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RESEARCH ARTICLE

CLINICAL OUTCOMES OF CRITICALLY ILL CHILDREN WITH CANCERS ADMITTED TO THE PEDIATRIC INTENSIVE CARE UNIT OF A REGIONAL CANCER CENTRE IN A DEVELOPING COUNTRY

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ABSTRACT

***Background*:** Improvements in supportive care strategies has contributed to improved survival of children with malignancies. PICU support is one of the pillars of such a supportive care system. Data from developing nations on the outcome estimates of critically ill pediatric oncology patients in the PICU is sparce. ***Methods*:** A retrospective review of case records of all PICU admissions from the Kidwai Cancer Institute pediatric oncology unit between May 2017 and April 2018 was undertaken. The aim of the study is to analyse outcome of pediatric oncology patients admitted to PICU and also determine factors predicting poor prognosis. ***Results*:** A total of 274 admissions were made in the PICU of the Institute during the study period. 80% of admissions were those with hemato-lymphoid malignancies while the remainder had solid tumours. Chidlren in remission status/newly diagnosed cases contributed to 86.5% of total admissions. The most common indication for ICU admission was sepsis followed by respiratory distress. Children admitted to the PICU in view of neurological deterioration had the highest mortality followed by those admitted for respiratory distress and cardiac complications. 26.3% and 21.5% required inotropic support and ventilation (Invasive/Non invasive) respectively with proportion of survivors being 58.3% and 51.8% in the respective groups. The median PRISM III score at admission in the survivor group was 9 (Range: 1-25) while that in the non-survivor group was 17 (Range: 3-35). Multiorgan dysfunction was present in 23.7% (n=65). Survival in those children with MODS was 29.2% (n=19). ***Conclusion*:** Risk factors such as disease status, presence of MODS, need for mechanical ventilation and inotropic support were found to be associated with poor prognosis in children with malignancies requiring PICU care.

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INTRODUCTION

Outcome of children with malignancies has improved manifold over the last few decades. Improvement in treatment protocols based on multicentric trials, newer modalities of treatment, risk stratification and better supportive care has contributed to this change in survival. PICU management is one of the important pillars of supportive care required to improve outcome in these children. Western data have revealed promising data with an overall survival rate of >80% in pediatric. Oncology patients admitted to the PICU (Dalton, 2003). The PICU therapy outcomes in critically ill children with malignancies in a developing country like India are not well defined. Our study intends to determine the outcome estimates in children with malignancies admitted to the PICU of a regional cancer centre in Southern India. Also, we aim to study the various prognostic factors that contribute to poor survival in these children.

MATERIALS AND METHODS

A retrospective review of case records of all children less than 15 years of age admitted to the Paediatric Intensive Care Unit over a period of 12 months between May 2017 and April 2018 was conducted in the Department of Paediatric Oncology of a Regional Cancer Centre in Southern India. The eligibility criteria for PICU admission included any oncologic emergency present at diagnsosis or during therapy, febrile neutropenia with SIRS (Systemic Inflammatory Response Syndrome) or septic shock, organ dysfunction related to chemo-radiotherapy

and post-operative patients for cardio-respiratory monitoring. All children fulfilling the eligibility criteria for PICU admission were included in the study. Those children without a definitive diagnosis at the time of death/DAMA (discharge against medical advice) from the PICU were excluded from the study. Clinical data including patient history, performance status, examination findings, diagnosis and staging, indication for PICU admission, duration of PICU stay, need for inotropic support, ventilation and immediate outcome (i.e., survival at the time of discharge) were all recorded from case files of patients. A written and informed consent was obtained from parents/caretakers of all children at the time of admission to the PICU. Statistical Analysis was performed using the Statistical Package for Social Sciences version 15. Data was interpreted using univariate analyses that included measures of central tendency, frequency distribution and dispersion. Qualitative variables were compared using the chi-square test. A P-value of 0.05 was considered significant.

RESULTS

A total of 274 admissions involving 227 patients were made in the PICU of the Institute during the study period. The PICU admissions constitute 6% of total admissions to the department of pediatric oncology. Male : Female ratio was 1.76:1. Median age at admission was 8 years (Range: 1 month-15 years). Table 1 describes the clinical characteristics of all the children admitted to the PICU. 80% of admissions were those with hemato-lymphoid malignancies while the remainder had solid tumours. Table 2 describes the various indications of admission to the PICU and the status of disease at the time of ICU admission.

While newly diagnosed cases contributed to 40.2% of total admissions, the remainder included those on therapy (46.3%) and those with progressive disease (13.5 %). The most common indication for ICU admission was sepsis followed by respiratory distress, neurological deterioration, abdominal complications and metabolic derangements.

Outcome analysis: Median duration of stay in the PICU during the 274 admissions was 5 days (Range: 1-31 days). Overall survival at the time of discharge from PICU was 68.6% and overall mortality was 31.4% (n=86). Among newly diagnosed cases, mortality was 29.1% (n=32), among those on therapy, mortality was 25.2% (n=32) and among those with progressive disease, mortality was 59.5% (n=22). Children admitted to the PICU in view of neurological deterioration had the highest mortality followed by those admitted for respiratory distress and cardiac complications. 72 (26.3%) required inotropic support. Among those requiring inotropes, about $2/3^{rd}$ (n-42) required single inotrope and $1/3^{rd}$ required more than one inotrope. Median duration of inotrope use in these children was 72 hours (Range: 12-168 hours). Proportion of survivors among those who required inotrope support was 58.3%. 5 (1.8%) required renal replacement therapy of which all of them survived till discharge from PICU. 59 (21.5%) percentage required ventilation (Invasive/Non invasive) and median duration of ventilation was 72 hours (Range: 24-144 hours). Mortality among patients requiring ventilation was 49.2% (n=29). 31 (11.3%) patients required both inotrope and ventilator support and among these, the proportion of survivors was 45.2% (n=14). The median PRISM III score at admission in the survivor group was 9 (Range: 1-25) while that in the non-survivor group was 17 (Range: 3-35).

Table 1. Clinical profile of children admitted to the PICU (*n* = 227)

Parameter	Number (n)	Percentage (%)
Sex		
Male	149	65.6
Female	78	34.4
Age (years)		
<1	12	5.3
1-5	69	30.4
5-10	71	31.3
>10	75	33.0
Type of malignancy		
Hemato-lymphoid malignancies	181	79.8
Non M3 AML	38	16.8
M3 AML	5	2.2
Pre B ALL	88	38.8
Pre T ALL	14	6.3
MPAL	1	0.4
JMML	1	0.4
Hodgkin lymphoma	9	3.9
T-lymphoblastic lymphoma	11	4.9
Anaplastic large cell lymphoma	4	1.8
Diffuse large B cell lymphoma	4	1.8
Burkitt Lymphoma	6	2.7
Solid tumours	46	20.2
Osteosarcoma	2	0.8
Ewing Sarcoma	3	1.2
Neuroblastoma	3	1.2
Langerhans cell histiocytosis	3	1.2
Hepatoblastoma	4	1.8
Hepatocellular Carcinoma	1	0.4
CNS tumours	4	1.8
Clear cell sarcoma kidney	1	0.4
Germ cell tumour	11	4.9
Retinoblastoma	1	0.4
Wilm's tumour	6	2.7
Rhabdomyosarcoma	7	3.2

Table 2. Disease Status At Admission & Indications For Admission To PICU (n=274)

Parameter	Number (%)	Mortality n (%)
Disease status at admission to PICU		
Newly diagnosed	110 (40.2)	32 (29.1)
During treatment for disease	127 (46.3)	32 (25.2)
Relapse/progressive disease	37 (13.5)	22 (59.5)
Indications for PICU admission		
Sepsis	99 (36.2)	22 (22.2)
Respiratory distress	43 (15.7)	18 (41.9)
Renal failure	5 (1.8)	0 (0)
Cardiac dysfunction	8 (2.9)	3 (37.5)
Neurological deterioration	39 (14.2)	24 (61.5)
Metabolic derangement	26 (9.5)	7 (26.9)
Abdominal complications	26 (9.5)	8 (30.8)
Mass effects	4 (1.5)	1 (25)
Anaphylaxis	8 (2.9)	0 (0)
Post operative care	3 (1.1)	0 (0)
Hematological	13 (4.7)	3 (23.1)

Table 3. Risk Factors Related to Survival of Pediatric Oncology Patients Admitted to Pediatric Intensive Care Unit

Risk factor	Number n (%)	Mortality n (%)	P value
Age			
<5 years	95 (34.7)	36 (37.9)	0.09
>5 years	179 (65.3)	50 (27.9)	
Sex			
Male	175 (63.8)	56 (32)	0.77
Female	99 (36.2)	30 (30.3)	
Diagnosis			
Hemato-lymphoid malignancy	220 (80.3)	66 (30)	0.31
Solid tumour	54 (19.7)	20 (37)	
Disease status			
In remission/newly diagnosed	237 (86.5)	64 (27)	0.002
Progressive disease	37 (13.5)	22 (59.5)	
PRISM III Score			
Survivors	188 (68.6)	6	< 0.05
Non-survivors	86 (31.4)	4	
Duration of PICU stay			
Survivors	188 (68.6)	9	< 0.05
Non-survivors	86 (31.4)	17	
Multiorgan dysfunction			
Present	65 (23.7)	46 (70.8)	<0.005
Absent	209 (76.3)	40 (19.2)	
Number of organ systems involved			
≤2	238 (86.9)	10 (4.2)	<0.005
>2	36 (13.1)	36 (100)	
Mechanical ventilation			
Required	59 (21.5)	29 (49.2)	0.001
Not required	215 (78.5)	57 (26.5)	
Renal replacement therapy			
Required	5 (1.8)	0 (0)	0.26
Not required	269 (98.2)	86 (31.9)	
Inotrope support			
Required	72 (26.3)	30 (41.7)	0.03
Not required	202 (73.7)	56 (27.7)	

Multiorgan dysfunction was present in 23.7% (n=65). While 44.6% (n=29) had ≤2 organ systems involved, 55.4% (n=36) had more than 2 organ systems involved. Survival in those children with MODS was 29.2% (n=19). While the proportion of survivors among the children with ≤2 organ systems involvement was 37.9% (n=11), the proportion of survivors with >2 organ system involvement was 0%.

Assessment of risk factors/prognostic factors for mortality: Disease status at admission to PICU, presence of MODS, PRISM III score, duration of PICU stay, need for ventilation and inotropic support were risk factors found to be associated with higher mortality. However, need for renal replacement therapy, age, gender and type of malignancy had no correlation with mortality.

DISCUSSION

This study was undertaken to describe the outcome of pediatric oncology patients admitted to the PICU of a regional cancer centre in India and also to determine the various factors that determine these outcomes. Our survival rate was found to be 68.6% which is similar to that reported by other studies (Abraham *et al*., 2002; Amany *et al*., 2016; Van Veen, 1996; Heney, 1992). Improvement in outcomes may be achieved by quality improvement strategies and introduction of in-house facilities for advanced ventilation strategies & intensive care such as dialysis. The indications for ICU admission was varied with sepsis being the most common followed by respiratory distress, neurological deterioration, abdominal complications and metabolic derangements. Of these, children admitted in view of neurological deterioration were found to have the

worst prognosis followed by those with respiratory and cardiovascular complications. In contrast, other studies reported circulatory collapse to be the most negative influence on outcome (Abraham *et al*., 2002; Amany *et al*., 2016). This is in part attributable to the fact that most patients with hematolymphoid malignancies are treated in-house at our centre as a result of which early detection of shock and immediate resuscitation is possible leading to better outcomes in those with shock. Survival following PICU admission was found to be better in those children with remission status of disease at the time of PICU admission, longer PICU stay, absence of MODS and need for organ support strategies such as ventilation and inotropic support. Risk factors identified in our study to portend a poor prognosis included: progressive disease, presence of MODS, number of organ systems involved, need for mechanical ventilation, need for inotropic support and PRISM III score (>15 points). A similar list of risk factors has also been identified in other retrospective studies (Abraham, 2002; Amany et al., 2016). Dursun *et al* found the PRISM score to be a good tool for predicting outcome with a sensitivity of 90.0% (95% confidence interval, CI: 68.3-98.5) and positive predictive value of 69.2%.[6] Also, the authors highlight the need to taken into consideration other factors such as need for mechanical ventilation and positive inotropic support, the presence and numbers of organ system dysfunction to make vital decisions with regard to patient admission to PICU or to forgo life-sustaining therapies (Oguz Dursun, 2009). Meyer *et al* describe a model for predicting poor outcome in pediatric oncology patients requiring intensive care treatment (Meyer, 2005). In this study, mortality rate was significantly related to the following factors: diagnosis of a hematolymphoid malignancy, number of organ failures, neutropenia, septic shock, mechanical ventilation and inotropic support. In comparison, in our study, hemato-lymphoid malignancies were not a risk factor for poor survival. A risk score was formulated by Meyers *et al*[7] that included these factors, each of which was given points based on the strength of prediction of a poor prognosis. This score yielded a sensitivity of 100%, specificity of 92%, a positive predictive value of 100% and a negative predictive value of 77.9%. Several other studies quote similar risk factors for poor prognosis in pediatric oncology patients admitted to the PICU (Amany *et al*., 2016; Heying, 2001; Nida Akhtar).

Conclusion

This retrospective study sheds light on the various risk factors such as disease status, presence of MODS, need for mechanical ventilation and inotropic support which were found to be associated with poor prognosis in children with malignancies requiring PICU care. The limitations of this study include the retrospective design and limitations in in-house access to therapies such as hemodialysis, newer forms of ventilation such as high frequency nasal cannula/oscillatory ventilation etc. Also, validation of scoring systems or predictive factors for mortality in these children could not be accomplished. Therefore, multicentre, prospective studies are required to better determine risk factors for mortality in this group of children and base treatment strategies accordingly.

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