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Treatment Outcome of Burkitt's Lymphoma in Adolescents and Adults: A Retrospective Study

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Abstract

Introduction Burkitt's lymphoma (BL) is a highly aggressive B cell non-Hodgkin lymphoma (NHL) having three distinct subtypes: endemic, sporadic, and immunodeficiency-associated BL. Sporadic BL accounts for only 1 to 2% of adult NHL.

Objectives The objective of this article was to study the clinical profile and treatment outcome of patients with BL.

Materials and Methods This was a retrospective study of 60 patients with BL conducted in the department of medical oncology at a tertiary cancer center in India during a 10-year period. Patients with BL/leukemia above 14 years of age diagnosed during the study period were included and their clinical presentation, treatment details, and outcome were studied.

Results Among 60 cases with BL, there were 41 males and 19 females. The median age at presentation was 42 years (range: 14–81 years). The main symptoms were lymphadenopathy, abdominal pain, and abdominal distension. Two patients each had paraparesis, breast lump, and jaw swelling and one patient had involvement of the cervix. Thirteen patients had features of tumor lysis at presentation. The Ann Arbor stage was I in 17, II in 16, III in 5, and IV in 22. Fifty-five patients received combination chemotherapy that included hyper-cyclophosphamide, vincristine, adriamycin, dexamethasone ± rituximab (hyper-CVAD ± R; 35), cyclophosphamide, adriamycin, vincristine, prednisolone/ cyclophosphamide, vincristine, prednisolone ± rituximab CHOP ± R (13), Berlin-Frankfurt-Munich protocol (4), and others (3). Thirty-four patients attained remission, 13 patients had progressive disease, and 8 patients died during chemotherapy. At a median follow-up of 113 months, 58% patients were alive.

Conclusions BL accounts for 1.57% of NHL above the age of 14 years with male preponderance. Intensive, short-duration chemotherapy is the standard treatment. Treatment with hyper-CVAD ± R gives 8-year progression-free survival and overall survival (OS) of 60%. Treatment with CHOP ± R is an alternative option in elderly frail patients with an 8-year OS of 46%.

Keywords
- Burkitt's lymphoma
- non-Hodgkin lymphoma
- clinical characteristics
- treatment outcome

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Introduction

Burkitt's lymphoma (BL) is an aggressive B-cell lymphoma characterized by a high degree of proliferation of the malignant cells and deregulation of the proto-oncogene c-myc.[1] BL is predominantly a disease of childhood, but it is also seen in the adult population. The World Health Organization (WHO) classification of BL describes three clinical variants: endemic, sporadic, and immunodeficiency-related.[2] These types are similar in morphology, immunophenotype, and genetic features. Endemic BL is the most common childhood cancer in equatorial Africa associated with Epstein–Barr virus (EBV) and plasmodium falciparum malaria. The sporadic type predominates in the rest of the world with no special climatic or geographical links, and is rarely associated with EBV infection. Sporadic BL (sBL), accounts for 1 to 2% of all adult lymphomas in Western Europe and the United States.[3] The diagnostic and therapeutic principles of BL in adults are the same as those in the pediatric population. A recent study of the Swedish Lymphoma Registry confirmed advanced age, poor WHO performance status, and elevated serum lactate dehydrogenase (LDH) as significant prognostic factors for adult BL.[4]

The present retrospective analysis provides information on clinical presentation, histology patterns, and outcome of adolescents, adults, and elderly patients with BL treated at a tertiary cancer center in India.

Objectives

The objectives of this article were to study the clinical characteristics, treatment response, and survival of BL in adolescent and adult patients. The primary outcome measures were treatment response and progression-free survival (PFS). The secondary outcome measure was overall survival (OS) at 8 years.

Materials and Methods

Study Setting: This was a retrospective study conducted in the department of medical oncology at a tertiary cancer center in India during a 10-year period (January 2005 to December 2014). Patients with BL/leukemia above 14 years of age treated during the study period were included. We analyzed 60 patients with BL.

Inclusion/ Exclusion Criteria: Eligibility criteria included all patients aged above 14 years with a histological diagnosis of BL/leukemia. Patients with relapsed BL and who received some prior treatments were excluded from the study.

Methodology: Medical records of patients were studied with respect to the demographic details, clinical history, physical examination, baseline investigations like complete hemogram, serum chemistry, and serum LDH. Staging work-up including histopathology report, bone marrow study, cerebrospinal fluid analysis, and imaging studies were noted. The disease was staged according to the Ann Arbor staging system. The treatment response at the end of induction and on completion of treatment was obtained. Clinical response was classified as complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease based on modified Cheson lymphoma response evaluation criteria.[5] OS was assessed from the initiation of definitive chemotherapy to the last follow-up or death and PFS was calculated from the initiation of chemotherapy till disease progression.

Statistical Analysis: The baseline patient characteristics, treatment details, and response assessment were analyzed using descriptive statistics. OS and PFS were obtained by Kaplan–Meier method, using SPSS v. 11. The risk analysis for OS and PFS was done using Cox regression analysis. Statistical significance was defined as a p-value less than 0.05.

Ethics: The study was approved by the Institutional Review Board (IRB No. 09/2016/03, dated September 1, 2016). Informed consent was waived off due to retrospective nature of the study. All procedures performed in study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Baseline Patient Characteristics (shown in ►Table 1)

During the period 2005 to 2014, 3,811 cases of non-Hodgkin lymphoma (NHL) above 14 years of age were treated in our

Table 1 Baseline patient characteristics

Baseline patient characteristics ($n = 60$)	Frequency, n (%)
Median age (years)	42 (range: 14–81)
M: F ratio	2.16: 1
B symptoms	39 (65)
Hb $<$ 10 g/ dL	15 (25)
Platelet count $<$ 1,00,000/mm^3	06 (10)
Elevated LDH	44 (73)
Biochemical TLS (S.UA$\geq$8mg/dL, S. K$\geq$6mEq/L, S. Ph$\geq$4.6mg/dL, S. Ca $\leq$ 7mg/dL)	13 (22)
Hypoalbuminemia (S. albumin $<$ 3.5 g/dL)	13 (22)
Renal impairment (S. Cr $>$ 1.5 of ULN)	06 (10)
Hepatic impairment (S. Bil $>$ 2 times of ULN)	7 (12)
Stage I II III IV	17 (28) 16 (27) 05 (8) 22(37)
Burkitt's leukemia (bone marrow blast $>$ 20%)	11(18)

Abbreviations: Hb, hemoglobin; LDH, lactate dehydrogenase; M: F, male: female ratio; S. Bil, serum bilirubin; S. Ca, serum calcium; S. Cr, serum creatinine; S. K, serum potassium; S. Ph, serum phosphorus; S. UA, serum uric acid; TLS, tumor lysis syndrome; ULN, upper limit of normal.

Table 2 Treatment summary

Treatment outcome	HCVAD ± R	CHOP/CVP ± R	BFM	R CODOX M-IVAC	Murphy's protocol
Total no.	35	13	4	1	2
Complete remission	22 (63%)	6 (47%)	3 (75%)	1 (100%)	2 (100%)
Progressive disease	9 (26%)	3 (23%)	1 (25%)	Nil	Nil
Death	4 (11%)	4 (30%)	Nil	Nil	Nil
Relapse	2 (6%)	NIL	1 (25%)	Nil	1 (50%)
8-year OS	60%	46.2%	50%	100%	50%

Abbreviations: BFM; standard Berlin-Frankfurt-Munich protocol; CHOP/ CVP ± R; cyclophosphamide, adriamycin, vincristine, prednisolone/ cyclophosphamide, vincristine, prednisolone ± rituximab; HCVAD ± R; cyclophosphamide, vincristine, adriamycin, dexamethasone ± rituximab; OS, overall survival; R CODOX M- IVAC, rituximab ± cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide and cytarabine.

department, of which 60 were BL (1.57%). The median age at presentation was 42 years (range: 14–81 years). There were 41 males and 19 females, with the male to female ratio of 2.16: 1. Twenty-five patients (42%) were less than 40 years of age and elderly patients above more than 65 years constituted 10% of our study population. The most common presenting symptoms were lymphadenopathy, abdominal pain and abdominal distension. Two patients each presented with paraparesis, breast lump, jaw swelling and one patient presented with vaginal mass. (►**Supplementary Material Table A**, available in the online version). Three patients presented to us following surgery for acute intestinal obstruction and diagnosis of BL was confirmed on histopathological examination of the surgically resected specimen. B symptoms were present in 39 patients (65%). The median duration of symptoms was 4 weeks (range: 1–16 weeks). Eleven patients had BL at presentation (18%) and 13 patients had features of tumor lysis syndrome (22%). Laboratory tumor lysis syndrome was present in all 13 patients and clinical tumor lysis syndrome in 6 patients (10%). Patient had a mean hemoglobin of 11.6 g/dL, mean total leucocyte count of 8,586/mm^3, and a mean platelet count of 2.8 lakhs/mm^3. In our study population, only one patient tested positive for human immunodeficiency virus (HIV) infection. Cerebrospinal fluid was positive for malignant cells in two patients (3%). Twenty-nine patients had extra nodal disease with bone marrow being the most common site (48%). The Ann Arbor stage was I in 17 (28%), II in 16 (27%), III in 5 (8%), and IV in 22 (37%).

All patients had a histopathological diagnosis either from lymph node biopsy or biopsy from the involved organ. Morphologically the tumor cells were seen in sheets having scanty cytoplasm with clumped chromatin, surrounded by normal phagocytic cells having "starry sky pattern." Immunohistochemically (IHC) the tumor cells were positive for CD 10, CD 19, CD20, BCL6 and Surface immunoglobulin M and negative for terminal deoxynucleotidyl transferase. Complete IHC marker panel was done in 40 patients. Out of 11 patients with BL, four patients were diagnosed as acute lymphoblastic leukemia L3 on flow cytometry (►**Supplementary Material Table B**, available in the online version). Thirty-nine patients had a MIB labeling index of 100% and the lowest MIB labeling index was 80%.

Treatment Characteristics (►Table 2)

Among the 60 patients, 55 (92%) received treatment and five refused to get treated. All received combination chemotherapy that included hyper-CVAD ± rituximab (HCVAD ± R) in 35 (63%), CHOP/ CVP ± rituximab (CHOP/CVP ± R) in 13 (24%), Berlin-Frankfurt-Munich protocol (BFM) in 4 (7%), Murphy's protocol in 2(4%), and rituximab ± cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide and cytarabine (R CODOX M-IVAC) in 1 (2%) patient depending on the time period when the diagnosis was made. Patients with poor performance status (ECOG - Eastern Co-operative Oncology Group performance status 3 or 4) and advanced age (age > 65 years) received CHOP/ CVP ± R (median age 69) and young and fit patients received intensive chemotherapy (median age 32). Thirty-four patients attained CR, 33 after chemotherapy, and 1 patient following radiation (RT) after chemotherapy. Thirteen patients had progressive disease and eight patients died during chemotherapy. Among the 34 (62%) patients who attained CR, 22 received HCVAD ± R, 6 had CHOP/ CVP ± R, 3 had BFM, 1 had R CODOX M-IVAC, and 2 patients received Murphy's protocol.

Thirty-five patients received HCVAD ± R among them, 22 (63%) attained complete remission, 9 (26%) had progressive disease, 2 (6%) relapsed, and 4 (11%) patients died during the treatment. The median cycles of HCVAD regimen were 8 (4 cycles of A and 4 cycles of B). Twenty-two out of thirty-five patients (63%) were able to complete all planned cycles of chemotherapy with a median duration of 7 months (range: 6–10 months). Out of thirteen patients who received CHOP/ CVP ± R chemotherapy, only six (46%) patients attained complete remission, three (23%) had disease progression, and four patients (31%) died during chemotherapy. All patients on R CODOX-M/IVAC, Murphy's protocol and three of four patients on BFM protocol attained complete remission.

Among the 34 patients who achieved remission, four patients (12%) relapsed and received palliative chemotherapy later. Two patients with central nervous system (CNS) disease at diagnosis, two with extra nodal primary and one patient with residual disease after chemotherapy received RT after completion of the chemotherapy.

Table 3 Survival data

Variables	8-year PFS (%)			8-year OS (%)		
	%	SE	*p*-Value	%	SE %	*p*-Value
Age (years) < 40 40–65 > 65	80.0 41.2 16.7	8.0 10.1 15.2	0.001	80.0 45.8 16.7	8.0 10.2 15.2	0.001
Sex Male Female	52.5 66.0	7.9 12.4	0.301	55.0 66.7	7.9 12.2	0.299
LDH < 2000 ≥ 2000	58.3 69.2	8.2 12.8	0.573	61.1 69.2	8.1 12.8	0.558
Burkitt's lymphoma Burkitt's leukemia	56.8 54.5	7.5 15.0	0.885	59.1 54.5	7.4 15.0	0.87
Stage 1 2 3 4	56.3 42.9 100 58.7	12.4 13.2 - 10.6	0.425	62.5 42.9 100 59.1	12.1 13.2 - 10.5	0.430
Chemo CHOP ± R HCVAD ± R	36.9 60.0	13.8 8.3	0.123	46.2 60.0	13.8 8.3	0.125

Abbreviations: CHOP/ CVP ± R; cyclophosphamide, adriamycin, vincristine, prednisolone/ cyclophosphamide, vincristine, prednisolone ± rituximab; HCVAD ± R; cyclophosphamide, vincristine, adriamycin, dexamethasone ± rituximab; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; SE, standard error.

Survival (►Table 3)

The PFS was 58.3 at 2 years and 56.2 at 5 and 8 years. The 2-year OS was 61.6% and 58.2% at 5 and 8 years (►**Fig. 1**). The 8-year OS for patients with age group less than 40 years, 40 to 65 years, and more than 65 years were 80, 41.2, and 16.7%, respectively. Both OS and PFS were significantly high in adolescents and young adults compared to patients above 40 years of age (*p*-value of 0.001). There was no significant survival difference with respect to sex, stage of disease, serum LDH, and site of involvement. Patients who received HCVAD-based chemotherapy had better survival compared with CHOP/CVP chemotherapy even though it was not statistically significant (8 years OS of 60.0% ± 8.3% vs. 36.9% ± 13.8% with a *p*-value of 0.123). Rituximab arm had a trend toward better survival compared with no rituximab arm, but it was not statistically significant (66.7 vs. 55.8%) with a *p*-value of 0.584. Univariate Cox regression analysis showed significance only for age with a *p*-value of 0. 001 with a hazard ratio of 10.3. (►**Supplementary Material Table C**, available in the online version) Twenty-four patients out of 55 did not receive rituximab.

Discussion

BL is one of the most aggressive types of cancer and yet one of the most curable. Mostly, BL originates from B cells in the

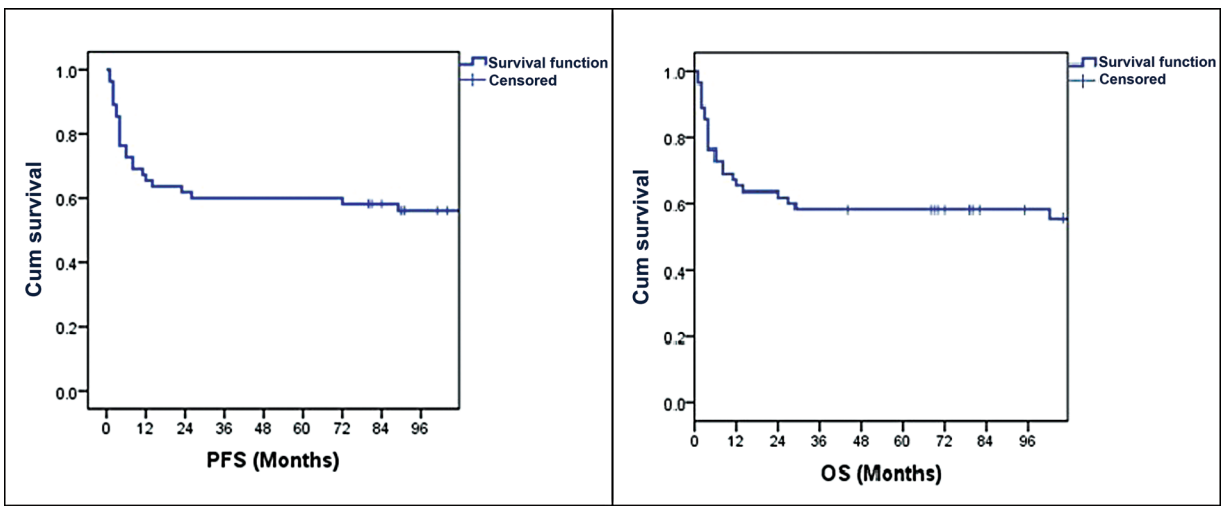

Fig. 1 Survival Chart Showing Progression Free Survival (PFS) and Overall Survival (OS) at 8 years.

follicular germinal center. BL is the first lymphoma reported to be associated with HIV infection.[6] sBL in North America and Europe makes up 30 to 40% of childhood NHL and 1 to 5% of adult NHL.[7] sBL attacks regions outside Africa, with an incidence of about 4 per million in the United States.[8] In India, BL constitutes 1.8 to 3.4% of all adult NHL.[9] BL is a classic example of a human malignancy whose pathogenesis involves a specific cellular genetic change characterized by a chromosomal translocation deregulating expression of the c-myc oncogene, complemented in many cases by the action the EBV.[10]

This is the largest case series from India describing the treatment outcome of adolescent and adult patients with BL. In our series, the median age at presentation was 42 years (range: 14–81 years) with 11% patients above 65 years of age. These findings are consistent with other case series.[3,11,12] In an Indian study including pediatric patients, BL constituted 3.5% of all NHL and the median age at presentation was 22 years.[13] In this study, patients have a higher frequency of B-symptoms (65%) and advanced disease compared to European studies.[14] In our study, bone marrow involvement was the most common extranodal site (30%) followed by gastrointestinal tract (22%). CNS involvement in our study was 3% compared to 15% in a study by Saleh et al.[14] Eleven patients (18%) had BL at presentation that was comparable with another study by Mbulaiteye et al.[7]

Treatment success of BL resulted from the introduction of dose-intense multidrug chemotherapy, prophylaxis of CNS disease, and improvements in supportive care. The management of this aggressive lymphoma is a challenge in our resource-limited setting and the published data from the Indian population is scarce. The frequently used regimens in adolescent and adults based on pediatric protocols are CODOX-M/IVAC, the German BFM, and the French Lymphome Malins B regimens. Other regimens used for adult BL include the HCVAD, the Cancer and Leukemia Group B regimen, and the dose-adjusted EPOCH.[15–17] In our study, most of the young and fit patients received HCVAD $\pm$ R (63.5%) and elderly patients with poor performance status received CHOP/CVP $\pm$ R (22%). The complete response rate in the entire population was 62%, 2-year PFS of 58.3%, and a 2-year OS of 61.6%. A study from India showed similar results with a complete response rate of 63% with 2-year PFS of 56%.[18] Patients above 65 years of age and frail patient who received less intense therapy, the 8-year OS was 46% that makes it an alternate option in elderly and frail patients. Similar studies in BL in adult patients receiving CHOP-based chemotherapy had a 2-year OS of 33 to 39%.[19,20] Patients who received HCVAD $\pm$ R chemotherapy had a complete response rate of 63%, 8-year PFS and OS of 60%. Review on treatment outcome in BL is given in ►**Table 4**.[12,17,21–25] In this study, only a few patients received other chemotherapy regimens like CODOX-M/IVAC, BFM, and Murphy's protocol to compare on survival. ►**Table 4** shows review of treatment outcome in BL.

Limitations

The study period was January 2005 to December 2014, during this period molecular study for BL was not available at our center. This is a retrospective data analysis. Patients were not treated with uniform protocol as they received different protocols depending on the time period the diagnosis was made.

Future Research Directions

Risk-adapted treatment that limits early and late drug toxicity ensuring optimal outcome should be adopted for BL. In elderly patients, R DA EPOCH is the preferred choice with better outcomes. Randomized control trials in Indian population are required to better define the treatment for elderly patients with BL.

Conclusions

BL accounts for 1.57% of NHL above the age of 14 years with male preponderance. Intensive, short-duration chemotherapy is the standard treatment. Treatment with HCVAD $\pm$ R gives 8-year PFS of 60% at 8 years. Treatment with R CHOP is an alternative option in elderly frail populations with an 8-year OS of 46%.

Table 4 Review of treatment outcome in Burkitt's lymphoma

Reference	Regimen	*n*	Median age (years)	EFS/PFS	OS
Thomas et al[21]	Hyper-CVAD	26	58	3-year CCR 61%	3-year OS 49%
Thomas et al[17]	R-hyper CVAD	31	46	3-year EFS 80%	3-year OS 89%
Mead et al[12]	CODOX-M/IVAC	53	37	2-year EFS 64%	2-year OS 67%
Magrath et al[22]	CODOX-M/IVAC	41	25	2-year PFS 92%	NA
Lacasce et al[23]	CODOX-M/IVAC	14	47	2-year PFS 92%	NA
Patekar et al[24]	CODOX-M/IVAC	18	38	1-year PFS 76%	1-year OS 81.1%
Rizzieri et al[25]	CALGB regimen	105	44	2-year EFS 74%	3-year OS 58%
Present study	Hyper-CVAD $\pm$ R	35	43	8-year PFS 56.3%	8-year OS 60%

Abbreviations: CALGB, Cancer and Leukemia Group B; CCR, continuous complete remission; CODOX-M/IVAC, cyclophosphamide, doxorubicin, vincristine, methotrexate, etoposide, ifosfamide and cytarabine; EFS, event-free survival; hyper-CVAD, hyper-cyclophosphamide, adriamycin, vincristine, prednisolone/ cyclophosphamide; OS, overall survival; PFS, progression-free survival.

Authors' Contributions
S.M.T. was involved in design, literature search, data acquisition, data analysis, statistical analysis, and manuscript preparation. G.N. contributed to conceptualization, designing, data acquisition, data analysis, manuscript preparation, manuscript editing, and manuscript review. A.T.M. helped in data acquisition and manuscript editing. S.G.N., P.N.P., and R.A.N. contributed to data acquisition. Jagathnath Krishna did statistical analysis.

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Conflict of Interest
None declared.

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