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CLINICAL PROFILE AND OUTCOMES OF ACUTE LYMPHOBLASTIC LEUKAEMIA IN CHILDREN; AN EXPERIENCE FROM A NEWLY ESTABLISHED PEDIATRIC ONCOLOGY UNIT FROM EASTERN ZONE OF INDIA

Medical Science

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ABSTRACT

Objective: One third of all childhood cancers are leukaemia; approximately 10,000 new cases are diagnosed in India each year. To describe the clinical characteristics and outcomes of paediatric acute lymphoblastic leukemia (ALL).

Material and Methods: Medical records of pediatric ALL diagnosed between April 2015-March 2018 were reviewed using a custom data collection sheet.

Results: Seventy one cases were enrolled; median age 4 years, 52% male. Common clinical findings at presentation were fever (77%), hepatosplenomegaly (70%), lymphadenopathy (37%) and pallor (30%). Ninety two percent patients achieved complete hematologic remission. Infection was the most common cause of mortality. Event-free survival and overall survival at 2 years were 67% and 79% respectively.

Conclusion: Clinical characteristics are similar to those reported in the literature. Cytogenetic study (conventional karyotyping and FISH analysis) needs to be monitored for a better result. Chemotherapy regimen used appears to be effective, tolerable and feasible.

KEYWORDS

Acute lymphoblastic leukemia, Pediatric oncology, Children

INTRODUCTION

Leukemia is the most common malignancy in children and accounts for almost one third of cancers occurring in children younger than 15 years (1,2). More than 10,000 cases have been reported annually in India (3,4). ALL accounts for 60 to 85% of all childhood leukemia as per published literatures (5,6). The diagnostic tests, risk stratification and treatment options have evolved and become more refined over the past few years. As a result, survival rates for childhood ALL have improved dramatically from 30% in 1970, to a current estimated five-year overall survival rate greater than 85 percent (7,8,9). Nevertheless significant challenges still remain. Many patients in developing countries present late; or die during treatment because of infections, unavailability of adequate infrastructure and supportive care (10). Limited data is available regarding epidemiological profile or treatment outcome from eastern zone of India. In this retrospective review we aimed to evaluate the clinical profile and survival outcome of children treated in a newly developed pediatric oncology unit at "Institute of Medical Sciences and Sum Hospital", Bhubaneswar, Odisha.

MATERIALS AND METHODS

A total of 86 cases of childhood leukemia were registered to the paediatric oncology department from April 2015 to March 2018. Among them 78 (90.6%) had ALL which was confirmed by a bone marrow/ peripheral blood morphology and flow cytometry. Seventy one cases were enrolled for this retrospective analysis; 7 cases were excluded (4 patients were diagnosed but not treated at our hospital, 2 cases received initial treatment outside and presented with relapse; one lost to follow-up immediately after starting treatment).

Medical records including outpatient notes, indoor charts and discharge summaries were reviewed for clinical findings, laboratory investigations and treatment details. Data regarding all events (failure to achieve remission; relapse or death) and the disease status at last follow up were recorded. The data were analysed using SPSS software version 20. Unadjusted time to event analysis was performed using Kaplan- Meier estimate. This was a chart review study, and there was no intervention or contact with the study subjects.

RESULTS

Of 71 children, 37 were boys and 34 girls, with a male to female ratio of 1.1:1. The median age at diagnosis was 4 years (range 1-13 years). Forty two percent were in the age group of 2-6 years. Common presenting symptoms were fever 77%, progressive pallor 30% and bone pain 25%. Physical finding included hepatosplenomegaly in 70% and lymphadenopathy in 37 %. Four patients had a CNS-3 status at diagnosis, two had a testicular involvement. At admission mean hemoglobin was 6.1 gm/dl (range 3.0 to 12.4), median total leukocyte count 19,000/mm^3 (range 900 to 844,000/mm^3) and total platelet count 42,000/mm^3 (range 2,000 to 384,000/mm^3). Twelve patient (17%) had a total leucocyte count >100,000/mm^3 and 21 had a total leucocyte count more than >50,000/mm^3. Twenty seven (38%) had a bulky disease. Bulky disease was defined by bulky lymph nodes (≥5 cm in peripheral region and in chest >5 cm on CT scan or occupying ≥1/3rd diameter on chest x-ray) and/or bulky liver/spleen reaching beyond the umbilicus.

Flow cytometry using panel of 8 tubes antibodies was performed for all cases; eighty six percent (n=61) had a pre B ALL, 13% (n=9) T cell ALL, 1 had a mixed phenotypic acute leukemia. Cytogenetic study was not done in any T cell ALL and 4 cases of B cell ALL. One third (n=19/57) had structural chromosomal abnormalities. Among the gene rearrangements detected by fluorescent in situ hybridization, the most common was t(12,21) in 9 cases (16%), followed by t(1,19) in 7 cases (12%), t (9,22) in 3 cases (5%). We didn't find any MLL translocation. Cases of B cell ALL were categorized into three risk groups. Risk stratification was based on the age at diagnosis, baseline WBC count, CNS or testicular involvement, presence or absence of bulky disease, cytogenetic alterations, day 8 prednisolone response and post induction bone marrow status. Twenty eight percent (17/61) were in the standard risk group, 46% (28/61) in the intermediate-risk group and 26% (16/61) in the high-risk group. Among T cell ALL, 44% (4/9) were standard risk, 56% (5/9) high risk. Eleven percent of B cell ALL and one third of T cell ALL had a poor prednisolone response. Poor prednisolone response was defined as presence of ≥1000/mm3 blasts after 1 week of prednisolone prephase at dose of 60mg/m2/day.

All patients received chemotherapy as per modified Berlin-Frankfurt-Munich (BFM) protocol for pediatric ALL. Five cases died during induction; 4 died because of infection, 1 CNS leukostasis and intracranial bleeding. Two patients had a refractory disease (M3 marrow post induction). M3 marrow was defined as presence of >25% blasts in the bone marrow aspirate assessed on day 35. Ninety two percent (65/71) achieved a complete hematologic remission. Till last

follow up 6 patients have completed therapy and in morphologic remission, one patient died during post induction therapy, 47 are alive on treatment. Nine patients (12.6%) relapsed, among which 7 died and 2 are on salvage treatment. Median follow up period is 16 months. Estimated event free survival and overall survival at 2 years is 67 % and 79% respectively (Figure 1,2).

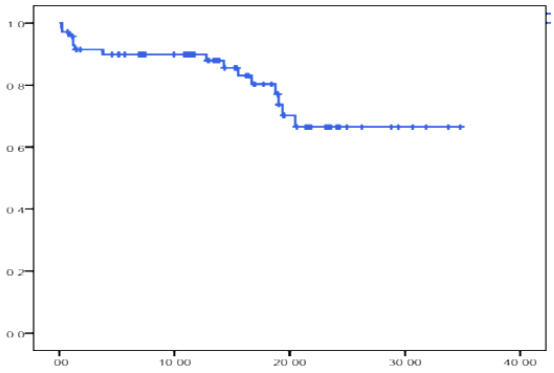

Fig-1: Kaplan-Meier survival curve of pediatric ALL, event free survival 67% at 2yr.

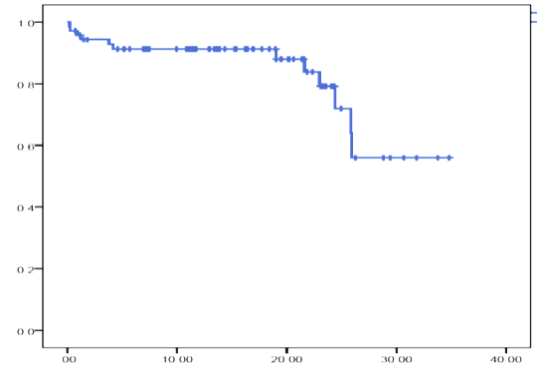

Fig-2: Kaplan-Meier survival curve of pediatric ALL, overall survival 79% at 2yr.

DISCUSSION

Acute lymphoblastic leukemia (ALL) is a clonal expansion of white blood cell precursors in the blood, bone marrow, and various extramedullary tissues. The diagnosis of ALL is determined by the presence of > 20% of blasts in the peripheral blood or bone marrow (11).

The clinical profile and outcome of childhood cancer in Odisha is unknown. There is no electronic medical data recording system in majority hospitals of this part of India. This study is a preliminary step towards a better understanding of the local epidemiologic pattern of childhood ALL, the most common childhood malignancy. We report the result of a newly developed pediatric oncology unit. In our study, the median age at presentation was 9 years. The peak age range of 3–6 years and a M/F ratio of 1.1:1 is similar to that reported in literature (12,13). Among the signs and symptoms, presentation with fever (85%) appears higher (14,15). The higher rate of fever in our study may be due to higher rate of infections at presentation. The median hemoglobin concentration on presentation was 6.4 gm%, one third patients had WBC count >50,000/mm3 and 38% had a bulky disease, which suggest a delay in diagnosis and referral to appropriate oncology centre (16). It indicates the need to increase awareness among the primary care physicians. The immunophenotype pattern (86% % B cell and 13% T cell) is within the percentage reported previously (17). Only one third of cases of B cell ALL had structural chromosomal abnormalities. The lower incidence of cytogenetic abnormalities may be probably related to the technical issues to detect these genetic changes as at present the cytogenetics and molecular investigations are being outsourced, or may reflect a racial, ethnic or geographic variation too (18).

End of induction remission rate (92%) reflect that the induction regimens used were effective and had tolerable toxicities. Minimal residual disease (MRD) was not available except for a few. The event free survival and overall survival at 2 years was 67% and 79% respectively. Most common cause of death was infection secondary to chemotherapy toxicity. Major factors which could have contributed for a inferior outcome include delay in presentation, poor socioeconomic background, inadequate infection control measures and unavailability of adequate supportive care. There are certain limitations in this study. First, this is a small series from a newly established pediatric oncology unit, which may not reflect the actual prevalence, clinical profile and outcome of all nearby treating centre. Second, being a retrospective review, there could have been some undocumented information, data regarding tolerability and drug toxicity. Third, the duration of follow up is short and many patients are still on treatment till the last data collection.

CONCLUSION

This study describes the clinical, immunophenotypic, cytogenetic profile and outcome of ALL in children. Clinical characteristics are similar to those reported in the literature. Cytogenetic study needs to be monitored for a better result. Chemotherapy regimen used appears to be effective, tolerable and feasible. Lack of awareness, delay in diagnosis, inadequate resources are the major hindrances for an optimal outcome.

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REFERENCES

1. Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 2014; 64:83.
2. Howlader N, Noone AM, Krapcho M, et al. Childhood cancer. In SEER Cancer Statistics Review, 1975-2010. Bethesda, Md: National Cancer Institute, 2013
3. Marwaha RK, Kulkarni KP. Childhood acute lymphoblastic leukemia: Need of a national population based registry. Indian Pediatr 2011;48:821.
4. Arora RS, Eden TO, Kapoor G. Epidemiology of childhood cancer in India. Indian J Cancer 2009;46:264-73.
5. Dario Campana, Ching-Hon Pui. Childhood leukemia. Abeloff's Clinical Oncology (Fifth Edition), 2014.
6. Biswas S, Chakrabarti S. Childhood acute leukemia in West Bengal, India with an emphasis on uncommon clinical features. Asian Pac J Cancer Prev 2009;10:903-6.
7. Hunger SP, Mullighan CG. Acute Lymphoblastic Leukemia in Children. N Engl J Med 2015; 373:1541.
8. Pui CH, Robison LL. Acute lymphoblastic leukaemia. Lancet 2008;371:1030-43.
9. Smith MA, Altekruse SF. Declining childhood and adolescent cancer mortality. Cancer 120 (16): 2014, 2497-506.
10. Kulkarni KP, Arora RS K. Survival Outcome of Childhood Acute Lymphoblastic Leukemia in India: A Resource-Limited Perspective of More Than 40 Years. J Pediat Hematol Onc. 2011 Aug; 33 (6): 475 -9.
11. Rabin KR, Gramatges MM. Acute lymphoblastic leukemia. Principles and Practice of Pediatric Oncology. 7th ed. Lippincott Williams and Wilkins, 2015, 463-97
12. Howlader N, Noone AM. Childhood cancer by the ICCC. SEER Cancer Statistics Review, 1975-2010. Bethesda, Md: National Cancer Institute, 2013.
13. Bartram C, Schrauder A. Acute lymphoblastic leukemia in children. Dtsch Arztebl Int. 2012; 109:652-8
14. Onciu M: Acute lymphoblastic leukemia. Hematol Oncol Clin North Am 2009; 23 (4): 655-74,
15. Clarke RT, Van den Bruel A. Clinical presentation of childhood leukaemia: a systematic review and meta-analysis. Arch Dis Child. 2016;101(10):894-901.
16. Chiaretti S, Vitale A. Clinico-biological features of 5202 patients with acute lymphoblastic leukemia enrolled in the Italian AIEOP and GIMEMA protocols and stratified in age cohorts. Haematologica 2013; 98:1702.
17. Hossfield DK. E.S. Jaffe. World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Ann Oncol 2002; 13: 490-1
18. Harrison CJ. The detection and significance of chromosomal abnormalities in childhood acute lymphoblastic leukaemia. Blood Rev. 2001;15(1):49-59.