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RESEARCH ARTICLE

AN 8 YEAR AUDIT OF HOSPITAL DEATHS IN CHILDREN WITH CANCER FROM A TERTIARY CARE CANCER INSTITUTE IN INDIA

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ABSTRACT

Background: The outcome in pediatric cancers have significantly increased in the last few decades. Early diagnosis and risk directed therapy have been the cornerstone for success. However high treatment related mortality and deaths due to progressive disease in low middle income countries still prevail affecting the overall survival. We have analysed the hospital deaths in our pediatric oncology department for the years 2010-2017 to assess the treatment related mortality, factors affecting the same and have devised strategies to address these issues. **Methods:** All 4051 children registered between the years 2010-2017 were included. Data regarding their diagnosis and metastatic status was collected. About 375 deaths were documented in the hospital during these 8 years. Retrospective data was collected from the medical records department from the death files. Data about age, gender, primary diagnosis, phase of therapy, response to treatment, disease status and cause of death were analysed. **Results:** About 375 deaths were documented in hospital. There was a male predominance noted. Leukemia contributed to 64.8% of deaths. Treatment related mortality was significantly higher in the leukemia group contributing 32.1% compared to 13.6% in Solid tumor group. Advanced/progressive disease was the most common cause of death in solid tumor group, 71.9%. About 35.4% of children had presented at advanced disease state and 18.9% were metastatic at presentation. Metastatic disease at presentation was a significant risk factor for mortality (p=0.00001), while age (p=0.11) or gender (p=0.58) were not statistically significant. **Conclusion:** Analysis of mortality statistics is essential for growth of every pediatric oncology department. It provides information regarding status of supportive care and also the optimization of therapy intensification strategies to strike balance between treatment related toxicity and adequate treatment dosage. strengthening of peripheral health support and blood bank facilities in combination with antibiotic policies shall help in minimizing early deaths in children diagnosed with cancer.

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INTRODUCTION

Mortality from paediatric cancers is the 9th most common cause of death in Indian children (http://www.censusindia.gov.in/Vital_Statistics/Summary_Report_Death_01_03.pdf.[Last accessed on 2013 Sep 24].). Leukemia being the commonest paediatric malignancy, contributing to 30% of all paediatric cancers, remains the most common cancer leading to death. This is followed by central nervous system tumors. Worldwide, approximately 215000 cancers are diagnosed every year in paediatric age group and 85000 deaths occur due to cancer (World Health Organization).

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Despite the recommended treatment, newer modalities of therapy and broad spectrum antibiotic usage, mortality is inevitable in some of these cases. Most of the data on cancer statistics comes from Population based cancer registries (PBCR) (Bashar, 2017). Currently there are 29 such PBCRs in India. In the Million death study, death due to cancer in children was estimated to be 39 per million population per year, which was higher than several previous estimates (Gupta *et al*., 2016). Sepsis and bleeding complicate most cases in the advanced stages. We have analysed the hospital deaths in children diagnosed with cancer in our institute between the years 2010-2017.We wish to highlight the major cancers resulting in mortality, primary cause for death and prevalence of treatment related mortality (TRM). This would help us understand the cause for mortality and provide improvised care to our patients.

METHODOLOGY

During the years 2010-2017, 4051 children were registered at the paediatric oncology department, including Leukemias, solid tumors and some non malignant conditions referred as suspected cancers. In our study we have included the deaths of all children diagnosed with a malignancy during their admission in the hospital (n= 375). Data was collected in a retrospective manner from case files and details of the patients such as age, gender, duration of symptoms, diagnosis, stage of disease, metastatic/non metastatic, phase of treatment and cause of death were recorded. Primary diagnosis was categorised to Leukemia and solid tumors for the purpose of analysis. Treatment related mortality for all practical purposes was defined as death in any child with cancer in the absence of progressive disease. Although there are varied definitions for TRM, this definition was considered in our study as several children with progressive disease may die due to toxicities from the intensive chemotherapy used in them. Advanced disease was used in cases of solid tumors that presented with metastasis and in children with leukemia that presented with organ dysfunction due to tumor lysis, hyperleukocytosis or superior mediastinal syndrome.

The term "Progressive disease" was used in children whose primary diagnosis was a solid tumor, with an evidence of progression of tumor clinically or radiologically while on chemotherapy. Response/ remission in case of solid tumors was considered when the child was clinically and radiologically showing response to chemotherapy with no evidence of progression, as defined by the RECIST criteria (Gurney *et al*., 2006). Remission in leukemia was considered only when there was documented clearance of blasts (<5%) in bone marrow specimen. Refractory disease was used to refer to those children with leukemia who were unresponsive to chemotherapy and did not achieve remission. Although these definitions are arbitrary, the purpose of analysing the data under these sub divisions was due to the fact that we had observed a stark difference in patterns of death in those children with leukemia versus those with solid tumors (unpublished data). Although equal number of children from both categories present in a decompensated state, treatment related toxicity was more frequently observed in children with leukemia, while children with solid tumors succumbed more to the advanced disease state/ progressive nature of the disease. Our data represents a clinical audit of hospital deaths in Paediatric oncology department during the years 2010-2017. This audit was done to analyse and identify the areas of interest to minimize mortality in our set up. Statistical analysis was performed with Microsoft Excel software and SPSS Statistics for Windows, version 24.0. Armonk, NY: IBM Corp. software.

RESULTS

A total of 4051 patients were registered in paediatric oncology department during the years 2010-2017. The most common malignancy was acute lymphoblastic leukemia in 32.6% of the total registered patients. The most common solid tumor was Hodgkin disease, followed by neuroblastoma, ewing sarcoma and wilms tumor in that order. Table 1 demonstrates the overview of various malignancies diagnosed during these 8 years. Solid tumors with metastatic disease at presentation are illustrated in Table 2.

Three hundred and four children diagnosed with a solid tumor had metastasis at presentation i.e., 18.9% (n=1612). The hospital deaths in our department during the period of study was 375 (9.2%). Leukemia was the most common malignancy resulting in death (64.8%). The various solid tumors contributing to the mortality is illustrated in Figure 1. The most common solid tumor causing death was Non Hodgkin lymphoma, lymphoblastic lymphoma (n=27). This was followed by neuroblastoma (n=20). Male predominance was noted among the deaths, however the difference was not statistically significant (p=0.58). The most common cause of death in children with leukemia was sepsis (38.2%). Culture proven sepsis was documented in only 3.7%. This was followed by hemorrhage, contributing to 25% of deaths in leukemia. The induction mortality was 4.1% (60% was sepsis and 20% refractory disease). In the solid tumor group, the most common cause of death was advanced disease (71.9%). Of the 375 deaths, 43.4% of the children had poor general condition, hence chemotherapy initiation was not feasible in these children.

The summary of results is represented in Table 3. The number of deaths occurring in the phase prior to initiation of chemotherapy (Pre CT), during chemotherapy and post completion of scheduled treatment were analysed (Figure 2). It demonstrates an unacceptably high percentage of deaths occurring prior to initiation of chemotherapy. This could indicate delayed referral, lack of stabilisation prior to referral or delay in diagnosis have played a role in preventing timely start of chemotherapy. Since these deaths are most preventable with early diagnosis and adequate supportive care, we analysed them in comparison to the number of children who presented with advanced disease at presentation among those who died (Figure 3). The line graph for advanced disease had plateaued over years , whereas the deaths prior to initiation of chemotherapy were on a constant rise. Therefore we concluded that although advanced disease was a major risk factor for mortality, additional factors were responsible for these deaths prior to initiation of chemotherapy. Possible delay in achieving a final diagnosis is the area that needs to be concentrated on to merge these lines in future. Post completion of therapy deaths, due to causes other than malignancy was negligible through out. Treatment related mortality in the leukemia group was 32.1% against treatment related mortality of 13.6% in the solid tumor group.

DISCUSSION

Recent advances in cancer chemotherapy have made a 5 year survival of 75% possible in most paediatric cancers (Gurney, 2006). The emergence of risk directed therapies has decreased long term complications for standard or low risk patients while the high risk patients still bear the brunt of increased treatment related toxicity and hence higher treatment related mortality. Supportive care in the form of early start of appropriate anti infective agent and blood components are essential for managing these high risk patients. Early administration of antibiotics in febrile neutropenia improves survival (Rosa, 2014). Thus availability and accessibility of supportive care plays an important role in determining final outcome in children with cancer. In our data, death in boys outnumbered girls with a Male: Female of 1.55:1. This is in concurrence with the latest ICMR data from the Million death study, M: F of 1.6:1 (Gupta, 2016). The previous studies have observed a female predominance, however this change could be attributed

Table 1. Summary of registered patients during the years 2010-2017

Tumor	ICCC3	Total (n=4051)	Percentage
Anaplastic ependymoma	IIIa	28	0.7%
Anaplastic large cell lymphoma	IIb	14	0.3%
Atypical rhabdoid teratoid tumor	IIIc4	12	0.3%
Burkitt lymphoma	IIc	59	1.5%
Clear cell sarcoma kidney	VIa3	11	0.3%
Diffuse intrinsic pontine glioma	IIId	9	0.2%
Diffuse large B cell lymphoma	IIb	6	0.1%
Ependymoma	IIIa	15	3.7%
Ewing sarcoma	VIIIc	164	4.0%
Germ cell tumor	Xb,c	99	2.4%
Glioblastoma multiformae	IIId	17	0.4%
Glioma	IIId	12	0.2%
Hepatoblastoma	VIIa	43	1.0%
Hodgkin lymphoma	IIa	194	4.7%
Langerhans cell histiocytosis	IXd5	34	0.8%
Lymphoblastic lymphoma	IIb	98	2.4%
Medulloblastoma	IIIc1	83	2.0%
Nasopharyngeal carcinoma	XIc	26	0.6%
Neuroblastoma	IVa	166	4.0%
osteosarcoma	VIIIa	70	1.7%
PNET kidney	VIa4	3	0.1%
Retinoblastoma	V	79	1.9%
Rhabdoid tumor	IXd3	16	0.3%
Rhabdomyosarcoma	IXa	93	2.2%
Wilms tumor	VIa1	128	3.1%
Rare tumors		157	3.8%
Non malignant conditions		659	16.3%
Acute lymphoblastic leukemia	Ia	1307	32.3%
Acute myeloid lymphoma	Ib	376	9.2%
Chronic myeloid leukemia	Ic	52	1.2%
Other leukemia	Id	21	0.5%
		4051	100%

Table 2. Summary of metastatic disease encountered at presentation during years 2010-2017

Solid tumors	Total	Percentage (n=304)
Anaplastic ependymoma	2	0.6%
Burkitt lymphoma	14	4.6%
Clear cell sarcoma kidney	1	0.3%
Ewing sarcoma	24	7.9%
Germ cell tumor	7	2.3%
Hepatoblastoma	3	0.9%
Hodgkin disease	15	4.9%
Langerhans cell histiocytosis	4	1.3%
Lymphoblastic lymphoma	41	13.5%
Medulloblastoma	23	7.6%
Nasopharyngeal carcinoma	11	3.6%
Neuroblastoma	101	33.2%
Osteosarcoma	7	2.3%
Rare tumors	12	3.9%
Retinoblastoma	15	4.9%
Rhabdomyosarcoma	9	2.9%
Wilms tumor	9	2.9%
Total	304	100%

to social issues and gender discrimination practices in the society. In our study, the most common malignancy leading to death was leukemia. The second common cause of mortality in paediatric cancers is brain tumor (Yang, 1984). However in our study, Non Hodgkin lymphoma was the second most common cause. This could be attributed to the referral bias in management of brain tumor. About 44.4% of deaths in acute leukemia were prior to initiation of chemotherapy, highlighting the lack of supportive care in these patients. Adequate blood product support and antibiotic usage could have decreased the deaths which were due to sepsis and hemorrhage. Only 5.3% of these deaths happened due to organ dysfunction resulting from tumor lysis or hyperleukocytosis. Strengthening peripheral health facilities and creating awareness about initial stabilisation and early referral is of prime importance to salvage these children who present with advanced disease. Induction mortality in ALL was only 4.1% and induction mortality in AML was 9.2 %. This is in concurrence with other studies that quote a higher induction mortality in myeloid leukemia in comparison to lymphoid malignancies. The induction mortality studied at Philadelphia varied from 1.12% to 27% across various institutes, highlighting the role of supportive care and expertise in management play a significant role (Seif, 2014). Induction mortality in a study from Central America was 5.8% of total deaths and 50% of this was due to sepsis while 20% was due to internal bleeding, which were similar to our results (Gupta *et al*., 2011). Although several myelotoxic chemotherapeutic agents are used in solid tumors, these children were found to have relatively lesser deaths due to hemorrhage and sepsis. Advanced disease was the most common cause of death in children with solid tumors contributing to 75.8% of deaths. This was in concurrence with other studies that state significantly lower rates of TRM in children with solid tumors. A population based analysis of paediatric cancers by Pole JD *et al*, stated a TRM of 26.4% (IPOMC, 2017). Treatment related mortality in the west have been less than 10% in many studies, whereas it was 25.6 % in our study. In the study by Gibson *et al*, it was shown how metastatic disease at presentation was associated with higher treatment related mortality (Gibson *et al*., 2018). Lower age at diagnosis, metastatic disease and relapse were most commonly associated with TRM. The incidence of metastatic disease is varied across different solid tumors, the highest being neuroblastoma (49%) (Perkins, 2019). Those with advanced disease at presentation tend to have increased incidence of organ dysfunction, poor general condition and decreased tolerance to chemotherapy. Therefore, they contribute a significant percentage to the mortality. In our study, metastatic disease at presentation was a definite risk factor for mortality (p=0.00001), while age (p=0.11) and gender (p=0.58) were not statistically significant risk factors.

According to National institute of Health data, the cancer deaths have decreased by 50% in 2014, in comparison to 1975 (Curtin, 2016). Although, certain malignancies are very aggressive eg., rhabdoid tumor, diffuse intrinsic pontine glioma and are invariably fatal (Pillay Smiley, 2018), risk stratification and risk adapted therapy have significantly improved outcomes in several childhood cancers. The outcome of paediatric acute lymphoblastic leukemia has improved significantly in the West, that central nervous system tumors are replacing ALL as the most common cause for death in paediatric malignancies (Siegel, 2018). However the deaths that need attention to create an impact on overall mortality are the early deaths, i.e prior to initiation of chemotherapy within few days from diagnosis, as they can be minimised with good supportive care. Taking into account that our institute caters to the needs of most economically underprivileged children, delayed presentation with metastatic disease is common. Lack of awareness, inaccessibility to a health facility as well as financial constraints are the major reasons for delay. The 43.4% of deaths which have happened prior to initiation of chemotherapy can be brought down to a zero percent if peripheral health facilities are strengthened with adequate health care personnel, laboratory support and blood bank facility. We would like to consider the mortality in " prior to initiation of chemotherapy" phase as a quality of services indicator. As shown in the figure 3, the number of deaths have been rising every year and so were the number of deaths during the pre CT phase. We therefore wish to propose certain interventions to help these lines merge in future. Such as,

Table 3. Summary of results

	Leukemia	Solid tumors
Total cases (n)	243(64.8%)	132(35.2%)
Male: Female ratio	1.6:1	1.5:1
Deaths prior to initiation of chemotherapy	108	55
Deaths while on Chemotherapy	133	74
Deaths post completion of scheduled therapy, while in remission	2	3
Advanced/refractory/progressive disease	n=38	n=95
prior to initiation of CT	13(34.2%)	44(46.3%)
while on CT	25(65.8%)	51(53.7%)
Relapse	30	5
Cause of death in newly diagnosed	n=95	n=11
sepsis	48 (50.5%)	7 (63.6%)
Intracranial hemorrhage	42 (44.2%)	3 (27.3%)
others	5 (5.2%)	1 (9.1%)
Cause of death in patients who were responding to treatment	n=78	n=18
sepsis	45 (57.6%)	15 (83.3%)
Intracranial hemorrhage	19 (24.3%)	0
others	14 (18.1%)	3 (16.7%)

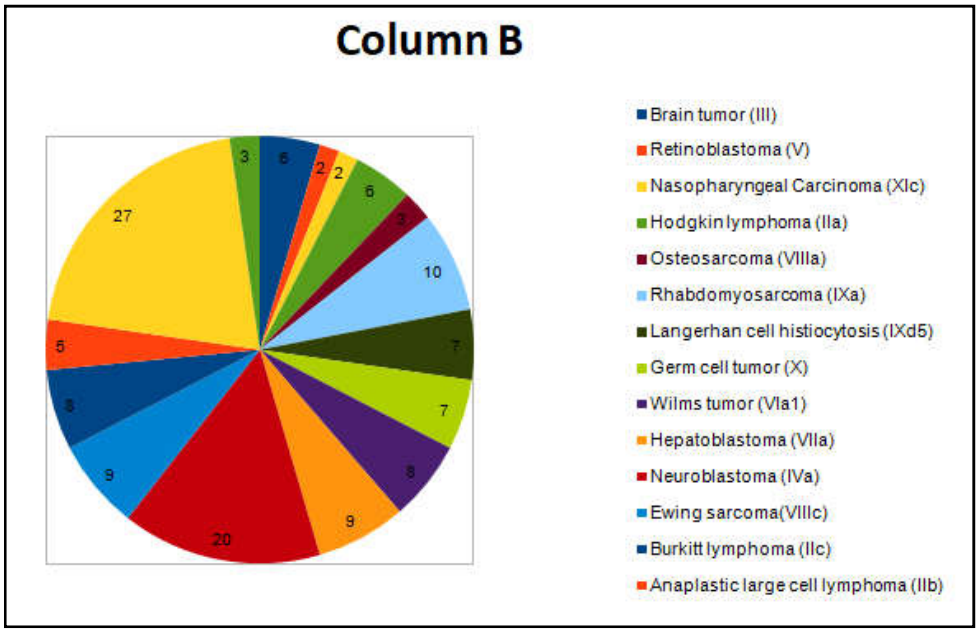

Figure 1. Distribution of deaths in Solid tumors

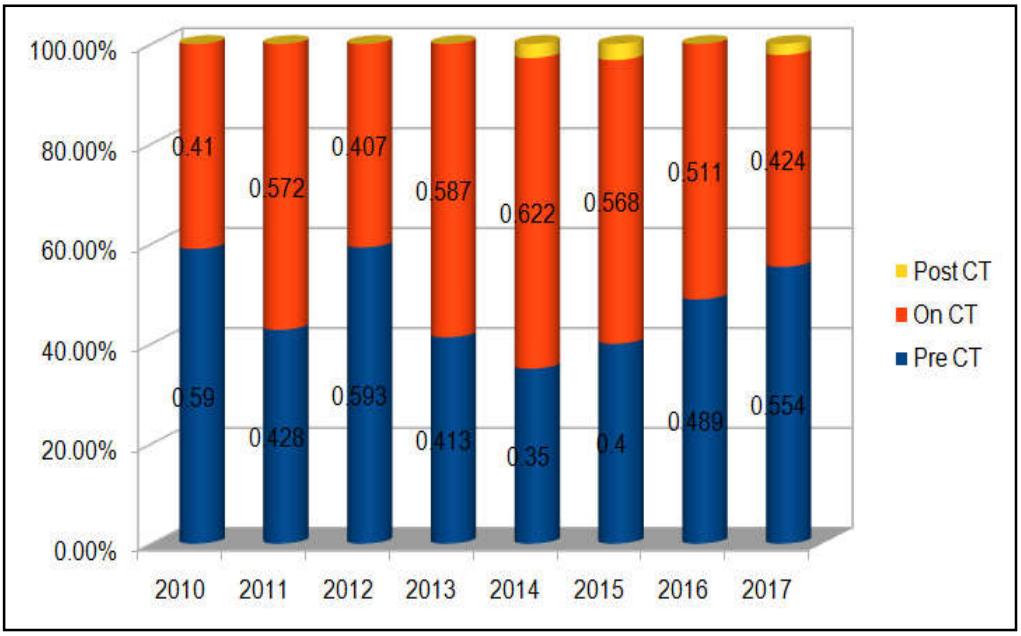

Figure 2. Phase of therapy distribution

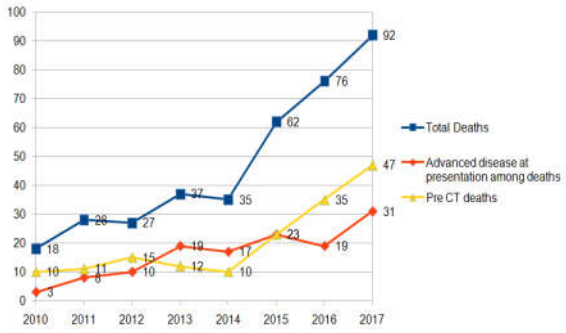

Figure 3. Correlation between total deaths, Pre chemotherapy deaths and advanced disease at presentation

- Creating awareness about early signs of cancer and prompt referral on suspicion of a malignancy
- Shared care model – Our Institute has come up with a model for peripheral health facilites, called the shared care model, which would help in early diagnosis and early referral of patients with a suspected malignancy. This model also includes provision for continuum of care for patients under palliation, by means of direct communication with doctors regarding details of treatment and child's condition through a common network. If successfully executed, through this we would also be able to get access to information about deaths that happen at home or peripheral health facilities without any fallacy.
- Availability of blood and blood products in all peripheral health facilities.
- Frequent revision of antibiotic policy and infection control practices
- Protocol review and analysis of outcome and mortality on a yearly basis for every tumor.
- Studies to elicit causes for delay in referral, delay in diagnosis, cause for mortality, infection control practices in the unit.

Increasing trend in treatment related mortality in resource limited setting indicates need for supportive care, appropriate antibiotic policies and adequate 24 hour blood bank support. Increase in progressive disease resulting in death indicates need for risk directed/ intensification of therapy. However the percentage of cases presenting at advanced stages have to be taken to account as it can confound the deaths due to progressive disease. The treatment acceptance rate have increased from less than 50% to more than 90% following introduction of social welfare schemes. Social welfare schemes are available for all patients belonging to below poverty line, through which free medications including antibiotics and anti cancer medicines can be procured. This has indeed been a boon to us. However the complete benefits of such schemes cannot be reaped until the patient reaches a tertiary care health facility at the earliest.

Conclusion

Paucity of mortality data in paediatric cancers has been quoted as a cause for lack of improvisation of facility suitable for our country. Through this article we wish to reach out to the paediatricians to ensure early referral and adequate supportive care. Routine review of mortality data is essential to analyse and formulate strategies to provide quality care to all the children with cancer.

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