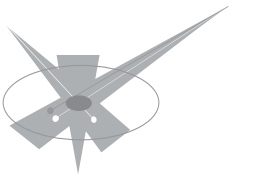
Rep Pract Oncol Radiother, 2007; 12(3): 171-174



Review Paper

Received: 2007.01.17
Accepted: 2007.05.28
Published: 2007.06.29

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Intensive care and outcome in children undergoing haematopoietic stem cell transplantation

Lynne M. Ball

Leiden University Medical Centre, Leiden, the Netherlands

Summary

Aim To review literature data concerning treatment of procedure-related complications in the intensive care unit in children undergoing allogeneic haematopoietic stem cell transplantation with a focus on clinical results, limitations of studies, recent improvements and remaining problems.

Materials/Methods A review of PubMed references based on evidence-based recommendations and own experience.

Results Modern ICU care both for adults and children undergoing HSCT has improved in the last decade. However, multi-organ system failure and those requiring mechanical ventilation have the worst outcome. Within the paediatric setting the majority of children are transferred for respiratory support and pulmonary complications. Septic shock and its consequences are associated with far fewer admissions to the ICU. The role of the ICU requires constant revision as protocols and treatments change both in the HSCT unit as well as in intensive care.

Conclusions An adequate scoring system such as an adapted O-PRISM should be developed and would lead to the possibility of multi-centre comparative data acquisition and develop future studies in this critically ill group of patients.

Key words **intensive care • transplant related complications • allogeneic HSCT in children**

Full-text PDF: http:/www.rpor.pl/pdf.php?MAN=10532

Word count: 1149
Tables: –
Figures: –
References: 18

Author's address: Lynne M. Ball, Leiden University Medical Centre, BMT Centre Leiden, P.O. Box 9600, 2300 RC Leiden, the Netherlands, e-mail: L.M.Ball@lumc.nl

Background

Haematopoietic stem cell transplantation (HSCT) can be the only curative option for some children with a life-threatening illness. However, be it related to procedural toxicities or pre-existing conditions, some children become critically unwell during the procedure and a proportion of these patients, mainly with visceral organ injury, systemic infection or GvHD, may benefit from specialized intensive care support.

Historically, the reported survival of these patients (mainly adults) has been poor [1]. Children have also been reported, albeit comparably less frequently, and may do better than their adult counterparts [2–10].

As such, the question of whether to admit such patients to the ICU remains an issue. However, many of the reports are now decades old and advances in intensive care medicine have mirrored those of HSCT. Recently these historical observations have been called into question [1].

Aim

To review literature data concerning treatment of procedure-related complications in the intensive care unit in children undergoing allogeneic haematopoietic stem cell transplantation with a focus on clinical results, limitations of studies, recent improvements and remaining problems.

Materials and Methods

References were retrieved using the online database of the National Library of Medicine (PubMed; *http://www.ncbi.nlm.nih.gov/PubMed*). Terms used included: intensive care, transplant related complications, allogeneic HSCT in children. The retrieved references were supplemented by references from the author's own database.

Results

To date, 9 single centre studies have been reported, ranging from 1983 to 2001 [2–10]. A total of 1075 (725 allogeneic and 350 autologous) bone marrow or peripheral blood stem cell transplants were included. As to be expected, the most were transplanted for malignant disease (49%). Respiratory complications accounted for approximately half of the admissions (n=410), with septic shock in only 6% of patients. The percentage of patients admitted to the ICU requiring ventilation ranged from 63 to 88% (median 84%).

Prior to 2000 rates of admission to the paediatric ICU ranged from 11 to 18% of HSCT patients, after which an increase was observed from 16 to 29%. There are no data other than pre 2000 for ventilation rates (7–23%) or reported survival to hospital discharge in these studies.

Survival to hospital discharge in ventilated patients was however reported in one study and improved from 11% pre 2000 to 28% post 2000 [8].

Three reports have described paediatric ICU support in children undergoing umbilical cord blood transplantation (UCBT) [5,8,10]. Only one of these contained sufficient numbers of children for a meaningful analysis, and included 98 ICU admissions in a 9-year period comparing 52 UCBT children and 34 BMT patients [8].

Forty-one percent survived the ICU period but only 28% survived to hospital discharge, with an overall survival at 2 years of 20%. There was no significant difference in survival (ICU and hospital discharge) between BMT and UCBT patients even though UCBT patients required longer mechanical ventilation (18.2 vs 9.1 days).

Multi-organ system failure (MSOF), prolonged mechanical ventilation and respiratory failure were associated with an increased risk of mortality, similar to that seen in adults [2–10]. Our experience in Leiden is similar in that patients are rarely transferred to the ICU other than for respiratory support and those with MSOF have a poor outcome. Children with neurological problems, bleeding and GI problems fare better, but often children have complex problems that combine to make management difficult.

The oncological paediatric risk of mortality score (O-PRISM) has been criticized in predicting outcome in the paediatric HSCT-ICU setting but remains the best predictive score of outcome to date [4].

Discussion

Limitations of studies

There is a great deal of variability in the patient population studies. Most studies in adults failed to calculate the percentage of patients admitted to the ICU as well as failing to address issues such

as patient selection bias. Over time the number of patients transferred to the ICU has diminished as have the mechanical ventilation rates. Almost all reports are single centre and comparisons cannot easily be made among centres as the threshold variables for ICU transfer and ventilation vary considerably among units [1].

Improvements

Certain improvements over the last decades can be attributed to the advances both in HSCT and ICU medicine. However, increased awareness of the "futility" of transferring some patients may contribute to the reports of improved survival. Two reports, both in adults, have concluded this to be the case.

Advances in HSCT which may contribute to overall survival and less toxicity, thus reducing transfer to the ICU, can be summarized as follows:

a. Use of new agents such as Defibrotide® and improved less toxic regimens such as Busulfex® with pharmacological monitoring has improved the visceral toxicity associated with VOD [11,12].
b. Blood product support such as leukocyte depleted red cells and the use of granulocyte transfusions have reduced the risks of lethal infections [13]. Close monitoring of PCR viral reactivations in the post-transplant period have allowed for the timely introduction of anti-viral medications and reduced systemic infection [14].
c. Developments in the management of steroid refractory GvHD such as the use of 3rd party mesenchymal stem cells have reduced the mortality associated with severe disease [15].
d. Use of G-CSF in the post-transplant period to reduce the period of neutropenia [16].
e. Use of reduced intensity regimens in children clinically unfit for standard conditioning regimens [17].
f. Initial multi-disciplinary management may improve patient outcome but this is as yet to be determined. What is important is the communication amongst haemato-oncologists, ICU staff and parents and child.

Progress in ICU techniques and knowledge has paralleled those of HSCT such as:

a. Lung protective strategies – lower tidal volume during mechanical ventilation.
b. Non-invasive positive pressure ventilation.
c. Early goal directed therapy in patients with septic shock (only in adults and not yet in HSCT).

Increasing risks

Increasing risk to patients undergoing HSCT indicates that assessment of the role of ICU support is a dynamic process and can be summarized as follows:

a. The increasing use of immune therapy such as DLIs with the increased risk of GvHD as a complication of treatment [18].
b. The expansion of donor stem cell sources inclusive of haploidentical and mismatch cord blood transplants with delayed immune and/or haematopoietic reconstitution leading to more infective complications.
c. Changing patient and donor selection criteria with less identical HSCT being undertaken compared to unrelated matched or mismatched transplants.

Conclusions

Modern ICU care both for adults and children undergoing HSCT has improved in the last decade. However, multi-organ system failure and those requiring mechanical ventilation have the worst outcome. Within the paediatric setting the majority of children are transferred for respiratory support and pulmonary complications. Septic shock and its consequences are associated with far fewer admissions to the ICU. The role of the ICU requires constant revision as protocols and treatments change both in the HSCT unit as well as in intensive care. An adequate scoring system such as an adapted O-PRISM should be developed and would lead to the possibility of multi-centre comparative data acquisition and develop future studies in this critically ill group of patients.

References:

1. Naeem N, Reed MD, Creger RJ et al: Transfer of the hematopoietic stem cell transplant patient to intensive care unit: does it really Matter? Bone Marrow Transplant, 2006; 37: 119–33
2. Diaz de Heredia C, Moreno A, Olive T et al: Role of intensive care unit in children undergoing bone marrow transplantation with life threatening conditions. Bone Marrow Transplant, 1999; 24: 163–8
3. Keenan HT, Bratton SL, Martin LD et al: Outcome of children who require mechanical ventilatory support after bone marrow transplantation. Crit Care Med, 2000; 28: 830–5
4. Schenider DT, Lemburg P, Sprock I et al: Introduction of the oncological pediatric risk of mortality score (O-PRISM) for ICU support

following stem cell transplantation in children. Bone Marrow Transplant, 2000; 25: 1079–86

5. Diaz MA, Vicent MG, Prudencio M et al: Predicting factors for admission to an intensive care unit and clinical outcome in pediatric patients receiving hematopoietic stem cell transplantation. Hematologica, 2002; 87: 292–8
6. Jacobe SA, Hassan A, Veys P, Mok Q: Outcome of children requiring admission to an intensive care unit after bone marrow transplantation. Crit Care Med, 2003; 31: 1299–305
7. Lamas A, Otheo E, Ros P et al: Prognosis of child recipients of hematopoietic stem cell transplantation requiring intensive care. Intensive Care Med, 2003; 29: 91–96
8. Hagen SA, Craig DM, Martin PL et al: Mechanically ventilated pediatric stem cell transplant recipients: effects of cord blood transplant and organ dysfunction on outcome. Pediatr Crit Care Med, 2003; 4: 206–13
9. Tomaske M, Bosk A, Eyrich M et al: Risks of mortality in children admitted to the pediatric intensive care unit after hematopoietic stem cell transplantation. Br J Haematol, 2003; 121: 886–91
10. Cheuk DK, Ha SY, Lee SL et al: Prognostic factors in children requiring admission to an intensive care unit after hematopoietic stem cell transplantation. Hematol Oncol, 2004; 22: 1–9
11. Corbacioglu S, Griel J, Peters C et al: Defribotide in the treatment of children with veno-occlusive disease (VOD): a retrospective multi-center study demonstrates therapeutic efficacy upon early intervention. Bone Marrow Transplant, 2004; 33: 189–95
12. Zwaveling Z, Bredius RGM, Cremers SCLM et al: Intravenous busulfan in children prior to stem cell transplantation: study of pharmacokinetics in association with early clinical outcome and toxicity. Bone Marrow Transplant, 2005; 35: 17–23
13. Drewniak A, Boelens JJ, Ball LM et al: Granulocyte concentrates and functional capacity after storage: use of granulocyte transfusion in pediatric oncology and disease. 2007; Submitted
14. Dini G, Castagnola E, Comoli P et al: Infections after stem cell transplantation in children: state of the art and recommendations. Bone Marrow Transplant, 2001; 28(Suppl.1): S18–21
15. Ringdén O, Uzunel M, Rasmusson I et al: Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease.Transplantation, 2006; 81: 1390–97
16. Locatelli F, Pession A, Zecca M et al: Use of recombinant human granulocyte colony-stimulating factor in children given allogeneic bone marrow transplantation for acute or chronic leukemia. Bone Marrow Transplant, 1996; 17: 31–7
17. Shenoy S, Gossman WJ, Di Persio J et al: A novel reduced-intensity stem cell transplant regimen for nonmalignant disorders. Bone Marrow Transplant, 2005; 35: 345–52
18. Bader P, Bbeck J, Schlegel PG et al: Additional immunotherapy on the basis of increasing mixed hematopoietic chimerism after allogeneic BMT in children with acute leukemia: is there an option to prevent relapse? Bone Marrow Transplant, 1997; 20: 79–81