Clinical Features and Treatment Outcomes of Children with Anaplastic Large Cell Lymphoma

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ABSTRACT

Objective: To describe clinical features and treatment options in pediatric patients with ALCL (Anaplastic large cell lymphoma) and their outcome over a span of 10 years.

Study Design: A retrospective-observational study.

Place and duration of study: Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, from January 2005 to December 2015.

Methodology: Medical records of pediatric patients with anaplastic large cell lymphoma was retrospectively collected after IRB approval. Data was reviewed for patients confirmed on histopathology and age less than 20 years at the time of diagnosis to see clinical features and treatment outcomes. Descriptive statistics were applied.

Results: A total of 40 children, 27 males (67.5%) and 13 females (32.5%) with ALCL (CD30 +), were reviewed. B symptoms were present in 32 (80%) patients, nodal involvement in 39 (97.5%), and mediastinum involvement was present in 8 (20%) patients. Visceral (lung, liver, spleen) and cutaneous involvement was seen in 16 (40%) and 6 (15%) patients, respectively. ALK was positive in 19 patients (48%) and Bone marrow was involved in 3 patients (7.5%). Stage III was seen in 29 (72.5%). All patients were treated on ALCL 99 protocol. Five-year EFS (event-free survival) and OS (overall survival) was 30 and 60%, respectively. There were 7 relapses, 2 progressive disease, 16 death and 3 refusal for treatment.

Conclusion: This analysis shows poor outcomes in pediatric ALCL. The most common cause of mortality was hematological toxicity and febrile neutropenia associated with it. Supportive care needs to be improved.

Key Words: *Clinical features, Outcomes, Anaplastic large cell lymphoma (ALCL), Children.*

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INTRODUCTION

Anaplastic large cell lymphoma (ALCL) is a rare disease in children. It is characterised by the proliferation of anaplastic cells of the T or null phenotype. ALCL comprises of nearly 10-15% of childhood lymphomas.[1,2] Pediatric ALCL is usually advanced disease when it presents; and it has a high frequency of extra nodal involvement. CNS involvement is rare in ALCL. Systemic ALCL is common than the cutaneous form, and commonly occurs during the early three decades of life.[2,3] Bone marrow involvement by ALCL is considered to be an uncommon event, its incidence ranges from 4% to 15%; and it is usually thought to be a poor prognostic factor.[4]

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The anaplastic large cell lymphoma kinase (ALK) protein is considered to be the main pathogenesis in the majority of ALCL patients. The most of ALCL in children is ALK positive; but ALK negative cases do occur. ALK positive state is associated with good outcome.[4,5] ALCL is regarded as the cell expression of CD30 and the interleukin-2 receptor.[6] Although there have been recent advances in ALCL characterisation, the optimal treatment of ALCL has not been fully established and the efficacy and safety of treatment are still under investigation.[7] Current treatment regimens using different chemotherapy drugs achieve 70% event-free survival; but relapse rate is still high, approximately 30%.[7,8]

Various second line treatment regimens for advanced and relapsed patients with ALCL have been investigated, ranging from single use of vinblastine to high-dose chemotherapy with hematopoietic stem cell transplantation (HSCT), but there is still no consensus on the optimal treatment strategy.[9] There is limited data from developing countries on ALCL as the number of cases are limited,

The aim of this study was to determine the clinical features and treatment outcomes of children diagnosed with ALCL at a single tertiary centre in Pakistan.

METHODOLOGY

Data of 40 pediatric patients registered at Hospital with anaplastic large cell lymphoma was retrospectively collected using Hospital information system (HIS) from January 2005 to December 2015 after IRB approval. Data was reviewed for patients with anaplastic large cell lymphoma on histopathology, and age less than 18 years. Demographic data, clinical features and treatment outcome were analysed. Patients had physical exam, LDH levels, skeletal scintigraphy, complete blood count, cerebrospinal fluid examination and bone marrow examination to determine the extent of disease. Staging was done by computed tomography (CT) scans, positron emission tomography scan (PET) and magnetic resonance imaging scan (MRI). Chemotherapy was based on the ALCL 99 trial. All patients received a 5 days pre-phase; after that, they received six alternating induction courses (courses AM and BM). The course AM started at Day 6 of pre-phase treatment, then each course at every 21 days interval. Pre-phase consisted of 3-agents for 5 days. Course AM consisted of 5 drugs for 5 days. Course BM consisted of 4-agents for 5 days (Table I).

Table I: Characteristics of patients according to age, gender, stage, B symptoms and ALK status.

Parameters	Range	Percentage
Age at diagnosis	1-5 years 5-10 years 11-15 years Above 15 years	5 (12 %) 11 (28%) 19 (48%) 5 (12%)
Gender	Male Female	27(67.5 %) 13 (32.5%)
B symptoms	Positive Negative	32 (80%) 8 (20 %)
Stage	II III IV	7 (17.5%) 29 (72.5%) 4 (10%)
Nodal involvement	Present Absent	39 (97.5%) 1 (2.5%)
Mediastinal involvement	Present Absent	8 (20%) 32 (80%)
Bone marrow	Positive Negative	3 (7.5%) 37 (92.5%)
CNS Involvement	Positive Negative	None 40
Visceral involvement	Positive Negative	16 (40%) 24 (60%)
ALK	Positive Negative Not done	19 (48%) 12 (30%) 9 (23%)
LDH	>450 <450 Not done	19 (47.5%) 12 (30%) 9 (23%)

Hospital pathology reviewed all cases to confirm the histopathologic diagnosis of anaplastic large cell lymphoma. ALK positive, CD 30, T and B cell lineage markers (CD20, CD3, CD43, and CD45) were also reviewed for all 40 patients.

Overall survival (OS) and EFS (event-free survival) rates were estimated using the Kaplan-Meier method. OS rates were measured using the time from the date of diagnosis to the date of death from any cause or to the date of the last follow-up visit for patients who were still alive. EFS rates were estimated using the time from the date of diagnosis to the date of first relapse or the date of death. Patients who experienced EFS were censored at the last follow-up date. Prognostic variables were tested in a log-rank test. Statistical analysis was carried out using SPSS software (version 20.0; SPSS, Chicago, IL, USA). Statistical significance was defined as a two-tailed p-value of 0.01.

RESULTS

Data of 40 children with ALCL (CD30 +) was reviewed retrospectively. Male showed predominance, as there were 27 males (67.5%) and 13 females (32.5%). Patients in age group 11-15 years were predominant, there were 19 (47.5%) patients in this age group, while only 11 (27.5%) patients in 5-10 years age group were seen. B symptoms were present in 32 (80%) patients. Nodal involvement was present in 39 (97.5%) patients. Mediastinum involvement was present in 8 (20%) patients. Extra-nodal disease was not commonly seen; visceral (lung, liver, spleen) involvement was seen in 16 (40%) patients. Cutaneous involvement was present in 6 (15%) patients. No patient had CNS involvement. ALK was positive in 19 (48%) patients. Bone marrow involvement was seen in 3 (7.5%) patients. LDH >450 in 19 (48%), <450 in 12 (30%), and was not performed in 9 (23%) of patients. CSF was negative in 39 (97.5%) and not done in 1 (2.5%) patient.

Skeletal scintigraphy was positive in 6 (15%), negative in 8 (20%) and not performed in 26 (65%) patients. Staging was done by scans including CT scan PET and MRI in patients. CT was performed in 33 (83%), PET in 5 (12.5%) and MRI in 2 (4.5%) patients. According to St Jude classification, Stage II was present in 7 (17.5%) patients, Stage III in 29 (72.5%), and stage IV in 4 (10%) patients. No Stage I patient was seen. The 5 years EFS was 30% and OS was 60%. There were 7 relapses (17.5%), 2 had progressive disease (5%). Twenty-one patients were alive (52.5%), 16 patients died (40%), and 3 patients (7.5%) refused treatment.

Relapse occurred early in 5 of 7 patients within the first 6 months of therapy; and 2 of 7 relapses occurring within 2 years of end of treatment. Seven deaths occurred within pre-phase or immediately after pre-phase. Nine deaths occurred at various interval ranging from 4 months to 2 years. The National Cancer Institute defined that common toxicity criteria was used to grade toxicity. Information for all 40 patients on toxicity was present in Hospital information system. Majority of deaths were due to infection during treatment. Hematologic grade IV toxicity was most commonly seen, 33 (82%) patients developed grade IV neutropenia, 27 had (68%) grade IV thrombocytopenia, and 16 (40%) patients had grade IV anemia.

The log rank test was used to identify factors affecting survival. Age at diagnosis, stage, gender, presence of B symptoms, lymph node involvement, extra-nodal involvement, serum LDH level, ALK status (Table II).

Table II: Phases and name of therapeutic agents used.

Phases	Medicines
Pre-phase	Cyclophosphamide, dexamethasone, intrathecal chemotherapy
AM	Dexamethasone, methotrexate, ifosfamide, cytarabine, etoposide
BM	Dexamethasone, methotrexate, cyclophosphamide, doxorubicin

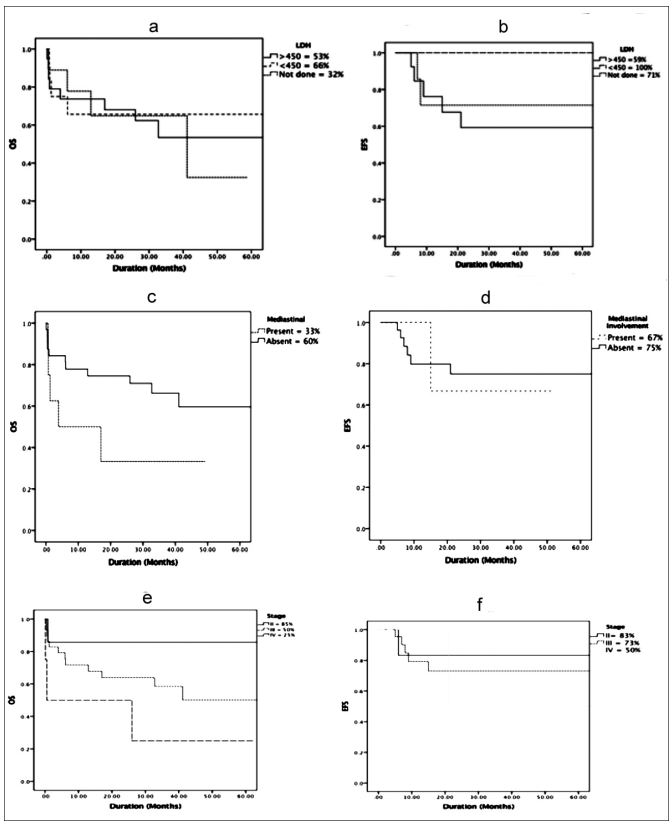

Figure 1: (a) Overall survival of patients according to LDH levels.
(b) EFS of patients according to LDH level.
(c) Overall survival with mediastinal involvement.
(d) Event-free survival with mediastinal involvement.
(e) Overall survival of patients according to stage.
(f) EFS of patients according to stage.

There were statistically significant factors affecting OS and EFS (Figure 1 a-f). Advanced stage (stages III and IV), the presence of B symptoms, visceral involvement, ALK negative status and bone marrow involvement were identified as poor prognostic factors for EFS and OS ($p<0.002$).

DISCUSSION

The definition of ALCL has recently been reviewed, and options for its treatment are under investigation. Retrospective review of 40 patients with ALCL in a single centre contributes to the establishment of the clinical features, prognostic factors and outcomes in children with ALCL in this hospital. Certain factors, like presence of B symptoms, stage, LDH levels, and lung or bone marrow involvement were prognostic factors affecting EFS and OS.

Different treatment regimens ranging from short pulse B cell lineage non-Hodgkin's lymphoma chemotherapy to prolonged lymphoblastic lymphoma and leukemia-like therapy have been the main subject of many trials of several pediatric oncology groups, but the optimal treatment for pediatric ALCL has not been established yet.[10]

In this study, five-year OS and EFS rates for the total of 40 pediatric ALCL patients were 60% and 30%, respectively, and all 40 patients were treated with ALCL99. These results were lower than the previous studies, because most of deaths in this study were due to hematologic toxicity leading to sepsis and death. Han *et al*., reported the five-year OS and EFS rates for the total of 28 pediatric ALCL patients as 88% and 69%, respectively. They treated patients on different chemotherapy regimens, and more than half of these patients were treated on CCG-5941.This chemotherapy regimen was designed for T cell lineage lymphoblastic leukemia. In this study, the presence of B symptoms, advanced stage that is stages III and IV, lung involvement, and bone marrow involvement were seen as poor prognostic factors for EFS ($p=0.02, 0.01, 0.01$, and 0.02, respectively).[10]

Low *et al*. in CCG 5941 reported the 5-year event-free survival as 68%, and the 5-year overall survival as 80%. There were four toxic deaths as first events and 21 patients relapsed. CG-5941 used an aggressive compressed multi-agent T cell lineage chemotherapy regimen, and total duration of therapy was 48 weeks.[11]

In this study, 7 out of 19 patients with ALK positivity died; and there were 12 patients with ALK negativity out of them 7 died, showing that being ALK +ve as a good prognostic factor. Similarly 2 out of 19 patients who were ALK positive relapsed compared to 2 out of 12 with those ALK negative, again showing ALK status as significant factor. Wang FH *et al* reported ALK-negative, high-intermediate/high score, especially extranodal invasion and high LDH level to poor prognosis. They reported overall response rate, CR rate and estimated 5-year OS rate of the patients undergoing first-line chemotherapy as 96.4%, 71.4% and 65.2%, respectively.[12]

Lamant *et al.* in ALCL 99 study showed the prognostic impact of phenotypic and morphologic features of childhood ALK positive Anaplastic Large Cell lymphoma in 375 patients, they demonstrated the adverse prognostic value of ALK negative status and they might have a high suspicion for future risk stratification and treatment.[13] Castellar *et al.* reported outcome of patients with ALK status. ALCL children with ALK negative status had OS rates inferior to those with ALK positive status (5-year OS: 52% *vs* 5-year OS: 85% respectively.[14]

In this study, significant prognostic factors were found for low OS and EFS. Factors, including B symptoms, advanced stage, visceral involvement, mediastinal involvement, LDH, and bone marrow involvement. LDH has prognostic significant, with LDH >450 have OS 53%, and LDH <450 have 66% OS. Those with mediastinal involvement have 33% OS than those with no mediastinal involvement 60% OS. Patients with B symptoms have OS

of 54% compared to 57% having no B symptoms. Similarly, stage also has prognostic significant, 85% OS with Stage-II, 50% OS with stage-III and only 25% those with Stage-IV. Patients with B symptoms have EFS Of 75% compared to 70% without BM involvement. In patients with mediastinal involvement, EFS is 67% as comapred to 75% those without medistainal involvement. Patients with stage –II have EFS of 83% compared to 73% and 50% in stage III and IV, respectively. Similarly, LDH also has prognostic significance for EFS, only 59% EFS in patients having LDH >450 compared to 100 EFS in patients having LDH <450. Stage visceral involvement and B symtoms also have impact on relapse and death, as 5 realpses were in patients having stage III and positive B symptoms, 3 have visceral involvement. Similarly, most of deaths were in patients having BM Involvement, B symptoms, visceral involvement stage III and LDH >450 with numbers of 2, 14,9,12 and 8, respectively.

Brugieres *et al.* studied the efficacy of chemotherapy regimens and identify prognostic factors in these children. The event-free survival at 3 years was of 66%. Factors such as lactic dehydrogenase (LDH) level above 800 UI/L, visceral involvement and mediastinal involvement were seen to be indicator of a higher risk of failure.[15] Le Delay *et al.* showed bad outcome for mediastinal involvement, visceral involvement, and skin lesions.[16]

In this study, 7 of 40 (17.5%) patients relapsed and 2 (5%) have progressive disease. Out of these 9 (relapse and progressive) 6 patients died. Vinblastine based salvage therapies were used for these relapse patients, none of them underwent stem cell transplant. Different treatment choices for patients with relapsed disease have developed because of clinical trials. Vinblastine mono therapy, high dose chemotherapy and autologous stem cell transplantation, allogeneic stem cell transplantation and new directed therapies have been proposed, but their effectiveness and harmlessness are still under exploration. In a previous reviewing analysis, 39 patients with relapsed or refractory ALCL who received HDCT &ASCT had a five-year EFS of 59%. Pro *et al*. studied role of brentuximab in relapsed refractory ALCL.[17] Alexander *et al.* reported EFS in advanced stage ALCL.[18] In another study, Woesmam *et al.* testified EFS with high risk relapsed or refractory ALCL who experienced allogeneic SCT.[19] Brugieres *et al*. studied second line therapy Vinbalstin and along with Stem cell transplant in relapsed patients.[20]

In spite of being restricted by the small number of patients, this study has shown that treatment outcomes of patients in Pakistani children with ALCL are poorer to those of previous western studies, as most of patients died due to sepsis, role of good supportive care can not be neglected for better survival. Further exploration of the role of new, directed treatments is necessary for relapsed pediatric patients. The question of strength and duration of therapy for pediatric patients with non-localised ALCL remains unrequited. National and international cooperation is needed to define the best treatment approach for children with ALCL.

CONCLUSION

This analysis shows poor outcomes in pediatric ALCL. The most common cause of mortality was hematological toxicity and febrile neutropenia associated with it. Supportive care needs to be improved.

ETHICAL APPROVAL:
Review Board approval was taken to obtain data from Hospital information system (HIS) before start of research project.

CONFLICT OF INTEREST:
Authors declared no conflict of interest.

AUTHOR CONTRIBUTION:
AM: Data collection and manuscript writing.
SR: Data analysis.
RW: Manuscript writing.

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