[Frontiers in Bioscience 6, g33-37, August 1, 2001]

PEDIATRIC STEM CELL TRANSPLANTATION AND CRITICAL CARE (AN OUTCOME EVALUATION)

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1. ABSTRACT

This paper reviews eight published studies of children who required critical care following a stem cell transplant. Approximately 14% of children required mechanical ventilation following stem cell transplant. Sixteen percent of these children survived. Eleven percent of children who had primary lung injury secondary to either infectious or non-infectious causes survived. Patients with respiratory failure induced by disease in organ systems other than the lungs had much better survival (33-39%). Children reported to have a non-bacterial infectious lung disease had very poor survival. Children who developed multi-organ system failure (MOSF) in addition to lung disease also had poor survival. The majority of children died of MOSF or pulmonary failure.

2. INTRODUCTION

Stem cell transplantation (SCT) is a high-risk procedure with potential for high morbidity and mortality. Patients may have complications related to the underlying disease, previous therapy, preparative regimen, and/or prolonged immune- incompetence. Some patients suffer complications necessitating pediatric critical care intervention. Adult patients undergoing stem cell transplant (SCT) who require mechanical ventilation (MV) have a dismal prognosis (1-10). The survival to hospital discharge ranges from 0 –8%. Data on pediatric patients requiring critical care following SCT is limited by the small numbers of patients at any individual institution.

This paper is a review of the current English literature regarding the outcome of pediatric patients requiring critical care and/or MV following SCT. The goals of this review are to determine the reasons for initiation of critical care, determine which patients have a reasonable chance of long-term survival (LTS), and to determine if a subset of patients can be defined for whom aggressive critical care should not be instituted and/or be terminated.

Each study was analyzed for the following data.

- Total number of SCT patients
- Number of patients requiring MV
- Survival of mechanically ventilated patients
- Reasons for MV and/or critical care.
    - Primary pulmonary failure
    - Non primary pulmonary failure
- Etiology of pulmonary failure
- Duration of MV
- Possible risk factors for requiring MV and/or critical care and for survival

2.1. Studies

Six studies dealt with pediatric SCT patients who required MV (11-16). Two studies dealt with patients who required pediatric critical care with or without MV (17, 18) (Table 1). The seven studies included 3445 patients who had stem cell transplants, of which, 492(14%) required MV. The eighth study included 43 patients who required

Table 1. Incidence and Long Term Survival of Patients Requiring Mechanical Ventilation

Study	Years	Total Patients	Mechanical Ventilation	LTS > 6 mos
Nichols [15]	1986-88	318	23 (7%)	2 (9%)
Rossi [11]	1986-88	355	39 (11%)	14 (36%)
Todd [14]	1973-90	285	54 (18%)	4 (7)
Warwick [13]	1976-92	869	196 (23%)	33 (16%)
Hayes [17]	1987-97	367	33 (9%)	4 (12%)
Diaz de Heredia [18]	1991-95	176	26 (15%)	6 (23%)
Keenan [16]	1983-96	1075	121 (11%)	19 (16)*
Total		3445	492 (14%)	
Bojko [12]	1986-93	nr	43	1 (2%)
TOTAL			535	83 (16%)

nr – not reported; LTS – long term survival * > 30 days

Table 2. Diagnosis and Stem Cell Source of Patients Requiring MV or PICU Admission

Study	Leukemia Lymphoma	Solid Tumors	Non Malignant	Allogeneic	Autologous
Nichols	22	0	1	16	7
Rossi	19	3	17	33	6
Todd	33	10	11	46	8
Warwick	92	21	83	154	42
Hayes	35	0	9	43	1
Diaz de Heredia	nr	nr	nr	20	6
Bojko	19	13	11	30	13
Keenan	59	nr	nr	112	9

nr – not reported

MV, but the total number of SCT patients in that series was not reported (12). The diseases and transplant type are depicted in Table 2. The majority of patients underwent an allogeneic SCT. More patients had leukemia than solid tumors or non- malignant conditions (aplastic anemia, immunodeficiency, or metabolic disorders). The most common reasons for admission to the Pediatric Intensive Care Unit (PICU) were pulmonary failure, sepsis/sepsis syndrome, and neurologic events. Other less common reasons for PICU admission were cardiac dysfunction, renal dysfunction, hemodynamic instability from hemorrhage or GI losses, and /or hepatic insufficiency.

2.1.2. Outcomes

2.1.2.1. Primary Pulmonary Disease

Of the 492 patients who required MV, 281 had respiratory failure secondary to primary lung injury (Table 3). The overall survival of these patients was 11%. Only 148 of these patients had data reported as to the *etiology* of the primary lung injury. Overall, infectious causes were diagnosed in 87 patients. The method of diagnosis was not always evident. Viral infections were diagnosed in 47 children (CMV 20 pts, RSV 5 pts, parainfluenza 3 pts, rubeola 1 pt, unspecified 18 pts). Fungal organisms were found in 29 patients (aspergillus 5 pts, candida 4 pts, unspecified 20 pts). Pneumocystis carinii (PCP) was found in 7 patients. One out of 39 children with a viral etiology of pulmonary failure for whom data was reported survived. No children with reported fungal or pneumocystis carinii pulmonary failure survived (Table 4). Bojko (12) reviewed pathologic specimens in 21 patients. Nine patients had an infectious etiology identified (4 viral, 5 fungal). Nine patients had specimens obtained by bronchoalveolar lavage, which identified pathogens in 5. Two of these pathogens correlated with the pathologic findings. Interestingly four children had non-diagnostic bronchoalveolar lavages (BAL) and one child had PCP on BAL but fungal organisms were found in their lung tissue. Non- infectious causes of primary pulmonary failure (interstitial pneumonitis, hemorrhage, capillary leak, pulmonary edema, and bronchiolitis obliterans) affected 54 children. The overall survival of these children was< 5%.

2.1.2.2. Secondary pulmonary failure

Overall, 153 patients required MV secondary to non-primary pulmonary disease. Sepsis and/or cardiovascular collapse (16/33pts survived), cardiac arrest (1/28 pts survived), airway protection for severe mucositis (18/61 pts survived) and mental status changes (13/27 pts survived) accounted for the majority of the children. Other causes were cardiac dysfunction, anaphylaxis, hemorrhage, and veno-occlusive disease of the liver. The overall long-term survival for this group of patients was 33%. If the group of patients who suffered a cardiac arrest were excluded, the survival was 39%.

2.1.3. Cause of Death

The cause of death was defined in 409 patients. Multi-organ system failure (47%) defined as two or more non-hematopoietic organ systems failing and primary pulmonary failure (33%) were the most common causes of mortality. Rossi[11] described 4 out of 20 patients surviving with 4 or more organ systems failed. Of 21 patients with up to 3 organ systems failing, 14 survived. Hayes (17) documented poor survival in children with 2 or more organ systems failing, particularly if associated with hepatic or

Table 3. Patients with Primary Lunch Injury

Study	Patients	LTS	Infectious (Survival)	Non-infectious (Survival)
Nichols	23	2(9%)	nr	nr
Rossi	39	14(35)	nr	nr
Todd	42	1(2%)	15(0)	27(2)
Warwick	71	8(11%)	nr	nr
Hayes	20	1(5)	9(0)	11(1)
Diaz de Heredia	12	2(17%)	8(nr)	4(nr)
Keenan	74	3(4%)	55(3)	19(0)
Total	281	31(11%)		
Bojko	21*	nr	9(nr)	12(nr)

nr – not reported * pathologic specimens only

Table 4. Etiology of pulmonary infections

Study	Viral	Fungal	Pneumocystis
Keenan	18(1)$^{+}$	18(0)	6(0)
Todd	12(0)	2(0)	1(0)
Hayes	9(0)	_	_
Total	39(1)	20(0)	7(0)
Bojko*	4(nr)	5(nr)	_
Diaz de Heredia	4(nr)	4(nr)	_

*pathologic specimens only $^{+}$ ( ) survivors

Table 5. Duration of Mechanical Ventilation

Study		# of Patients	Mean days (range)
Rossi	Alive >6 mos	14	5.5 (1 – 55)
	Non-survivors	23	3 (0 - 19)
Todd	Extubated	6	2 (.5 – 13)
	Non-survivors	48	8 (1 – 52)
Keenan	Alive >1 mo	19	6 (2 – 41)
	Non-survivors	102	9 (1 – 77)

renal failure. The study by Keenan[16] addressed MOSF at three different time periods of the PICU course (intubation day, day +2,and day+7). No patient who had adult respiratory distress syndrome (ARDS) and renal insufficiency at the time of intubation or developed renal failure by day +7 survived. Patients with ARDS and hepatic insufficiency or vasopressor requirements had a very poor outcome. The children with ARDS, renal failure, and hepatic insufficiency all died.

2.1.4. Timing and Duration of MV

The median time from transplant to requiring MV ranged from 15.5-47 days post stem cell infusion (range day –12 to day +4798). The duration of mechanical ventilation for survivors and non-survivors were compared in 3 studies. (Table 5) (11, 14, 18) The mean time for successfully extubated patients to require MV was < 1 week. Some patients survived following prolonged intubations. It is not clear if patients with primary lung injury were among the survivors of prolonged intubations. Nichols' (15) paper described 2 patients with primary lung disease that survived MV courses of 7 and 12 days. This data is in contrast to a statement in an adult series (6) that MV for more than 4 days is futile. Indeed, the mean times of survivors requiring MV in two series (11, 18) were greater than 4 days.

2.1.5. Risk Factors

Predictors of the need for MV were GVHD, HLA mismatched marrow transplants, and the underlying diagnosis (immune deficiency, metabolic disorders, and neuroblastoma) (13). An elevated serum creatinine and/or a serum bilirubin predicted a shortened time to the onset of respiratory failure (15). Warwick found that patients with metabolic disorders were more likely to be successfully extubated (13). Paradoxically patients described by Warwick with high grade GVHD were also more likely to be successfully extubated in contrast to the patients described by Diaz de Heredia (18) who found that patients with high grade GVHD were more likely to die. However, Rossi did not find the underlying disease, type of transplant or degree of GVHD to be significantly associated with survival (11).

In studies that compared patients with autologous SCT or allogeneic SCT who required critical care, 8 out of 37 (22%) autologous SCT patients survived compared to 15 out of 94 (16%) allogeneic transplant patients (13, 14, 18).

Two studies compared Pediatric Risk of Mortality (PRISM) scores in survivors and non-survivors (11, 17). In a general pediatric intensive care unit, a PRISM score of less than 10 had a mortality risk of less than 1% (19). The surviving patients in one study (11) had a median score of 7. The non- survivors median score was 14 ($p<.05$). However, there was a large amount of overlap between the two groups. The other study found a mean score of 21 in survivors and 34 in non-survivors ($p=.21$) (17).

2.1.6. Dialysis

Lane *et al*. reviewed their experience with 30 SCT children who required dialysis (20). Sixteen children had a hypotensive episode prior to development of renal failure. Two patients had urinary tract obstruction secondary to hemorrhagic cystitis. The etiology of renal failure in the other 12 patients was unknown. The indications for dialysis were hypervolemia, hyperkalemia, acidosis, hyperphosphatemia, and uremia. Twenty-three patients died without recovery of renal function. Seven patients were able to have dialysis discontinued. Three children survived to be discharged from the hospital. Rossi described 8 patients who required dialysis.[11] One patient survived to be discharged. Therefore, only 4 out of 38(10%) children who required renal replacement therapy survived.

3. DISCUSSION

Children undergoing SCT are at risk for complications requiring critical care intervention. The overall experience in adult SCT patients who require MV has been dismal with less than 5 % LTS (2). The LTS is even worse when lung injury is associated with liver and renal failure and the need for vasopressors (2). The poor prognosis of these adult SCT patients raises the question of whether aggressive interventional care is warranted in patients undergoing SCT. When children develop complications that require critical care, decisions must be

made regarding the utility and futility of aggressive PICU intervention. PICU care is expensive, utilizes limited resources (blood products), is invasive, and is painful. It also carries a tremendous emotional burden for families and health care workers. Knowing which patients have virtually no chance of survival with current therapeutic supportive and diagnostic measures would be helpful in reaching decisions regarding the institution and/or termination of critical care.

An analysis of eight series of pediatric SCT patients reveals that approximately 14% of SCT children require MV at some time during their transplant course. The overall survival of these patients is approximately 16%. Children who suffer a non-bacterial infectious or non-infectious primary lung injury fare worse (11% survive) than SCT patients requiring MV for non-pulmonary injury without a cardiac arrest (39% survive). Children reported with non-bacterial infectious lung injury have a dismal prognosis (<2% survive). The onset of MOSF with increasing amounts of organ dysfunction and/or the need for dialysis is associated with poor survival.

There are major difficulties in drawing any firm conclusions regarding the data from these studies. The criteria for admission to the PICU are not universal. Some institutions may admit less sick children to the critical care unit than others. The PICU care regarding ventilator management, vasopressor use and diagnostics may alter the outcome data. Most of the institutions report on relatively small numbers of patients. Only one study has data tracking the progress of the children from the time of intubation until day +7. The deterioration in organ function over a one-week period markedly lessens the chance for survival. Tracking serial changes in oxygenation index, alveolar- arterial oxygen gradient, and other measures of lung function may help predict the outcome of these children. Collecting more serial data might be helpful when deciding to terminate or continue care. Data is also needed to determine which children might benefit from earlier intervention, aggressive diagnostic procedures, new supportive therapies and/or discontinuation of aggressive management. Each clinical situation needs to be assessed and reevaluated frequently regarding the feasibility of continued aggressive management. It is not always in the child's or family's best interest to initiate or continue aggressive critical care when care is futile.

Pulmonary disease predominates as the reason for critical care intervention. Some studies suggest that perhaps earlier intervention or more aggressive diagnostic procedures would improve the prognosis in SCT patients with pulmonary failure (11, 12). Data from adult patients suggest that prolonged ventilatory support is futile (6). However, some pediatric patients are survivors following prolonged ventilatory support (11, 15, 18). Patients with a predictably poor prognosis with current therapeutic modalities may be candidates for studies involving other means of supportive care such as extracorporeal membrane oxygenation, surfactant, or liquid ventilation in an investigational study (21, 24). Because of the small numbers of patients at any given institution, multi - institutional data needs to be collected to assess the efficacy of new therapies in pediatric stem cell transplant patients who require critical care intervention.

When respiratory failure occurs, attempts should be made to determine the cause of the illness, assess other organ system function and determine whether intervention is appropriate. While an initial attempt at MV may be appropriate while evaluating the problem, frank discussions with family members regarding the likelihood of reversibility of the condition and the appropriateness of continued care need to be done frequently. Children who have primary lung injury and deteriorating organ function during their PICU course should be reevaluated frequently as to the utility versus futility of continued aggressive management. Everything that can be done must be distinguished from everything that should be done (25).

4. ACKNOWLEDGMENTS

My thanks to Dr. Dennis O'Connor and Dr. Robert Lynch for their review of this manuscript.

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Key Words: Pediatric Stem Cell Transplant, Critical Care, Review

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