RESEARCH PAPER

Predictors of Outcome in Pediatric Anaplastic Large Cell Lymphoma

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Objective: To determine the event-free survival (EFS), overall survival (OS) and predictors of outcome in pediatric anaplastic large cell lymphoma treated with a uniform protocol. **Method:** This hospital record review was done between June, 2016 to March, 2019 and data was extracted from January, 2003 to May, 2016 for anaplastic large cell lymphoma (ALCL) in patients aged 1 to 18 years (*n*=27). EFS and OS were calculated by the Kaplan Meier method. Cox proportional model and the Cox regression model were used for univariate analysis and multivariate analysis respectively. **Results:** EFS and OS at three years was 70.4% (CI: 0.49-0.84) and 77.2% (CI: 0.56 -0.89), respectively. On univariate analysis stage III and IV, hemoglobin less than 10 g/dL and presence of pleural effusion predicted lower survival. On multivariate analysis, pleural effusion was a significant predictor of low EFS and OS. **Conclusion:** Pleural effusion is a potential clinical marker of poor outcome among children with anaplastic large cell lymphoma.

Keywords: *Management, Non-Hodgkin's lymphoma, Predictor, Prognosis*.

Anaplastic large cell lymphoma (ALCL) has been recognized as a unique subset of peripheral T cell lymphoma by the World Health Organisation (WHO) and is the most common subtype [1]. In children, it comprises 10% of pediatric non-Hodgkin lymphoma [2]. The clinical presentation is varied with extranodal site involvement commonly posing challenges in diagnosis. Event-free survival (EFS) of 60-75% with intensive protocols has been reported worldwide [3-5]. A characteristic anaplastic lymphoma kinase (ALK) mutation is present in the majority of pediatric ALCL [6,7]. Literature from South Asia is limited in this subset due to the rarity of the disease. Here we report EFS, overall survival (OS) and predictors of the outcome of pediatric ALCL treated uniformly at our center Berlin-Frankfurt-Munster (BFM).

METHODS

We retrieved data from medical records of our institute of pediatric ALCL managed from January, 2003 to May, 2016. The institute and ethics committee approved the study. The diagnosis of ALCL was based on clinical presentation, morphology, histopathology, and immunohistochemistry. Data of all patients of age 1 to 18 years were analyzed, except partially treated, relapsed patients and patients who did not receive treatment. The B symptoms were defined as non-infectious fever (no obvious focus of infection) more than 100.4ºF without evidence of infections, significant weight loss of more than 10%, and history of night sweats. For completion of staging workup, all patients underwent contrast-enhanced computed tomography (CECT) of neck, chest, and abdomen along with cerebrospinal fluid cytopathology, and bone marrow aspiration and biopsy examination. Symptom duration before presentation at our centre was categorized into early (≤30 days) and delayed (>30 days) presentation. The staging was done as per St Jude staging [8].

We categorized patients' performance status into 1 and 2 *vs* 3 and 4 [9], nodal and extra nodal sites, presence or absence of pleural effusion, B symptoms, and expression of a Anaplastic lymphoma kinase (ALK) and cluster of differentiation (CD) 3.

All patients of early stage were treated with chemotherapy protocol as per Link, *et al.* [10] and those with advanced disease were treated with Berlin-Frankfurt-Munster (BFM) BFM 90 NHL protocol [11]. After the end of two blocks of treatment, patients underwent CECT of neck, chest, and abdomen for response evaluation. After completion of treatment post six cycles of therapy, the response was documented with re-imaging. After completion of treatment, patients were followed up every three months for the initial two years and then every six-months till five years, and yearly thereafter. Patients who did not attend the scheduled visit were contacted telephonically. Relapse was defined as disease recurrence after the achievement of complete remission

post completion of therapy and progressive disease was defined as progression during treatment.

Statistical analyses: Baseline patient characteristics were assessed for survival. An event was defined as relapse, the progression of the disease, lost to follow up or death due to any cause. The EFS was calculated from the day of diagnosis until the date of the event. OS was calculated from the date of diagnosis until the date of death due to any cause. The data were censored on 31 March, 2019 or the date of the last follow-up for survival analysis.

STATA ver.13 (StataCorp, USA) was used for statistical analyses. Kaplan-Meiler method was used for survival analysis and the Log-rank test was used for comparison. The chi-square method was used to see the association between variables affecting outcomes. Cox proportional model was used for hazard calculation for univariate analysis, and for multivariate analysis Cox regression model was used. The significant univariate variables of value up to P=0.10, were considered for multivariate analysis.

RESULTS

A total of 27 patients (3 females) of pediatric ALCL were studied. The baseline clinicopathological characteristics and demographics are shown in ***Table* I**. Stage IV disease was observed in 7 (26%) patients. Extranodal involvement was seen in 20 (74%) patients; the most common site was bone in 9 (33%) patients and skin involvement in 5 (18%); other uncommon sites were adrenal glands, breast and lung parenchyma in one patient each. No patient had bone marrow involvement. Two patients had involvement of parenchymal central nervous system involvement; one patient had temporal lobe mass and the other had suprasellar mass. We also evaluated baseline absolute neutrophil count divided by total leukocyte count (ANC/TLC) ratio; categorized into two groups based on the median value of 0.65.

EFS at 3 years of the whole cohort was 70.4 (8.8)% (CI: 0.49-0.84) and OS was 77.2 (8.2)% (CI: 0.56-0.89), respectively. Median EFS and OS were not reached. Ten events occurred from the date of diagnosis. Three patients progressed while on therapy. There were four deaths unrelated to disease, progression or relapse; two patients died of chemotoxicity (one with gastrointestinal bleed and other with septic shock); one died of complication of complex congenital heart disease (patient was in CR at three years of follow up); cause of death in the fourth patient was viral hepatitis. There were three nodal relapses, out of which one died while two patients were treated with salvage therapy and autologous stem cell transplant. Of these, one died 3 years post-transplant due to central nervous system infection and refractory seizures, and the other patient is alive without disease.

The univariate analysis of prognostic factors for EFS and OS are depicted in ***Table* II**. On univariate analysis, stage III and IV, hemoglobin less than 10 g/dL and presence of pleural effusion had a trend towards predicting inferior EFS and OS with P<0.1. On multivariate analysis, only pleural effusion emerged as a significant predictor for EFS (P=0.011) and OS (P=0.02).

Notably, there was no significant difference in pleural effusion patients with hypoalbuminemia (40%) and in those without hypoalbuminemia (12%), P=0.09. We also did not find any significant difference in pleural effusion in patients with poor performance status (36%) and good

Table I Baseline Characteristics of Children With Anaplastic Large Cell Lymphoma (N=27)

Age, y*	12 (1-17)
Male gender	24 (89)
Symptom duration, mo*	3 (0.5-12)
>30 days	23 (85)
Stage	
I	1 (4)
II	2 (7)
III	17 (63)
IV	7 (26)
Performance status (ECOG)	
1 and 2	14 (52)
3 and 4	13 (48)
Extranodal site	20 (81)
B symptom	21 (78)
Pleural effusion	6 (22)
ALK positive	18 (95)
CD 3 negative	13 (62)
Hemoglobin, (g/dL)*	10.1 (4.3-15.1)
WBC*, per cu.mm	9100 (2300-26200)
>12000 per cu.mm	11 (41)
ANC/TLC ratio*	0.65 (0.29-0.86)
Serum albumin, (g/dL)*	3.7 (2.3-5.3)
≤3.5 g/dL	10 (37)
Normal serum LDH[#]	15 (68)

LDH: *Lactate dehydrogenase; ANC*: *Absolute neutrophil count*; *TLC*: Total leucocyte count; ECOG*: Eastern co-operative group; Values in no. (%) except *median (range). ALK*: *anaplastic large kinase*[#], *ALK evaluated in 19 children, CD3 in 21 children, and LDH in 22 children*.

Table II Factor Predicting Event Free Survival in Children with Anaplastic Large Cell Lymphoma (*N*=27)

Variable	*No*	*Event free survival HR (CI)*	*P*	*Overall survival HR (CI)*	*P*
Age <12 y	13	0.52 (0.15-1.86)	0.32	0.53 (0.15-1.90)	0.33
Female sex	3	1.35 (0.17-10.69)	0.77	1.41 (0.18-11.17)	0.75
Rural residence	14	1.25 (0.36-4.36)	0.73	1.43 (0.41-5.05)	0.57
Symptom duration >30 d	23	1.78 (0.38-8.45)	0.47	1.13 (0.24-5.34)	0.88
Performance status ECOG 1 and 2	14	0.42 (0.11-1.62)	0.21	0.35 (0.09-1.37)	0.13
No B symptom	6	1.07 (0.23-5.04)	1.07	1.13 (0.24-5.34)	0.88
No Pleural effusion	21	8.51 (2.34-30.90)	0.00	1 7.77 (2.14-28.19)	0.002
[#]CD 3 positive (*n*=21)	8	4.04 (0.73-22.18)	0.11	2.58 (0.46-14.34)	0.28
Hb ≤10.0 g/dL	13	0.32 (0.08-1.24)	0.10	0.29 (0.07-1.12)	0.07
WBC ≤11 × 10^9	16	0.71 (0.20-2.51)	0.59	0.64 (0.18-2.27)	0.49
ANC/TLC ratio ≤0.65	13	1.78 (0.50-6.33)	0.37	2.41 (0.66-8.76)	0.18
Serum albumin (g/dL) ≤3.5	10	0.36 (0.10-1.29)	0.12	0.39 (0.11-1.40)	0.15
[#]Raised Serum LDH (*n*= 22)	7	1.62 (0.33-7.80)	0.55	1.57 (0.33-7.61)	0.57

ALK: Anaplastic large kinae; ANC/TLC: Absolute neutrophil count /Total leukocyte count; CD: Cluster differentiation; CI: Confidence interval; ECOG: Eastern co-operative group, Hb: hemoglobin; HR: Hazard ratio, LDH: Lactate dehydrogenase; ULN: Upper limit of normal; WBC: White blood count; [#]Data was not available for all patients; [$]As all patient in stage I and II survived, hazard ratio and confidence interval was not evaluable; Since only one patient was ALK negative, data was not evaluable and it was excluded from multivariate analysis.

performance status (8%), *P*=0.08. Out of six patients who had pleural effusion, one patient received anti-tubercular therapy. In our study, pleural effusion was not drained and on the initiation of therapy, it resolved.

DISCUSSION

In this cohort of pediatric non-Hodgkin lymphoma, we only analyzed clinical factors as predictors of EFS and OS. Minimal disseminated disease in peripheral blood and bone marrow at diagnosis, minimal residual disease, and Anaplastic large kinase titer which are novel biological predictors of outcome were not evaluated [12]. The strength of this study is that it includes a cohort of a relatively rare subtype of NHL treated with a uniform protocol. However, the fact that it is a retrospective study with a limited number of subjects is a limitation of the study.

In this study, the EFS of patients with ALCL is 10-15% lower as compared to other contemporary series from developed countries [3-5,13,14]. When the results are compared with developing countries, the outcomes are similar [9,15,16]. Our study highlights some of the challenges as almost 90% of our patients presented in an advanced stage of the disease and more than 50% of subjects had a poor performance status. Further, the median duration of symptoms was three months, and one-fifth of the patients received anti-tubercular therapy before being diagnosed as a malignancy. This is similar to the observation in pediatric Hodgkin lymphoma [17].

Prognostic factors for ALCL are not consistent across studies due to mostly retrospective series, a small number of patients and varying protocols [18]. We found pleural effusion as a predictor of poor EFS and OS. In a study of 225 patients [19], the involvement of the lymph nodes, mediastinum, skin and liver was associated with the risk of relapse; however, it is to be noted that three different protocols were used in treating these groups of patients. In NHL-BFM 90 trial, only B symptoms were associated with poor EFS [4].

Our study implies that the presence of pleural effusion is a potential clinical marker of poor outcomes in pediatric patients with ALCL. Pleural effusion resolves with treatment and that no additional intervention is usually required. There is a need to spread awareness about this subtype of NHL amongst pediatricians and primary care physicians so that they are referred early for treatment and thereby presentation of the disease in advanced stages is minimized.

Ethical clearance: Institutional Ethics Committee of AIIMS, Delhi; No. IESC/T-331, June 23, 2015.
Contributors: AP: designed the research study, analysed the data, drafted the paper; DP: analyzed the data and drafted the paper; MCS,ST: acquisition and interpretation of the data for the paper, drafted the paper; SB: conception and designed the research study, analyzed the data, drafted the paper. All authors contributed to the drafting of the work, finally approved the work and agreed to be accountable for integrity of the data.
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WHAT THIS STUDY ADDS?

Pleural effusion is a potential clinical predictor of poor outcome in pediatric anaplastic large cell lymphoma.

REFERENCES

1. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, *et al*. The 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms. Blood. 2016;127:2375-90.
2. Burkhardt B, Zimmermann M, Oschlies I, Niggli F, Mann G, Parwaresch R, *et al*. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. Br J Haematol. 2005;131:39-49.
3. Lowe EJ, Sposto R, Perkins SL, Gross TG, Finlay J, Zwick D, *et al*. Intensive chemotherapy for systemic anaplastic large cell lymphoma in children and adolescents: Final results of Children's Cancer Group Study 5941. Pediatr Blood Cancer. 2009;52:335-9.
4. Seidemann K, Tiemann M, Schrappe M, Yakisan E, Simonitsch I, Janka-Schaub G, *et al*. Short-pulse B-non-Hodgkin lymphoma-type chemotherapy is efficacious treatment for pediatric anaplastic large cell lymphoma: A report of the Berlin-Frankfurt-Münster Group Trial NHL-BFM 90. Blood. 2001;97:3699-706.
5. Rosolen A, Pillon M, Garaventa A, Burnelli R, d'Amore ES, Giuliano M, *et al*. Anaplastic large cell lymphoma treated with a leukemia-like therapy: report of the Italian Association of Pediatric Hematology and Oncology (AIEOP) LNH-92 protocol. Cancer. 2005;104:2133-40.
6. Gambacorti-Passerini C, Messa C, Pogliani EM. Crizotinib in anaplastic large-cell lymphoma. N Engl J Med. 2011; 364:775-6.
7. Mossé YP, Lim MS, Voss SD, Wilner K, Ruffner K, Laliberte J, *et al*. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: A Children's Oncology Group phase 1 consortium study. Lancet Oncol. 2013;14: 472-80.
8. Murphy SB, Fairclough DL, Hutchison RE, Berard CW. Non-Hodgkin's lymphomas of childhood: An analysis of the histology, staging, and response to treatment of 338 cases at a single institution. J Clin Oncol. 1989;7:186-93.
9. Lakshmaiah KC, Guruprasad B, Shah A, Kavitha S, Abraham LJ, *et al*. Anaplastic large cell lymphoma: A single institution experience from India. J Cancer Res Ther. 2013;9:649-52.
10. Link MP, Shuster JJ, Donaldson SS, Berard CW, Murphy SB. Treatment of children and young adults with early-stage non-hodgkin's lymphoma. N Engl J Med. 1997;337: 1259-66.
11. Reiter A, Schrappe M, Tiemann M, Ludwig WD, Yakisan E, Zimmermann M, *et al*. Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: A report of the Berlin-Frankfurt-Münster Group Trial NHL-BFM 90. Blood. 1999;94:3294-306.
12. Damm-Welk C, Pillon M, Woessmann W, Mussolin L. Prognostic factors in paediatric anaplastic large cell lymphoma: Role of ALK. Front Biosci Sch Ed. 2015;7: 205-16.
13. Pillon M, Gregucci F, Lombardi A, Santoro N, Piglione M, Sala A, *et al*. Results of AIEOP LNH-97 protocol for the treatment of anaplastic large cell lymphoma of childhood. Pediatr Blood Cancer. 2012;59:828-33.
14. Alexander S, Kraveka JM, Weitzman S, Lowe E, Smith L, Lynch JC, *et al*. Advanced stage anaplastic large cell lymphoma in children and adolescents: results of ANHL0131, a randomized phase III trial of APO versus a modified regimen with vinblastine: A report from the Children's Oncology Group. Pediatr Blood Cancer. 2014; 61:2236-42.
15. Ceppi F, Ortiz R, Antillón F, Vasquez R, Gomez W, Gamboa J, *et al*. Anaplastic large cell lymphoma in Central America: A report from the Central American Association of Pediatric Hematology Oncology (AHOPCA): Treatment of ALCL: A Report From a LMIC. Pediatr Blood Cancer. 2016;63:78-82.
16. Resham S, Khan R, Ashraf S, Rizvi A, Altaf S. Clinical features and treatment outcomes of children with anaplastic large cell lymphoma in Pakistan: A multicenter study. J Pediatr Hematol Oncol. 2019;41:5.
17. Arya LS, Dinand V, Thavaraj V, Bakhshi S, Dawar R, Rath GK, *et al*. Hodgkin's disease in Indian children: outcome with chemotherapy alone. Pediatr Blood Cancer. 2006;46: 26-34.
18. Lowe EJ, Gross TG. Anaplastic large cell lymphoma in children and adolescents. Pediatr Hematol Oncol. 2013;30: 509-19.
19. Le Deley M-C, Reiter A, Williams D, Delsol G, Oschlies I, McCarthy K, *et al*. Prognostic factors in childhood anaplastic large cell lymphoma: Results of a large European intergroup study. Blood. 2008;111:1560-6.