ORIGINAL ARTICLE

CHARACTERISTICS AND OUTCOMES OF ANAPLASTIC LARGE CELL LYMPHOMA PATIENTS-A SINGLE CENTRE EXPERIENCE

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Background: Anaplastic large cell lymphoma (ALCL) is the second most common T cell lymphoma and 2% of all non-hodgkin lymphoma (NHL). It is an aggressive lymphoma with three subtypes, primary cutaneous ALCL, primary systemic ALK +ve ALCL and primary systemic ALK-ve ALCL depending upon rearrangement of Anaplastic Lymphoma Kinase (ALK) gene into ALK +ve and ALK -ve ALCL. Purpose of study is to determine the outcome of patients with ALCL treated at our institute. **Methods:** In this retrospective analysis, 49 patients with ALCL from 2000 to 2012 were included. Their base line IPI score, stage at presentation, bone marrow involvement, type of chemotherapy, ALK status, extra nodal sites and outcome were recorded. **Results:** Median age was 34 years (range 20–72 years), with males' predominance, i.e., 75.5%. At presentation, 7 (14.3%), 12 (24.5%), 14 (28.6%) and 16 (32.7%) were in stage I-IV, respectively. According to IPI risk categorization, there were 27 (55.1%) in low risk, 12 (24.5%) in low intermediate risk, 8 (16.3%) in high intermediate risk and 2 (4%) in high risk. Seventeen patients (34.7%) were ALK +ve while 21 patients (43%) were ALK +ve and 11 patients (22.4%) had unknown status. Kaplan Meir overall survival (OS) at 5 years was 49.9%. Five-year OS in ALK +ve tumour was 67.4% compared to 39.7% in ALK -ve, p=0.05. **Conclusion:** Based on our study results, ALCL is common in males with a trend towards better outcome in Alk+ disease. The majority of patients are in advanced stage of disease at the time of presentation.

Keywords: Anaplastic large cell lymphoma; Pakistan; Survival; Remission; Chemotherapy

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INTRODUCTION

Peripheral T cell lymphoma (PTCL) is an uncommon group of disorders, constituting 15% of all Non-Hodgkin lymphoma.[1] Among PTCL, peripheral T cell lymphoma not otherwise specified (PTCL NOS), anaplastic large cell lymphoma (ALCL) and Angioimmunoblastic T cell lymphoma (AITL) are most common subtypes. ALCL is considered as an aggressive lymphoma, with male predominance and constitute 13.8% of all PTCL.[2]

ALCL is of three subtypes, primary cutaneous ALCL and primary systemic ALK +ve ALCL and primary systemic ALK –ve ALCL. ALK +ve ALCL involves rearrangement of anaplastic lymphoma kinase (ALK) gene located on chromosome 2p23 with nucleophosmin gene (NPM) located on chromosome 5 resulting in NPM/ALK fusion protein.[2–4] Primary cutaneous ALCL is ALK –ve disease. ALK +ve ALCL is common in younger patient (Median=34years) and is associated with better outcome than ALK-ve, which is more prevalent in older patient (Median=58years).[5]

According to largest retrospective study on PTCL, the incidence of ALCL in Asia is low as compared to North America and Europe.[5] The incidence of ALK +ve ALCL in North America, Europe and Asia are 16%, 6.4% and 3.2%, respectively. Whereas the prevalence of ALCL ALK-ve are 7.8%, 9.4% and 2.6% in North America, Europe and Asia respectively.[5] Most patients present with stage III–IV. Bone marrow involvement is present in 12% and 07% of ALK positive and negative patients, respectively.[3] Clinical outcome is better in ALK ve+ compared to ALK-ve ALCL, with a 5 years overall survival of 70% in ALK +ve and 49% in ALK-ve patients.[5] Survival of ALCL ALK-ve tumours are inferior to ALK +ve tumours but they are better as compared to PTCL-NOS (OS=32%), AITL (OS=32%), natural killer/T-cell lymphoma (NKTCL) and adult T-cell leukaemia/ lymphoma (ATLL) subtype of PTCL.[5]

International prognostic index (IPI) is a tool for risk stratification in ALCL.[3] Patients with low risk IPI have a 5-year overall survival of 90% in ALCL ALK+ve and 49% in ALK -ve ALCL.[5]

MATERIAL AND METHODS

In this retrospective study, patients with the diagnosis of ALCL, treated at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan which is a tertiary care cancer hospital from 2000–2012 were included. Data collection was done through computerized data based system. This study was approved by Hospital ethical board. Patient medical record number, age and gender were recorded. Baseline pathology reports were studied for morphology of the biopsy material. Immunohistochemistry stains with CD30, EMA (epithelial membrane antigen), CD 3 and CD 15 were

performed on all samples. ALK status was also recorded. Results of staging CT scan and bone marrow biopsy were noted. Disease was staged using Ann Arbor staging system. Age, LDH, performance status (PS), extra nodal sites, bone marrow involvement and type of chemotherapy were recorded.

After collecting above data, IPI score and IPI risk categorization was done, i.e., low risk 0–1, low intermediate risk 2 and high intermediate risk 3 and high risk with 4 or more factors. Complete response (CR) was defined as disappearance of all evidence of disease as determined by clinical, radiographic and laboratory parameters. Partial response (PR) was defined as a reduction of 50% or more of measurable disease. No response (NR) was any response less than a PR. Progressive disease (PD) was defined as the recurrence of previously evident disease that had responded, measurable increase in known disease or the development of disease at a new site.

Statistical analysis was done using SPSS-19.0. Primary end point of the study was overall survival (OS). Overall survival was calculated from the date of registration to the last date of follow up or death from any cause. Kaplan–Meier survival curves were compared using the log-rank test.[6,7]

RESULTS

There were 49 patients with the diagnosis of ALCL were identified during this specified period. Median age was 34 years (range 20–72years), with males 37 (75.5 %) and 12 (24.5%) females. Stage I–IV at the time of presentation was 7 (14.3%), 12 (24.5%), 14 (28.6%) and 16 (32.7 %), respectively. Bone marrow involvement was found in 4 patients (8.2%). Based on international prognostic index (IPI) risk categorization, patients in low risk (LR), low intermediate risk (LIR), high intermediate risk (HIR) and high risk (HR) groups were, 27 (55.1%), 12 (24.5%),08 (16.3%) and 2 (4%), respectively. Seventeen patients (34.7%) were ALK +ve while 21 patients (43%) were ALK –ve and 11 patients (22.4%) had unknown status. In ALK positive patients, 12 patients (70.5%) were LR, 2 patients (11.7%) were in LIR, 3 patients (17.3%) were in HIR, while no patients in HR group. In ALK negative patients, 7 (41.1%) were in LR, 8 (47.05%) were in LIR, 4 (23.5%) were in HIR while 2 (11.7%) were in HR group, respectively. Commonest extra nodal sites were liver 12 (24%) patients, bone 6 (12%) and lung 5 (10%). Thirty-four (69%) patient was treated with CHOP chemotherapy, 9 (18.4%) patients were treated with CHOP plus XRT, 5 patients treated with HCVAD regimen and one patient was treated with ICE chemotherapy due compromised cardiac status.

Complete response (CR) was observed in 27 (55%) patients, partial response (PR) 7 (14.3%), stable disease (SD) 2 (4%) and progressive disease (PD) 11 (22.4%). In two patients, response could not be assessed due to early death during the treatment. Out of sixteen death, 6 (12.2%) deaths were chemotherapy related febrile neutropenia and 10 (32.7%) were due to disease progression. At the time of study, twenty-seven patients (55.1%) were alive, 22 patients (44.9%) were dead.

Kaplan Meir overall survival (OS) at 5 years was 49.9%. Five-year OS in ALK positive tumour was 67.4% compared to 39.7% in ALK –ve patients, p=0.05 (patients with unknown status of ALK were excluded). OS for patients treated with chemotherapy and chemoradiation was 44.5% and 75% (p=0.08), respectively. In addition, there was no difference in the OS in patients with age below or above 40 years, (67.3% vs 66.7%, p= 0.7).

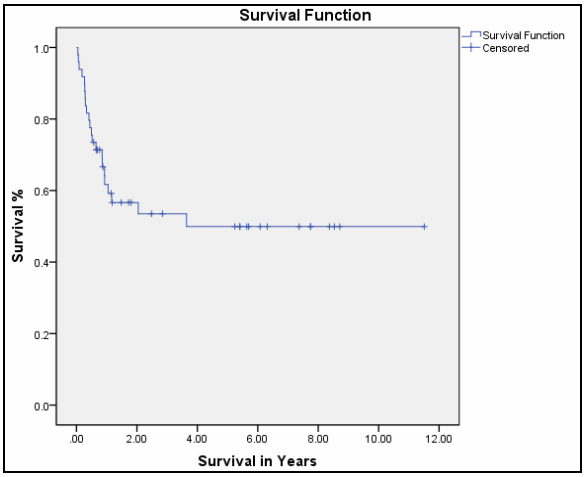

Figure-1: Overall survival at 5 years

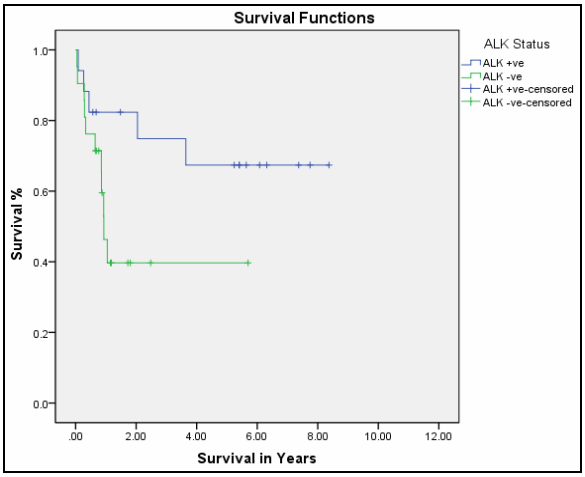

Figure-2: Overall survival at 5 years for ALK +ve and ALK –ve ALCL

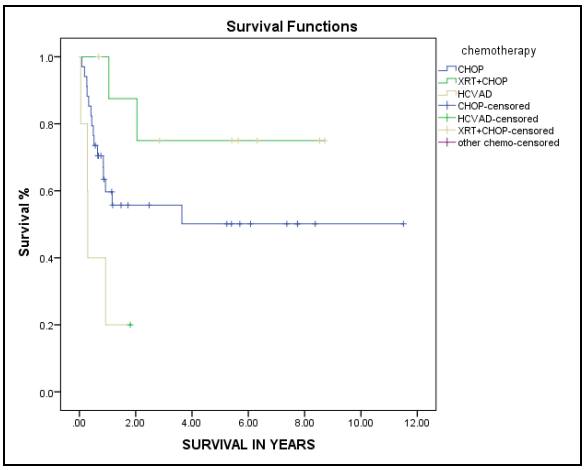

Figure-3 Overall survival at 5 years for patients treated with CHOP, CHOP + XRT and HCVAD chemotherapy.

Table 1: Clinicopathological characteristics of patients with ALCL

Characteristic's	Total number of patients n=70	%age
Median Age	34 years (range 20–72)	
Median age for ALK+ve ALCL	31 years (range 2–271)	
Median age for ALK-ve ALCL	30 years (range 2–070)	
Gender		
M	37	75.5
F	12	24.5
Current status		
Alive	27	55
Dead	22	45
Stage at presentation		
I	07	14.3
II	12	24.5
III	14	28.6
IV	16	32.7
IPI Risk Group		
Low risk	27	55.1
Low Intermediate risk	12	24.5
High intermediate risk	08	16.3
High risk	02	04
ALK Status		
ALK Positive	17	34.7
ALK Negative	21	43
Unknown	11	22.3
Type of chemotherapy		
CHOP	34	69.4
CHOP + XRT	09	18.4
HCVAD	05	10.2
Other	01	02
Response to chemotherapy		
CR	27	55.1
PR	07	14.3
SD	02	4.1
PD	11	22.4
Unknown	02	04.1

DISCUSSION

T-Cell lymphomas are heterogeneous group of disorders with variation in survival among different subtype of T-cell lymphoma. ALCL is considered as an aggressive T-cell lymphoma. Prognosis of ALCL is dependent on ALK status and IPI risk categorization.[8,9] According to IPI risk categorization 5 years OS in ALK +ve ALCL are 90, 68, 23, and 33 percent for patients with an IPI of low risk, low intermediate risk high intermediate risk and high risk group respectively. Five-year survival according to IPI risk categorization in patients with ALK- ALCL were 74, 62, 31, and 13 percent, respectively.[4] Five years OS in ALK+ve ALCL has been reported in range of 70-93% and 37–49% in case of ALK-ve ALCL.[5,8] As compared to the other subtype of T cell lymphoma, ALCL has better overall survival moreover patients with ALK-ve ALCL has better overall survival then the rest of T-cell lymphoma.[5]

Since the T-cell lymphoma is considered as aggressive tumours, several regimens containing anthracyclines and alkylating agents are commonly used for the treatment of these disorders. Intensive chemotherapy regimens have been used to improve response rate and survival however, did not prove to be better than CHOP in terms of OS and EFS benefit.[10,11] Addition of etoposide to CHOP has shown better EFS when compared to CHOP alone, particularly in younger age group and normal LDH.[9] Hence, CHOP chemotherapy has emerged as first line chemotherapy in patients with ALCL. CHOP with etoposide can be considered for younger patients with ALK negative disease.

Role of consolidative therapy like radiation remains to be defined. In DLBCL, the number of cycles of chemotherapy is reduced if consolidative radiation is used but in T-cell lymphoma the number of cycle remains 6–8 with addition of radiation therapy in selected cases. Role of stem cell transplant (SCT) is emerging in some subtypes of peripheral T-cell lymphoma. Some small prospective studies used stem cell transplant upfront after first CR and these studies have shown some OS benefit with 5 years OS ranging from 48 to 61.5% but these studies had mixed population of different subtype of peripheral T-cell lymphoma specially ALK+ve ALCL which already has good prognosis with chemotherapy.[12,13]

In our study, median age of presentation was 34 years among all patients. Median age of presentation among ALK +ve ALCL patient were 31 years while it was 30 years among patients with ALK-ve ALCL which is quite younger age of presentation as compared to western data.[5] Majority of the patients (60%) presented with advance stage, i.e., stage III and IV similar to western data. Only four patients presented with bone marrow involvement with three patients (14.3%) among ALK-ve ALCL, one in unknown ALK ALCL status while none in ALK +ve ALCL patients however according to international data 12% patients in ALK

+ve ALCL and 7% in ALK-ve patients presents with bone marrow involvement.[3]

In our cohort, seventy percent of patients in ALK+ve ALCL group were in low risk, while only 33.3% were in low risk among ALK-ve ALCL. In international data review shows 51.7% of ALK+ve ALCL patients while 64% in ALK-ve ALCL patients in low risk group.[14]

In extra nodal involvement, our observation showed that liver, lung and bone was common organ involved by the disease. More over 35% ALK+ve ALCL had extra nodal involvement while 62% in case of ALK-ve ALCL which is different as compared to western data that shows 48% and 35% in ALK+ and ALK-ve ALCL respectively.[14]

Complete Response rate (CRR) in our cohort was 70.5% and 47.6% in ALK+ve and ALK-ve ALCL using CHOP like chemotherapy. While in international data CRR were 70.5% and 58.8% in ALK+ve and ALK-ve ALCL.[14] Second most, common chemotherapy used was HCVAD. No patient was treated with etoposide combination chemotherapy however, consolidative XRT was used for residual disease or bulky disease at the time of presentation which resulted in some survival benefit but the number of patients was small in this group. In our observation, CHOP like chemotherapy is a reasonable choice in ALK+ve patients with good response rate while HCVAD chemotherapy has shown to be very toxic in our part of world as most of our patient did not tolerate HCVAD chemotherapy well. Also, role of HCVAD chemotherapy in treatment of ALCL is not well defined in term of survival benefit.[10] More over adding etoposide to CHOP chemotherapy is reasonable choice for ALK-ve patients. Moreover, five years' survival among patients with ALK +ve ALCL was 67.4% while in ALK-ve ALCL was 39.7 respectively which is close to international data.

For recurrent/relapse/refractory ALCL case emerging phase II data of Brentuximab vedotin is promising with CR rate of 57% with grade 3 and 4 haematological toxicity of 21% neutropenia and 14% of thrombocytopenia.[15]

Crizotinib which is an ALK inhibitor have been used in small study with heavily pre-treated ALK+ve ALCL patients with ORR of 90.9% with OS and PFS at 2 years of 72.7% and 63.7% respectively.[16]

CONCLUSION

Based on our study results, ALCL is common in males with a trend towards better outcome in Alk+ disease. The majority of patients are in advanced stage of disease at the time of presentation. CHOP is the commonest chemotherapy regimen used to treat these patients. More studies are needed to clarify role of etoposide and consolidative radiotherapy in the treatment of ALCL. Brentuximab along with combination chemotherapy warrants future trail.

AUTHORS' CONTRIBUTION

SA: Idea, retrieval of data, analysis and writing-up the manuscript. NS: Helped in analysis and write up of the manuscript. AH: Supervised the study and write up of the manuscript.

REFERENCES

1 Morton LM, Wang SS, Devesa SS, Hartge P, Weisenburger DD, Linet MS. Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001. Blood 2006;107(1):265–76.

2 Eyre T A, Khan D, Hall GW, Collins GP. Anaplastic lymphoma kinase-positive anaplastic large cell lymphoma: current and future perspectives in adult and paediatric disease. Eur J Haematol 2014;93(6):455–68.

3 Savage KJ, Harris NL, Vose JM, Ullrich F, Jaffe ES, Connors JM, *et al*. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood 2008;111(12):5496–504.

4 Jaffe ES. The 2008 WHO classification of lymphomas: implications for clinical practice and translational research. Hematology Am Soc Hematol Educ Program 2009:523–31.

5 Vose J, Armitage J, Weisenburger D. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. J Clin Oncol 2008;26(25):4124–30.

6 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc1958;53(282):457–81.

7 Peto R, Pike MC. Conservatism of the approximation Sigma (O-E) 2/E in the logrank test for survival data or tumor incidence data. Biometrics1973;29(3):579–84.

8 Gascoyne RD, Aoun P, Wu D, Chhanabhai M, Skinnider BF, Greiner TC, *et al*. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood 1999;93(11):3913–21.

9 Schmitz N, Trümper L, Ziepert M, Nickelsen M, Ho AD, Metzner B, *et al*. Treatment and prognosis of mature T-cell and NK-cell lymphoma: an analysis of patients with T-cell lymphoma treated in studies of the German High-Grade Non-Hodgkin Lymphoma Study Group. Blood 2010;116(18):3418–25.

10 Escalón MP, Liu NS, Yang Y, Hess M, Walker PL, Smith TL, *et al*. Prognostic factors and treatment of patients with T-cell non-Hodgkin lymphoma: the M. D. Anderson Cancer Center experience. Cancer 2005;103(10):2091–8.

11 Simon A, Peoch M, Casassus P, Deconinck E, Colombat P, Desablens B, *et al*. Upfront VIP-reinforced-ABVD (VIP-rABVD) is not superior to CHOP/21 in newly diagnosed peripheral T cell lymphoma. Results of the randomized phase III trial GOELAMS-LTP95. Br J Haematol 2010;151(2):159–66.

12 Chen AI, McMillan A, Negrin RS, Horning SJ, LaportGG. Long-term results of autologous hematopoietic cell transplantation for peripheral T cell lymphoma: the Stanford experience. Biol Blood Marrow Transplant 2008;14(7):741–7.

13 Czyz A, Romejko-Jarosinska J, Helbig G, Knopinska-Posluszny W, Poplawska L, Piatkowska-Jakubas B, *et al*. Autologous stem cell transplantation as consolidation therapy for patients with peripheral T cell lymphoma in first

remission: long-term outcome and risk factors analysis. Ann Hematol 2013;92(7):925–33.
14 Wang FH, Li YH, Zeng J, Rao HL, Xia ZJ, Sun XF, *et al*. Clinical analysis of primary systemic anaplastic large cell lymphoma: a report of 57 cases. Ai Zheng 2009;28(1):49–53.
15 Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, *et al*. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. J Clin Oncol 2012;30(18):2190–6.
16 Gambacorti Passerini C, Farina F, Stasia A, Redaelli S, Ceccon M, Mologni L, Messa C, *et al*. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. J Natl Cancer Inst 2014;106(2):djt378.

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