A Study on Clinical and Immunophenotypic Profile of Acute Leukaemia among Paediatric Patients in a Tertiary Care Centre

Bipsa Singh[1], Piyush Ranjan Sahoo[2], Swarupa Panda[3], Sudha Sethy[4], Bibhu Prasad Nayak[5]

[1]Assistant Professor, Department of Paediatrics, SCB Medical College, Cuttack, Odisha, India. [2]Senior Resident, Department of Paediatrics, SCB Medical College, Cuttack, Odisha, India. [3]Associate Professor, Department of Paediatrics, SCB Medical College, Cuttack, Odisha, India. [4]Assistant Professor, Department of Clinical Haematology, SCB Medical College, Cuttack, Odisha, India. [5]Assistant Professor, Department of Paediatrics, SCB Medical College, Cuttack, Odisha, India.

ABSTRACT

BACKGROUND

Acute leukaemias are one of the most common malignancies in children aged < 15 years, accounting for nearly one third of all paediatric malignancies. Fortunately, it is one of the curable malignancies in children and hence early diagnosis is of supreme priority. Flow cytometry has now become a standard tool for diagnosing and monitoring acute as well as chronic leukaemia. Immunophenotyping by flow cytometry enables accurate diagnosis, guides treatment, and enables risk stratification.

METHODS

This is a hospital based cross sectional study, carried out in the Paediatrics and Clinical Haematology wards, SCB Medical College & Hospital, Cuttack, from December 2017 to November 2019. All patients fulfilling inclusion criteria were included in the study. Demographic details, history and examination findings were recorded in all cases**.** Complete blood count, peripheral smear, CSF analysis, RFT, LFT, chest X ray, CT scan brain and chest, USG abdomen, microbiological investigations, bone marrow aspiration, immunophenotyping were done and documented in pre-structured proformas in all cases.

RESULTS

Among 209 acute leukaemia cases, ALL was the commonest (60.8 %) followed by AML (24.9 %). Among the B-ALL cases, Pre-B ALL patients had the majority (78.4 %) followed by T-ALL (12.4 %), Pro-B ALL (2.9 %), MPAL (1.9 %) and Mature B - ALL (< 1 %). Mean age was 6.81 years and SD ± 4.10. Male : female ratio among ALL patients was 1.78:1. Fever was the commonest symptom and hepatosplenomegaly, the commonest sign. CD13 and CD33 were the commonly co-expressed myeloid markers in all.

CONCLUSIONS

Immunophenotyping should be done in all cases of leukaemia, even in resource limited settings for accurate diagnosis, prognostication and tailoring of treatment. Presence of extra-medullary organ involvement, including CNS and kidneys, should be looked for carefully at the initial presentation.

KEYWORDS

Acute Leukaemia, Flow Cytometry, Immunophenotyping

Corresponding Author:
Dr. Bibhu Prasad Nayak,
Flat No - 303,
SR Residency,
Patrapada, Bhubaneswar,
Odisha – 751019, India.
E-mail: bipsasingh@gmail.com

DOI: 10.18410/jebmh/2020/415

How to Cite This Article:
Singh B, Sahoo PR, Panda S, et al. A study on clinical and immunophenotypic profile of acute leukaemia among paediatric patients in a tertiary care centre. J Evid Based Med Healthc 2020; 7(37), 1994-1999. DOI: 10.18410/jebmh/2020/415

Submission 03-07-2020,
Peer Review 11-07-2020,
Acceptance 12-08-2020,
Published 14-09-2020.

BACKGROUND

Acute leukaemias are one of the most common malignancies in children aged < 15 years, accounting for nearly one third of all paediatric malignancies. Once considered to be a universally fatal disease, modern therapy has achieved excellent outcome and the majority of children achieve long term cure. Yet it is the leading cause of cancer related deaths among paediatric patients.[1-2] Survival from acute leukaemia has improved dramatically over the last five decades, mainly due to intensive chemotherapeutic regimens, comprehensive supportive care and risk-adapted therapeutic regimens. Among children living in the United States and Europe, 5 - year overall survival after acute lymphoblastic leukaemia (ALL) increased from less than 5 % in the early 1960s[3] to 80% – 90% at present.[4-6] Survival has also increased substantially for children and adolescents with certain subtypes of acute myeloid leukaemia (AML).[7] Though several risk factors have been proposed, a specific aetiology has not been determined till date. Fortunately, it is one of the curable malignancies in children and hence early diagnosis is of supreme priority. Studies from India have reported variable outcomes, with few specialized centers showing a favourable outcome in more than 70 %.[8] Leukaemia is a malignant neoplasm from the clonal proliferation of abnormal haematopoietic stem cells. It is characterized by diffuse replacement of the bone marrow by neoplastic cells leading to Bone marrow failure.[9] There are two main subtypes, the more common one being ALL and other one, AML. A small proportion may have chronic myeloid leukaemia (CML) and juvenile myelomonocytic leukaemia (JMML). Studies from India have reported that ALL accounted for 60 to 85 % of all childhood Leukaemias.[10] Some cases, however, either show no clear evidence of differentiation along a single lineage or express differentiation antigens highly specific of more than one lineage. These cases are categorized separately as acute leukaemia of ambiguous lineage**,** including both acute undifferentiated leukaemia (AUL) and mixed phenotype acute leukaemia (MPAL). So, it is important to identify the clinical presentation and pattern of leukaemia in children for planning further management and predicting outcome in Indian scenario, primarily for better risk stratification, as not all children have access to the regional Cancer Institutes of India. Flow cytometry has now become a standard tool for diagnosing and monitoring acute as well as chronic leukaemia. Immunophenotyping by flow cytometry enables accurate diagnosis and treatment on the basis of which further treatment is planned. Immunophenotyping also enables risk stratification.

Aim and objective to find out the clinical and immunological profile of acute leukaemia among the paediatric patients.

Inclusion Criteria

1. Paediatric patients of age < 14 years admitted with a diagnosis of acute leukaemia.
2. The leukaemia patients with detailed immunophenotyping records.

Exclusion Criteria

1. Patients with a negative bone marrow aspirate test.
2. Patients who died or got discharged against medical advice (DAMA) before confirmation of diagnosis.
3. Relapsed cases of leukaemia.

METHODS

It was a hospital based cross-sectional study conducted at department of Paediatrics and Clinical Haematology, Srirama Chandra Bhanja Medical College & Hospital, Cuttack, from December 2017 to November 2019. Institutional ethical committee clearance (IEC / IRB no: 918 / 14.10.19) was taken prior to the study. All patients full filling inclusion criteria were included in the study and those fulfilling exclusion criteria were excluded from the study. The demographic details, history and examination findings were recorded in all cases. The investigations details like complete blood count, peripheral smear, CSF analysis, RFT, LFT, chest X ray, CT scan brain and chest, USG abdomen, microbiological investigations, bone marrow aspiration, immunophenotyping were documented in the pre-structured proformas in all cases. Acute lymphoblastic leukaemia was defined if the bone marrow blast cells were > 25 %. Acute myeloid leukaemia (with maturation) was defined by the presence of ≥ 20 % blasts in the bone marrow or peripheral blood and evidence of maturation (≥ 10 % maturing cells of neutrophil lineage). The diagnosis was given as per the WHO 2008 criteria. Bone marrow aspiration followed by flow cytometric immunophenotyping was done in all patients with strong history, clinical signs for Leukaemia and with presence of > 20 % leukemic blasts in bone marrow. In suspected cases of leukaemia, peripheral blood smear and bone marrow aspirates taken from iliac crest of patients was sent to Clinical Haematology department for immediate staining and analysis. Slides were stained with PAS, Sudan Black B and MPO stains and reports were given accordingly. For each patient, 5 mL of EDTA venous blood sample was taken for immunophenotype analysis. The cells were gated according to percent viability, processed in a flow cytometer by indirect immunofluorescence technique using single colour method. Age, sex, initial WBC count, haemoglobin, platelet count, hepatomegaly, splenomegaly, lymphadenopathy, presence, or absence of mediastinal involvement, renomegaly, sub - type of ALL based on immunophenotyping were analysed. EGIL scoring system was applied to find any Bi-phenotypic or Mixed-Phenotype Acute Leukaemia (MPAL). After confirmation of diagnosis including subtype of acute leukaemia, appropriate therapy was started in respective wards.

Statistical Analysis

All data were entered in Excel sheet and statistical analysis done using statistical software SPSS version 20. Categorical variables were expressed as number of patients and percentage of patients, and compared across the groups using Pearson's Chi Square test for Independence of Attributes / Fisher's Exact Test as appropriate. Continuous

variables were expressed as Mean and Standard Deviation and compared across the groups using One Way ANOVA Test. For categorical data proportion with 95 % CI was calculated and chi square test was used to calculate the P value. For continuous data mean with SD was calculated. An alpha level of 5 % has been taken, i.e. P value < 0.05 was considered significant.

RESULTS

In our study, among 226 cases, 17 cases were excluded as per exclusion criteria. Finally, 209 cases were analysed. Among the acute leukaemia cases, ALL was the commonest (n - 153, 60.8 %) followed by AML (24.9 %). Among the B - ALL cases, Pre - B ALL patients had the majority i.e. 94.5 % of B - ALL patients and 78.4 % of overall ALL cases (Table 1).

The age of patients ranged 3 months to 14 years with a mean age being 6.81 ± 4.10 years (Table 2). While comparing the mean age between different types of leukaemia groups using One Way ANOVA the p (0.038) value was statistically significant. The overall M : F ratio in our study population of paediatric acute leukaemia was 1.64 : 1. Also in all subtypes of acute leukaemias males outnumbered females (Table 3). While comparing the proportion of male and female children among various subtypes of acute leukaemia using chi square test the p value came to be 0.372 which was not statistically significant.

Amongst various presenting symptoms fever was the most common complaint (86.1 %) followed by easy fatigability, and abdominal distension. 32.5 % of our cases had bleeding from gum, oral mucosa, including 7 patients who presented with epistaxis. 29.7 % patients had either unilateral or bilateral swellings in neck. 21 patients (10 %) had new onset cough, breathing difficulty in conjunction with other symptoms but not as isolated complaints. Only 10 (4.8 %) patients complained of musculoskeletal problems in the form of bone pain. Recent weight loss as a complaint could be elicited in 12 (5.7 %) patients (Table 4). Systemic involvement in the form of hepatomegaly and / or splenomegaly were the most common findings followed by cervical lymphadenopathy**.** Parotidomegaly was also noted in 2 T - cell patients and the mature B - cell ALL patient. 21 patients had sternal tenderness (Table 5).

Pallor of varied degree was present in 164 (78.5 %) cases. The haemoglobin value ranged from 2.9 g / dL to 13 g / dL with a mean ± SD of 5.97 ± 2.89 g / dL. Petechiae, purpura and bruises were present in 29.2% cases. Platelet counts ranged from 10,000 to 2,90,000 / cu.mm with a median of 67,000 / cu.mm. CD13, CD33, CD117, MPO were positive in all cases of AML (100 %). CD19 was a consistent marker in B - ALL (82.80 %) along with CD10 (82.80 %). 12 out of the total 126 patients of B - ALL had myeloid co-expression. CD13 and CD33 were the commonly co-expressed myeloid markers in ALL. CD117 and cMPO were expressed in 5 cases each. Among 153 ALL cases, 26 were T - cell ALL, remaining 127 cases were B-cell ALL (Pre - B cell 120, Pro - B cell – 6, Mature B cell – 1). 17 cases showed myeloid co expression (11.1 %).CD3 was positive in all cases of T - ALL (100 %) and 2 cases of MPAL. Among aberrant myeloid co - expression in T - ALL cases CD5 and CD7 were maximum. 5 patients had positive myeloid markers such as CD13 and / or CD33 and were labelled as T - cell ALL with aberrant myeloid expression.

Type	Frequency	%
Pre - B ALL	120	57.4
Pro - B ALL	6	2.9
Mature B - ALL	1	0.5
T - ALL	26	12.4
AML	52	24.9
MPAL	4	1.9
Total	209	100.0

Table 1. Frequency of Each Type of Leukaemia in the Present Study (n = 209)

ALL: Acute Lymphoblastic Leukaemia, AML: Acute Myeloid Leukaemia, MPAL: Mixed - Phenotype Acute Leukaemia

Diagnosis	Mean Age	Standard Deviation
B - ALL	6.24	3.80
T - ALL	8.31	4.50
MPAL	9.50	5.45
AML	7.27	4.31
Overall	6.81	4.10
p Value	0.038	
Significance	Significant	

Table 2. Mean Age at Diagnosis of Acute Leukaemia in the Present Study

		Diagnosis					P Value	Significance
		B - ALL	T - ALL	MPAL	AML	Total		
Sex	Female	49 (38.58)	6 (23.08)	2 (50)	22 (42.31)	79 (37.8)	0.372	Not Significant
	Male	78 (61.42)	20 (76.92)	2 (50)	30 (57.69)	130 (62.2)		
Total		**127 (100)**	**26 (100)**	**4 (100)**	**52 (100)**	**209 (100)**		

Table 3. Sex Distribution in Acute Leukaemia In the Present Study (n = 209)

Symptoms	Frequency	%
Fever	180	86.1
Abd Distension	87	41.6
Bleeding	68	32.5
Neck Swelling	62	29.7
Bone Pain	10	4.8
Cough / Breathlessness	21	10.0
Easy Fatigue	114	54.5
Weight Loss	12	5.7

Table 4. Frequency of Symptoms at Presentation In the Present Study

Systemic Involvement	Number of Patients (n = 209)	%
Lymphadenopathy	149	71.3
Pallor	164	78.5
Bone Tenderness	21	10.0
Hepatomegaly	181	86.6
Splenomegaly	174	83.3
Petechiae / Purpura	61	29.2
CNS Manifestation	7	3.3
Gonadal Involvement	0	0.0

Table 5. Frequency of Signs at Presentation in the Present Study

Marker	No. of Cases	%
CD - 45	156	99.40
CD - 5	35	22.30
CD - 7	30	19.10
CD - 10	130	82.80
CD - 19	130	82.80
CD - 13	26	16.60
CD - 33	17	10.80
CD - 117	5	3.20
CCD - 3	28	17.80
CD - 79a	129	82.20
cMPO	5	3.20
CD - 34	144	91.70
HLA - DR	137	87.30

Table 6. Commonly Co-Expressed Myeloid Markers in ALL

DISCUSSION

This study was conducted to describe the clinical and immunophenotype profile of ALL patients who were treated in our center. Currently, these patients are being followed up for the survival rate. We performed flow cytometric immunophenotyping in all cases but a small proportion of patient could not undergo karyotyping and FISH analysis as they were expensive and not affordable by a few. That was a limitation in our study. Over the study period of two years, 209 cases of acute leukaemia were diagnosed. Acute lymphoblastic leukaemia (73.2 %) was the most commonly diagnosed acute leukaemia, a data which is comparable to studies from the west as well as from other parts of India but less than that of study by Pandian et al (90.3 %).[11] According to pre-existing literature, the most common age group is 3 - 9 years.[12] 5 infantile acute leukaemia cases (2.3 %) were noted in the present study as opposed to 3 - 5 % in other studies.[13] Leukaemia contributes to 25 – 40 % of all childhood malignancies in India, of which 60 – 80 % is ALL.[14] ALL in children is associated with male preponderance.[15-19] Similar observation was noted in American population by Adelman et al[20] and in Indian paediatric population.[21] Kulkarni et al also noted a significant male preponderance of 2.5 : 1 after an analysis of data from India.[22] Our study supports this finding with definite male predominance among ALL patients (M : F ratio = 1.78 : 1) which has been observed to be slightly higher compared to other studies conducted in this part of the country.[23] Earlier studies have shown slightly higher male preponderance in T - ALL as compared to B - ALL. Our study finding goes in favour of them as M : F ratio in our T -ALL patients is 3.33 : 1 as compared to 1.59 : 1 in our B-ALL cases. In our study, no male or female predominance was found among MPAL cases (n = 4, M: F ratio = 1 : 1) in contrast to study by Gupta et al, in which majority of them were males (57.1 %, n = 8).[24] AML accounts for approximately 20 % of acute leukaemia in children and is the second most common leukaemia in Indian children as per current data.[25,26] Higher incidence of AML in male children in our study supports previous studies. Peak incidence of paediatric ALL has been reported in age group 2 - 5 years.[27,28] Khalid et al[16] reported 58.7 % of ALL in the age group of one to nine years while Aryaet al[17] reported mean age as 7.6 years. In India, ALL is found to be more prevalent in children < 5 years of age[29] but Biswas et al[30] reported the average age as 6.12 years (SD ± 2.98). Our study supports the results of the previous studies, with 46.4 % of ALL patients in 1 - 5 years and 20.9 % in 6 - 10 years age group. Mean age in our study for ALL was 6.24 years with SD ± 3.80, which is slightly higher to that observed by Idris et al[31] in Pakistani children (4.5 years). Overall mean age for paediatric acute leukaemia in our study was 6.81 years with SD ± 4.10.

Usual clinical manifestations of acute leukaemia cited in the literature are fever, fatigue, pallor, and weight loss. CNS involvement is less common, with < 5 % of children presenting with this feature. In our study, clinical presentations were in similar lines with the previous studies,[29-31] but with a similar incidence of fever (86.1 %) prompting it to be the commonest presenting symptom followed by easy fatiguability (54.5 %). Cough or breathlessness, bone pain and recent weight loss were the least common presenting symptoms in our set up. In the present study, bone pain was present in 4.8 % of acute leukaemia patients, whereas certain other studies report bone pain in 21 % to 38 % of the patients with ALL.[32-34] Hepatomegaly and / or splenomegaly were overall the most common signs at presentation. Pallor of varied degree was present in 78.5 % cases. Petechiae, purpura and bruises were present in 29.2 % cases which was much higher in study of Siddaiahgari et al.[14] Thrombocytopenia with platelet counts < 100,000 were seen in about 75 % of patients in their study.[14] Bleeding seen in leukaemia patients appear to be multifactorial, and not related to thrombocytopenia alone. For example, gum bleeding was present in children with platelet count of one lakh cells and few patients had no bleed despite a platelet count of few thousand cells only. Parotidomegaly, CNS involvement (6.80 %), widened mediastinum (4.85 %) and testicular enlargement (nil) were reported to be infrequent signs in our study, which is comparable to other studies.

Available data in literature on CNS involvement in ALL is 4.3 % and enlarged mediastinum in 2.2 % patients.[16] Not many cases in our study population presented very late as is evident by the less frequency of extra - medullary organ involvement which indirectly indicates tumour burden. The presence of parotidomegaly and renomegaly; and their significant association with T - cell ALL is apparently mentioned in existing literatures. [35-37] Previous studies[15] have shown the preponderance of Pre - B ALL and our study supports this indicating that the study population was under standard group. However, higher proportion of T - cell ALL has been mentioned in the literature[12] in India; it has been estimated that about 20 – 50 % ALL reported are found to be of T-cell type contrast to the scenario in developed world which is 10 - 20%[15] and it is 16.9 % in our study. Mukhopadhyay et al have documented high rate of T - cell immunophenotypes (50.4 %, 252 patients) in their patients.[38] Presence of CD10 determines the prognosis and also treatment response. Previous study[39] has reported CD10 positive, Pre-B ALL as the predominant phenotype and it was in similar lines in our study (78.4 % of all the ALL cases). Among the ALL cases in present study, T-cell ALL flow cytometry accounted for 17 %, and the remaining 83 %

being B cell ALL. This is very close to similar study in Indian population conducted by Pandian et al,[11] in which T - cell ALL flow cytometry accounted for 14 %, and 86 % was B - cell ALL. Diagnosis of ALL by flow cytometry done in 1774 Japanese children yielded a similar result. Here T - cell and B - cell ALL were responsible for 13 % and 87 % cases respectively.[40] In our study, the B - cell ALL cases were further characterized and 94.4 % (n - 120) of these cases were found to be Pre - B cell type. CD19 and CD10 were consistent markers in B - ALL (each present in 82.80 % cases). As per existing literature, CD13 and CD33 which are markers of myeloid lineage are occasionally noted in ALL, both B - cell and T - cell. In our study, 12 out of the total 126 B - ALL patients had myeloid co-expression. CD13 and CD33 were the commonly co-expressed myeloid markers in ALL. CD117 and cMPO were expressed in 5 cases each. 17 cases showed myeloid co expression (11.1%). CD13, CD33, CD117, MPO were positive in all cases of AML (100 %).CD3 was positive in all cases of T - ALL (100 %) and 2 cases of MPAL. Among aberrant myeloid co-expression in T - ALL cases, CD5 and CD7 were maximum. 5 patients had positive myeloid markers such as CD13 and / or CD33 and were labelled as T - cell ALL with aberrant myeloid expression. Statistically significant difference in myeloid expression between T and B - cell ALL was reported in a study of Japanese children with ALL.[40]

This study provides a baseline data which can guide further planned data collection. Also, it provides an insight into observation of T - cell leukaemia and myeloid co-expression in immunophenotype results and look carefully for organ enlargement including CNS, kidneys. Our study has certain limitations, the main one being a small sample size. A larger sample size would have found more significant factors which affected outcome in these children. Further it should be emphasized that establishing a national and regional cancer registry will enable systematic data collection.

CONCLUSIONS

ALL is the most common acute leukaemia in children < 15 years of age. Mean age at diagnosis was 6.81 ± 4.10 years with male sex predilection in overall paediatric acute leukaemia patients in this part of the country. Fever was the most common symptom (86.1 %) and hepatosplenomegaly was the most common sign (>80 %). B-cell (83 %) was more common than T-cell (17 %). Myeloid antigen co-expression was seen in 11.1 % of ALL cases. CD10 positive, Pre-B ALL was the predominant phenotype reported among the B-ALL cases. CD13 and CD33 were the most commonly associated myeloid markers. CD19 and CD10 were the most consistent markers in B-ALL.

Recommendations

Immunophenotyping should be done in all cases of leukaemia, even in resource limited settings for accurate diagnosis, prognostication and tailoring of treatment. Presence of extramedullary organ involvement, including CNS and kidneys, should be looked for carefully at the initial presentation.

Financial or Other Competing Interests: None.

REFERENCES

[1] Wingo PA, Cardinez CJ, Landis SH, et al. Long-term trends in cancer mortality in the United States, 1930-1998. Cancer 2003;97(Suppl 12):3133-3275.
[2] Deschler B, Lubbert M. Acute myeloid leukaemia: epidemiology and etiology. Cancer 2006;107(9):2099-2107.
[3] Thames Cancer Registry. Cancer in South East England 1991 cancer incidence, prevalence and survival in residents of the district health authorities in South East England (Sutton). Thames Cancer Registry 1994.
[4] Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE- 5 --a population-based study. Lancet Oncol 2014;15(1):35-47.
[5] Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol 2010;28(15):2625-2634.
[6] Pui CH, Evans WE. A 50-year journey to cure childhood acute lymphoblastic leukaemia. Semin Hematol 2013;50(3):185-196.
[7] Brunner AM, Blonquist TM, Sadrzadeh H, et al. Population-based disparities in survival among patients with core-binding factor acute myeloid leukaemia: a SEER database analysis. Leuk Res 2014;38(7):773-780.
[8] Kulkarni KP, Arora RS, Marwaha RK. Survival outcome of childhood acute lymphoblastic leukaemia in India: a resource-limited perspective of more than 40 years. J Paediatr Hematol Oncol 2011;33(6):475-479.
[9] Tubergen DG, Bleyer A. The Leukaemias. In: Kliegman RM, Behrman RE, Jenson HB, et al. eds. Nelson Textbook of Paediatrics. 20th edn. Philadelphia: Saunders 2016: p. 2437-2438.
[10] Chaudhuri K, Sinha A, Hati GC, et al. Childhood malignancies at BS Medical College: a ten year study. Indian J Pathol Microbiol 2003;46(2):194-196.
[11] Pandian G, Sankarasubramaian ML. A study on clinical, immunophenotypic pattern in paediatric acute leukaemias in a teaching hospital. Inter J Contemp Paediatr 2018;5(4):1183-1189.
[12] Pui CH. Acute lymphoblastic leukaemia. The Paediatric Clinics of North America: Paediatr Oncol 1997;44(4):P831-846.
[13] Neimeyer CM, Sallan SE. Acute lymphobalstic Leukaemia. In: Nathan and Oskis hematology of infancy and childhood. 5th edn. W.B. Saunders 1998: p. 1245-1269.

[14] Siddaiahgari SR, Awaghad MA, Latha MS. Clinical, immunophenotype and cytogenetic profile of acutelymphoblastic leukaemia in children at tertiary health care centre in India. Muller J Med Sci Res 2015;6(2):112-118.
[15] Arora RS, Eden TOB, Kapoor G. Epidemiology of childhood cancer in India. Indian J Cancer 2009;46(4):264-273.
[16] Khalid S, Moiz B, Adil SN, et al. Retrospective review of paediatric patients with acute lymphoblastic leukaemia: a single center experience. Indian J Pathol Microbiol 2010;53(4):704-710.
[17] Arya LS, Padmanjali KS, Sazawal S, et al. Childhood T-lineage acute lymphoblastic leukaemia: management and outcome at a tertiary care center in North India. Indian Paediatr 2011;48(10):785-790.
[18] Padhi S, Sarangi R, Mohanty P, et al. Cytogenetic profi le of paediatric acute lymphoblastic leukaemia (ALL): analysis of 31 cases with review of literature. Inter J Cytol Cytosystem Cytogen 2011;64(1):33-41.
[19] Kulkarni KP, Marwaha RK, Trehan A, et al. Survival outcome in childhood ALL: experience from a tertiary care centre in North India. Paediatr Blood Cancer 2009;53(2):168-173.
[20] Petridou E, Alexander FE, Trichopoulos D, et al. Aggregation of childhood leukaemia in geographic areas of Greece. Cancer Causes Control 1997;8(2):239-245.
[21] Mazloumi SHM, Kumari P, Madhumathi DS, et al. Rare and recurrent chromosomal abnormalities and their clinical relevance in paediatric acute leukaemia of South Indian population. Ind J Med Paediatr Oncol 2012;33(3):166-169.
[22] Kulkarni KP, Marwaha RK. Significant male preponderance in childhood acute lymphoblastic leukaemia in India and regional variation: tertiary care center experience, systematic review and evaluation of population-based data. Paediatr Hematol Oncol 2013;30(6):557-567.
[23] Panda SP, Mallick B, Samal P, et al. Clinical profile and outcomes of acute lymphoblastic leukaemia in children: an experience from a newly established paediatric oncology unit from eastern zone of India. Int J Sci Res 2018;7(7):56-57.
[24] Gupta N, Pawar R, Banerjee S, et al. Spectrum and immunophenotypic profile of acute leukaemia: a tertiary center flow cytometry experience. Mediterr J Hematol Infect Dis 2019;11(1):e2019017.
[25] http://www.rightdiagnosis.com/a/acute_myeloid_leukaemia/stats-country html.
[26] http://www.cancertreatmentinindia.com/leukaemia_cancer_treatment_in_india.html.
[27] Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. Lancet 2008;371(9617):1030-1043.
[28] Pizzo PA, Poplock DG. Principle and practice of paediatric Oncology. 5th edn. Philadelphia: Lippincott Williams & Wilkins 2006: p. 539-590.
[29] Swaminathan R, Rama R, Shanta V. Childhood cancers in Chennai, India, 1990-2001: incidence and survival. Int J Cancer 2008;122(11):2607-2611.
[30] Biswas S, Chakrabarti S, Chakraborty J, et al. Childhood acute leukaemia in West Bengal, India with an emphasis on uncommon clinical features. Asian Pac J Cancer Prev 2009;10(5):903-906.
[31] Idris M, Farid J, Sarwar J, et al. Response rate of Pakistani children with acute lymphoblastic leukaemia to medical research council acute lymphoblastic leukaemia 97 chemotherapy protocol. J Ayub Med Coll Abbottabad 2010;22(3):8-11.
[32] Rogalsky RJ, Black GB, Reed MH. Orthopaedic manifestations of leukaemia in children. J Bone Joint Surg Am 1986;68(4):494-501.
[33] Hann IM, Gupta S, Palmer MK, et al. The prognostic significance of radiological and symptomatic bone involvement in childhood acute lymphoblastic leukaemia. Medi Paediatri Oncology 1979;6(1):51-55.
[34] Jonsson OG, Sartain P, Ducore JM, et al. Bone pain as an initial symptom of childhood acute lymphoblastic leukaemia: association with nearly normal hematologic indexes. J Paediatr 1990;117(2 Pt 1):233-237.
[35] Saha A, Dandekar S, Milla S, et al. Bilateral parotid gland enlargement and palpable nephromegaly in infant acute lymphoblastic leukaemia: case report and review of the literature. J Paediatri Hematol Oncol 2014;36(3):246-248.
[36] Biswas S, Chakrabarti S, Chakraborty J, et al. Childhood acute leukaemia in West Bengal, India with an emphasis on uncommon clinical features. Asian Pac J Cancer Prev 2009;10(5):903-906.
[37] Mantan M, Singhal KK, Sethi GR. Acute lymphoblastic leukaemia: an unusual cause of nephromegaly in infancy. Indian J Paediatr 2010;77(5):583.
[38] Mukhopadhyay A, Gangopadhyay S, Dasgupta S, et al. Surveillance and expected outcome of acute lymphoblastic leukaemia in children and adolescents: an experience from Eastern India. Indian J Med Paediatr Oncol 2013;34(4):280-282.
[39] Hamouda F, El-Sissy AH, Radwan AK, et al. Correlation of karyotype and immunophenotype in childhood acute lymphoblastic leukaemia: experience at the National Cancer Institute, Cairo University, Egypt. J Egypt Natl Canc Inst 2007;19(2):87-95.
[40] Iwamoto S, Deguchi T, Ohta H, et al. Flow cytometric analysis of de novo acute lymphoblastic leukaemia in childhood: report from Japanese Paediatric Lymphoma/Leukaemia study group. Int J Hematol 2011;94(2):185-192.