivariate Analysis

Cox logistic regression analysis and log rank tests were used for univariarte and multivariate analysis. Significant risk factors in univariate analysis were included in the multivariate analysis. On multivariate analysis, MAC-AlloHSCT was independently and significantly associated with higher incidence of mucositis (p = 0.0113), risk of infection (p = 0.0034), number of platelet transfusions (p = 0.0021), PICU transfers (p = 0.0021), and number of days with fever (p = 0.0239), PCA (p = 0.0047), and TPN requirements (p = 0.0078) (see Table 3). The only other risk factors significant on multivariate analysis were that males (p = 0.0389) had higher risk of infections and patients who received AlloHSCT from matched related donors (p = 0.0395) had lower number of platelet transfusions compared to UCB transfusions.



[a] p < 0.001 for fever, TPN, and PCA
PCA—patient-controlled analgesia; TPN—total parenteral nutrition

Figure 2. Incidence for Days With Fever, Days of TPN, and Days of PCA (Day +30)

Discussion

This retrospective study found that RIC-AlloHSCT significantly decreased the incidence of acute post-transplantation toxicities, including patients who developed grade 3 or higher mucositis and reduced days with fever. This, subsequently, reduced the amount of supportive care required, including decreased need for PCA and TPN. The decrease in the incidence of these complications may be attributed to the fact that many of the patients in the RIC-AlloHSCT group had shorter periods of neutropenia and lower grades of mucositis. The reduction in severity of mucositis may decrease the probability of translocation of bacteria from the gut and, therefore, contribute to the substantially lower incidence of infections found in patients undergoing RIC-AlloHSCT versus MAC-AlloHSCT. Infections can lead to escalated care needs such as transfer to PICU, increased cost, complex nursing care, and, ultimately, longer hospital stays for patients. An illustration of decreased costs associated with a decreased number of infections was presented in a report by the Centers for Disease Control and Prevention (2011). The report found that a 58% reduction in central line-associated blood stream infections from 2001 to 2009 "represents up to 6,000 lives saved and $414 million in potential excess healthcare costs in 2009 and about $1.8 billion in cumulative excess healthcare costs since 2001" (p. 243). The decrease in TPN requirement also could be linked to the lower incidence of severe mucositis in patients following

Table 3. Multivariate Analysis for Significant Risk Factors Associated With Need for Supportive Care at Day +30 in Pediatric Recipients of AlloHSCT

Characteristic[a]	Odds Ratio/ Hazard Ratio	95% Wald/Hazard Confidence Interval	p
Mucositis			
RIC	1		
MAC	4.25	[1.388, 13.016]	0.0113
Infections			
RIC	1		
MAC	4.751	[1.675, 13.474]	0.0034
Female	1		
Male	2.905	[1.056, 7.995]	0.0389
Platelet transfusions			
RIC	1		
MAC	7.42	[2.069, 26.613]	0.0021
Cord blood	1		
MRD	0.273	[0.079, 0.939]	0.0395
PICU transfers			
RIC	1		
MAC	7.513	[1.77, 31.882]	0.0062
Fever[b]			
RIC	1		
MAC	3.109	[1.162, 8.317]	0.0239
PCA			
RIC	1		
MAC	2.656	[1.348, 5.231]	0.0047
TPN			
RIC	1		
MAC	2.122	[1.219, 3.695]	0.0078

[a] Significant on univariate analysis

[b] A fever for seven days versus a fever of more than seven days. Analysis was based on logistic regression model, adjusted for age and disease type.

AlloHSCT—allogeneic hematopoietic stem cell transplantation; MAC—myeloablative conditioning; MRD—matched related donor; PCA—patient-controlled analgesia; PICU—pediatric intensive care unit; RIC—reduced-intensity conditioning; TPN—total parenteral nutrition

Note. Day +30 includes all incidences that occurred in the first 30 days post-HSCT.

Note. Mucositis was adjusted for age, disease type, risk status, and donor source; platelet transfusion was adjusted for risk status and donor source; PICU transfer was adjusted for age and donor source; PCA was adjusted for age, disease type, risk status, and donor source; and TPN was adjusted for age and disease type.

RIC-AlloHSCT. Avritscher et al.'s (2004) review on mucositis examined cost of mucositis, including TPN and PCA, and reported multiple studies with additional costs associated with the presence of mucositis ranging from $23,850–$43,000 per patient undergoing HSCT.

Another time-consuming and costly part of caring for pediatric patients undergoing AlloHSCT is blood product administration. Each blood product administered puts the patient at risk for transfusion-related complications, such as infections and allergic reactions. The number of platelet transfusions required was significantly reduced for patients in the RIC-AlloHSCT group compared to the MAC-AlloHSCT group. As corroborated in the authors' results, it has been previously reported that many patients who receive RIC-AlloHSCT have less thrombocytopenia (Diaconescu et al., 2004). Shelburne and Bevans (2009) highlighted the importance of "the decreased degree and length of anemia and thrombocytopenia. . . . This translates into fewer red cell and platelet transfusions" (p. 123). Consequently, lower transfusion requirements mean decreased risk of transfusion-related complications, less time spent administering transfusions for nursing staff, and reduced costs for hospitals. The cost of a single platelet transfusion varies based on each hospital's contract with a blood center. At New York-Presbyterian Hospital, for example, the average cost of a single donor platelet transfusion is $500 (J. Schwartz, personal communication, September 20, 2011).

Complexity of care is directly affected by acute toxicities in the immediate post-transplantation period. Pediatric patients who receive RIC-AlloHSCT have less acute toxicities, and this may positively impact the emotional and psychological well-being of patients and their families. Again, however, lower transplantation-related complications also could result in decreased time nurses need to spend on direct patient physical care, decreased resource use (i.e., medications, TPN, PICU beds), and, therefore, cost. Saito et al. (2007) found that RIC-AlloHSCT costs, on average, $53,030 per patient less than MAC-AlloHSCT in the first year post-transplantation.

Future studies examining psychosocial impact, nursing hours, medication use, and overall cost of RIC- versus MAC-AlloHSCT are needed. Reduction in transplantation-related morbidities might result in decreased length of hospital stay and cost of hospitalization. Going forward, as healthcare providers learn more about RIC-AlloHSCT, transplantations may be performed in outpatient settings. That would be cost effective for hospitals as well as beneficial to families who have the resources and the educational support from nurses to care for their children in a home setting.

This study was unable to show a significant difference in specific organ toxicities (renal and liver) or incidence of acute GVHD in the first 100 days post-transplantation. That was most likely from limitations related to a small sample size. Similarly, because of a limited amount of data published pertaining to this pediatric population, it was not possible to compare the results of this retrospective study with other studies. That was impacted even more by the fact that this study looked at acute toxicities as opposed to other studies, which concentrated on longer-term TRM.

Limitations

This study is limited by the small number of patients with different diagnoses and different conditioning regimens within the group. The demographics of the RIC- versus MAC-AlloHSCT groups were comparable, except that more patients had nonmalignant diseases, more patients had matched sibling donors, and fewer high-risk patients were in the RIC-AlloHSCT group. All of these factors may contribute to fewer or less severe acute toxicities in the RIC-AlloHSCT group. On multivariate analysis, the authors were able to demonstrate that MAC-AlloHSCT was independently associated with higher-grade mucositis, higher risk of infections, greater need for platelet transfusions, a higher number of PICU transfers, and increased need for PCA and TPN. However, retrospective studies are inherently subjected to various biases and that cannot be ruled out in the current study.

Conclusions

Despite these limitations, this study did confirm the working hypothesis and reveals promising data that RIC-AlloHSCT results in decreased acute toxicities, reduced supportive care needs, and, most importantly, reduced TRM. And, regardless of the decreased incidence and degree of acute toxicities and the amount of supportive care needed, the ultimate goal of any transplantation is cure, and the results show that RIC-AlloHSCT was associated with lower TRM before day 100 than MAC-AlloHSCT.

Implications for Nursing

Nurses are now at the forefront of collecting data for National Quality Forum based on the National Database of Nursing Quality Indicators (NDNQIs). The American Nurses Association (2010) defined the NDNQIs to include patient outcomes that are determined to be nursing sensitive—outcomes that improve if a greater quantity or quality of nursing care is indicated. Currently, healthcare-associated infections and nursing care hours provided per day are NDNQIs. In the current study, patients in the RIC-AlloHSCT group had fewer infections—and additional research is still needed—but, based on the decreased supportive care needs (e.g., blood transfusions and days on TPN with PCA), pediatric patients receiving RIC-AlloHSCT most likely required fewer nursing care hours per day than pediatric patients receiving MAC-AlloHSCT. An important area of additional research will be to more closely look at the NDNQI in patients receiving RIC- versus MAC-AlloHSCT in hopes of continuing to illustrate the fewer toxicities and potential benefits of RIC-AlloHSCT in pediatric patients. In addition, the regimen should always be chosen with the goal of the best possible patient outcome of survival and the least number of toxicities. However, in the current state of rising healthcare costs, a secondary gain of RIC-AlloHSCT is an appropriate regimen choice and the potential cost saving through decreased nursing care hours.

Nurses play a vital role in the education of patients and their families. HSCT nurses must understand this new and evolving field of RIC-AlloHSCT and, subsequently, the difference between RIC-AlloHSCT and MAC-AlloHSCT and the potential impact the different types of transplantation may have on their patients. Nursing assessment of patients' symptoms (e.g., anorexia, pain, fatigue) often play a direct role in the supportive care that is used, including the need for TPN, PCA, and blood transfusions. Therefore, understanding findings from the current study will aid the nurse in anticipating patients' supportive care needs as well as help nurses provide accurate anticipatory guidance to patients and their families.

The authors gratefully acknowledge the contributions of Monica Bhatia, MD, Mitchell S. Cairo, MD, Bradford Tallamy, BA, and Tracey Schonfeld, RN, BSN, in the preparation of this article. The authors also extend sincere thanks to the nursing team for providing excellent care to the HSCT recipients.

Catherine Barrell, RN, MSN, PNP-BC, is a pediatric nurse practitioner in the Home Parenteral Nutrition Program at Children's Hospital Boston in Massachusetts; and Danielle Dietzen, RN, MSN, CPNP, is a pediatric nurse practitioner of blood and marrow transplantation at New York-Presbyterian Morgan Stanley Children's Hospital, Zhezhen Jin, PhD, is an associate professor in the Department of Biostatistics in the Mailman School of Public Health at Columbia University, Sharon Pinchefsky, RN, MSN, CPNP, is a pediatric nurse practitioner of blood and marrow transplantation at New York-Presbyterian Morgan Stanley Children's Hospital, Kristen Petrillo, RN, BSN, is a research nurse of pediatric blood and marrow transplantation at New York-Presbyterian Morgan Stanley Children's Hospital, and Prakash Satwani, MD, is an assistant professor of pediatric blood and marrow transplantation at New York-Presbyterian Morgan Stanley Children's Hospital, all in New York. No financial relationships to disclose. Barrell can be reached at barrellc@yahoo.com, with copy to editor at ONFEditor@ons.org. (Submitted September 2011. Accepted for publication December 1, 2011.)

Digital Object Identifier: 10.1188/12.ONF.E451-E458

References

American Nurses Association. (2010). *Guidelines for data collection on the American Nurses Association's National Quality Forum Endorsed Measures*. Washington, DC: Author.

Avritscher, E., Cooksley, C., & Elting, L. (2004). Scope and epidemiology of cancer therapy-induced oral and gastrointestinal mucositis. *Seminars in Oncology Nursing, 204*, 3–10.

Barker, J.N., Weisdorf, D.J., DeFor, T.E., Blazar, B.R., Miller, J.S., & Wagner, J.E. (2003). Rapid and complete donor chimerism in adult recipients of unrelated donor umbilical cord blood transplantation after reduced-intensity conditioning. *Blood, 102*, 1915–1919. doi:10.1182./blood-2002-11-3337

Bhatia, M., Militano, O., Jin, Z., Figurski, M., Shaw, L., Moore, V.,

. . . Cairo, M.S. (2010). An age-dependent pharmacokinetic study of intravenous and oral mycophenolate mofetil in combination with tacrolimus for GVHD prophylaxis in pediatric allogeneic stem cell transplantation recipients. *Biology of Blood and Marrow Transplantation, 16,* 333–343. doi:101.1016/j.bbmt.2009.10.2007

Bradley, M.B., Satwani, P., Baldinger, L., Morris, E., van de Ven, C., Del Toro, G., . . . Cairo, M.S. (2007). Reduced intensity allogeneic umbilical cord blood transplantation in children and adolescent recipients with malignant and non-malignant diseases. *Bone Marrow Transplantation, 40,* 621–631. doi:10.1038/sj.bmt.1705785

Centers for Disease Control and Prevention. (2011). Vital signs: Central line-associated blood stream infections—United States, 2001, 2008, and 2009. *Morbidity and Mortality Weekly Report, 60,* 243–248.

Champlin, R., Khouri, I., Shimoni, A., Gajewski, J., Kornblau, S., Molldrem, J., . . . Anderlini, P. (2000). Harnessing graft-versus-malignancy: Non-myeloablative preparative regimens for allogeneic haematopoietic transplantation, an evolving strategy for adoptive immunotherapy. *British Journal of Haematology, 111,* 18–29. doi:10.1111/j.1365-2141.2000.02196

DeLeve, L.D., Shulman, H.M., & McDonald, G.B. (2002). Toxic injury to hepatic sinusoids sinusoidal obstruction syndrome (veno-occlusive disease). *Seminars in Liver Disease, 2*(22), 27–41. doi:10.1055/s-2002-23204

Del Toro, G., Satwani, P., Harrison, L., Cheung, Y.K., Bradley, B., George, D., . . . Cairo, M.S. (2004). A pilot study of reduced intensity conditioning and allogeneic stem cell transplantation from unrelated cord blood and matched family donors in children and adolescent recipients. *Bone Marrow Transplantation, 33,* 613–622. doi:101.1038/sj.bmt.1704399

Diaconescu, R., Flowers, C.R., Storer, B., Sorror, M.L., Maris, M.B., Maloney, D.G., . . . Storb, R. (2004). Morbidity and mortality with nonmyeloblative compared with myeloablative conditioning before hematopoetic stem cell transplantation from HLA-matched related donors. *Blood, 104,* 1550–1558. doi:10.1182/blood-2004-03-0804

Pulsipher, M.A., Boucher, K.M., Wall, D., Frangoul, H., Duval, M., Goyal, R.K., . . . Katoda, R. (2009). Reduced-intensity allogeneic transplantation in pediatric patients ineligible for myeloablative therapy: Results of the Pediatric Blood and Marrow Transplant Consortium Study ONCO313. *Blood, 114,* 1429–1436. doi:10.1182/blood-209-01-196303

Roman, E., Osunkwo, I., Militano, O., Cooney, E., van de Ven, C., & Cairo, M.S. (2008). Liposomal amphotericin B prophylaxis of invasive mold infections in children post allogeneic stem cell transplantation. *Pediatric Blood Cancer, 50,* 325–330. doi:10.1002/pbc.21239

Saito, A.M., Zahrieh, D., Cutler, C., Ho, V.T., Antin, J.H., Soiffer, R.J., . . . Lee, S.J. (2007). Lower costs associated with hematopoietic cell transplantation using reduced intensity vs. high-dose regimens for hematologic malignancy. *Bone Marrow Transplantation, 40,* 209–217.

Satwani, P., Morris, E., Bradley, B., Bhatia, M., van de Ven, C., & Cairo, MS. (2008). Reduced intensity and non-myeloblative allogeneic stem cell transplant in children and adolescents with non-malignant and malignant diseases. *Pediatric Blood Cancer, 50,* 1–8. doi:10.1002/pbc.21303

Shelburne, N., & Bevans, M. (2009). Non-myeloblative allogeneic hematopoietic stem cell transplantation. *Seminars in Oncology Nursing, 25,* 120–128. doi:10.1016/j.soncn.2009.03.006

Shereck, E.B., Cooney, E., van de Ven, C., Della-Lotta, P., & Cairo, M.S. (2007). A pilot phase II study of alternate day ganciclovir and foscarnet in preventing cytomegalovirus (CMV) infections in at-risk pediatric and adolescent allogeneic stem cell transplant recipients. *Pediatric Blood Cancer, 49,* 306–312. doi:10.1002/pbc.21043

Socie, G., Stone, J.V., Wingard, J.R., Wesidorf, G., Henslee-Downey, P.J., Bredesen, C., . . . Klein, J. (1999). Long-term survival and late deaths after allogeneic bone marrow transplantation. *New England Journal of Medicine, 341,* 14–21. doi:10.1056/NEJM199907013410103

Thomas, E.D. (1983). Karnofsky Memorial Lecture: Marrow transplantation for malignant disease. *Journal of Clinical Oncology, 1,* 517–531.