

Adult Burkitt lymphoma: An institutional experience with a uniform chemotherapy protocol

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Abstract

Background: Burkitt lymphoma (BL) is treated with short, intensive, noncross resistant multidrug chemotherapy regimens. The management of this aggressive lymphoma is a challenge in our resource-limited setting, and the published data from India is scarce. **Aim:** This retrospective study aims to evaluate the clinical features and treatment outcomes in adult patients with BL treated with uniform chemotherapy, cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine (CODOX-M/IVAC) protocol (\pm Rituximab). **Materials and Methods:** The hospital records between 2011 and 2017 were reviewed to identify adult patients (age ≥ 18 years) who were treated with CODOX-M/IVAC protocol (\pm Rituximab). The demographic and clinical details, treatment, outcomes, and toxicity were recorded from the patient's prospectively maintained case records. **Results:** Eighteen patients were included in this study. The median age was 38 years with male:female ratio 3.5:1. The majority of patients were high risk (14/18). All patients had extranodal site of involvement. The treatment completion rate was 83.3%. The overall response rate = 77.8% including complete response rate = 66.7%. Five patients (27%) had progressive disease on therapy. The estimated 2-year overall survival and event-free survival were 73% and 68.4%, respectively. The most common toxicity was myelosuppression (grade 3/4 neutropenia = 88.8%, grade 3/4 thrombocytopenia = 77.7%, and grade 3/4 anemia = 66.6%), febrile neutropenia was seen in 66.6% cases. Most common nonhematological toxicity was mucositis (grade 3/4 = 33.3%). No toxic death was seen. **Conclusion:** This one of the first retrospective analyses of treatment outcomes from India suggests that our patients are demographically and clinically similar to the western counterpart. The treatment completion rate is high despite significant toxicity. BL has a good outcome if treated adequately.

Key words: Burkitt lymphoma, cyclophosphamide, cytarabine/uniform protocol/treatment, doxorubicin, etoposide, ifosfamide, methotrexate, outcome, vincristine

Introduction

Burkitt lymphoma (BL) is a highly aggressive B-cell NonHodgkin lymphoma (NHL). It was the first tumor which was discovered to be associated with a viral infection (Epstein-Barr virus) and a chromosomal translocation which activates an oncogene (c-MYC). The BL and Burkitt leukemia is considered to be the part of the same disease spectrum.^[1] WHO describes three distinct clinical forms of BL: endemic (African), sporadic (nonendemic), and immunodeficiency-associated.^[1] BL is predominantly a disease of childhood, but it is also seen in the adult population. The diagnostic and therapeutic principles of BL in the adult are an extension of those used in the pediatric population.

The challenges of diagnosis and treatment of an aggressive lymphoma, like BL, is unique in low-income and resource-limited settings. The paucity of an adequate molecular diagnostic facility, trained hematopathologist, and limited access to health facility is an impediment in the adequate care of these patients. The data of the outcome of these patients from the low-income countries are sparse. Therefore, we, hereby present our experience of treating patients with BL with a uniform chemotherapy protocol from a tertiary care center in North India.

Materials and Methods

Patient information

We have retrospectively reviewed the case records of patients with BL registered in our clinics. The database included search from the digital records and case files of patients with a diagnosis of BL. We identified 22 cases of adult BL (age ≥ 18 years) during 2011–2017. Eighteen patients received cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide,

cytarabine (CODOX-M/IVAC) regimen with or without rituximab (cyclophosphamide, adriamycin, vincristine, high-dose methotrexate/Ifosfamide, cytarabine along with intrathecal therapy), four patients received other chemotherapy protocols and were excluded. We have included patients who received CODOX-M/IVAC (with or without Rituximab) for analysis in this study [Table 1].

Diagnostic and staging procedures

The demographic details, clinical history, physical examination, and assessment of site of involvement and staging at presentation were recorded. The complete blood cell count, lactate dehydrogenase, electrolytes, liver, and kidney function were noted at presentation. The staging workup included computed tomography scan or positron emission tomography of the whole body, bone marrow aspirate, and biopsy and cerebrospinal fluid (CSF) analysis. Clinical stage was evaluated in accordance with conventional Ann Arbor criteria. The extranodal disease was defined as a contiguous involvement of a nonlymphoid organ. Primary extranodal lymphoma was diagnosed when the initial or major site of disease was in an extranodal organ, and there was none or only regional lymph node involvement. Extensive involvement of any nonlymphoid organ system was taken as Stage IV disease, any lymph nodal mass >7.5 cm in longest diameter or a mediastinal mass occupying more than one-third of the thoracic diameter was taken as bulky disease. Toxicity of chemotherapy was assessed as per common toxicity criteria version 4.0.

Clinical response evaluation

Clinical response was classified as complete remission (CR), partial remission (PR), stable disease (SD), and progressive

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How to cite this article: Patekar M, Gogia A, Tiwari A, Kumar L, Sharma A, Mallick SR, *et al.* Adult Burkitt lymphoma: An institutional experience with a uniform chemotherapy protocol. South Asian J Cancer 2018;7:195-9.

Access this article online

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Website: www.sajc.org

DOI: 10.4103/sajc.sajc_230_17

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Table 1: Rituximab-cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine regimen

Drug	Drug	Days
R-CODOX-M regimen*		
R	375 mg/m ² IV	D1
Cyclophosphamide	800 mg/m ² IV	D1
Cyclophosphamide	200 mg/m ² IV	D2 to d4
Vincristine	1.5 mg/m ² (maximum 2 mg) IV bolus	D1 and d8
Doxorubicin	40 mg/m ² IV	D1
Methotrexate	Age < 65years: 3 gm/m ³ with leucovorin rescue	D10
	Age > 65 year: 1gm/m ² with leucovorin rescue	
Intrathecal medications	IT cytarabine 70 mg	D1 and D3
	IT methotrexate 12 mg	D15
R-IVAC regimen*		
R	375 mg/m ²	D1
Ifosfamide	Age < 65 years: 1500 mg/m ² IV with mesna	D1- D5
	Age >65 years: 1000 mg/m ² IV with mesna	
Etoposide	60 mg/m ²	D1-D5
Cytarabine	Age < 65 years: 2 g/m ² IV every 12 hours	D1, D2
	Age >65 years: 1 g/m ² IV every 12 hours	
Intrathecal medications	IT methotrexate 12 mg	D5

*with granulocyte colony stimulating factor support till absolute neutrophil count > 1000/ μ l R-CODOX-M=Rituximab-cyclophosphamide, vincristine, doxorubicin, methotrexate, R-IVAC=Rituximab--ifosfamide, etoposide, cytarabine

disease based on Modified Cheson lymphoma response evaluation criteria. The overall response rate (ORR) was calculated including CR and PR.^[2]

The time period from the beginning of the treatment to the date of death from any cause or to the date of the last follow-up was defined as overall survival (OS). Progression-free survival (PFS) was defined as the time from the beginning of treatment to disease progression or relapse.

Statistical analysis

Statistical analysis was done using IBM SPSS version 20. The Chi-square test was used to analyze the correlation between treatment regimen and achievement of response to therapy. Survival was calculated by Kaplan-Meier analysis and factors significantly affecting the survival outcomes were analyzed by Cox's proportional hazard method. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

The median age at presentation was 38 years (19.0–64.0). Elderly patients (Age >60 years) constituted 11% of our study population. The majority of patients were male, with the male to female ratio being 3.5:1. The median duration of symptom duration before the presentation was 2 months (0.2–6 months). Extranodal involvement was seen in all the cases, the bone marrow was most common extranodal (9/18 [50%]). The other extranodal sites were gastrointestinal (GI) tract (8/18 [44.4%]), lung (3/18 [16.6%]), breast, adnexa, liver, central nervous syndrome (CNS), nasopharynx, tonsillar fossa, and bone. Pleural effusion and ascites were present in 5 (27.8%) cases, respectively. The CSF cytology was negative in all cases. In our study population, 4 (22.2%) patients had Burkitt leukemia whereas one patient had primary GI Lymphoma (ileoceleal region).

Majority of our patients (14/18 [77.8%]) presented with advanced stage (Stage III/IV) of disease. B-symptoms (fever, night sweat, and loss of weight or appetite) were present in 12/18 (66.6%) cases, and bulky disease was present in 9/18 (50%) of patients. 17/18 (94.5%) cases were of high-risk BL. In our study population, only one patient was HIV positive. Most of our patients had poor performance status, 10/18 (55.5%) patients had Eastern Cooperative Oncology Group performance status of ≥ 2 . Low albumin (serum albumin <3.5 g/dl) was seen in 6/18 (33.3%) cases [Table 2].

Information on fluorescence *in situ* Hybridization (FISH) for c-MYC (8q24) gene was available in 5/18 (27.7%) cases; of which 2/5 (40%) cases were $t(8,14)$ positive while 2/5 (40%) cases did not reveal MYC gene rearrangement, one of these patients was tested only for $t(8,14)$ and turned out to be negative.

Four patients underwent an initial surgery and diagnosis of BL was confirmed on histopathological examination of the surgically resected specimen. Two patients presented with acute intestinal obstruction and underwent exploratory laparotomy, biopsy, and diversion colostomy. One of the patients presented with ileocecal mass and underwent right hemicolectomy. The 4th patient presented with bilateral adnexal mass and omental deposits; she underwent exploratory laparotomy with total abdominal hysterectomy with bilateral salpingo-oophorectomy along with right hemicolectomy.

Treatment and outcome

Four patients were given prephase chemotherapy with cyclophosphamide and dexamethasone. Two patients initially received one cycle of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), each in view of the delay in the confirmed diagnosis of BL. All the 18 patients included in this study were treated with a uniform protocol using CODOX-M/

Table 2: Baseline clinical characteristics

Variable (n=18)	Frequency (%)
Median age, years (range)	38 (19-64)
Sex	
Male	14 (77.8)
Female	4 (22.2)
Performance status	
0-1	8 (44.4)
2 or more	10 (55.6)
Stage	
I + II	4 (22.2)
III + IV	14 (77.8)
Risk stratification	
High risk	17 (94.4)
Low risk	1 (5.6)
LDH (IU/L)	
Normal	3 (16.7)
Elevated	15 (83.3)
Serum albumin (g/dl)	
>3.5	12 (66.6)
≤3.5	6 (33.4)
BM status	
Positive	9 (50.0)
Negative	9 (50.0)
CSF status	
Positive	0
Negative	18 (100.0)

LDH=Lactate dehydrogenase, CSF=Cerebrospinal fluid, BM=Bone marrow

IVAC, of these 12 (66.6%) patients received rituximab. The ORR and complete response (CR) rate was 77.8% and 66.7%, respectively. In the subgroup of patients who received Rituximab RCODEX-M/IVAC (RCODEX-M/IVAC), the ORR, and CR rate was 75.0%, and 66.6% respectively while the ORR and CR rate in the CODEX-M/IVAC subgroup was 83.3.0% and 66.6%, respectively. Five (27%) patients had a progression of disease while on therapy, of these two patients developed new-onset cranial nerve palsy and on evaluation was found to have CNS disease along with nodal and medullary involvement. Of the other three patients, one patient developed new skin lesions and the other developed fulminant hepatic failure, both these patients were on evaluation confirmed to have disease progression. One patient with Burkitt leukemia had persistent bone marrow involvement despite therapy. All these five patients succumbed to their illness.

One patient had a partial response after completion of treatment; he received radiotherapy (36 Gy/20#) to residual disease. He achieved a CR after completion of radiotherapy.

Out of 18 patients on CODEX-M/IVAC, 14 high-risk patients and one low-risk patient received all 4 cycles and 3 cycles, respectively, i.e., 83.3% patients were able to complete scheduled treatment. Three high-risk patients received only 3 cycles as they had disease progression.

Toxicity

In our study, 16 (88.8%) patients had grade 3/4 neutropenia, 14 (77.7%) had grade 3/4 thrombocytopenia, 12 (66.6%) patients had febrile neutropenia, and 12 (66.6%) patients had grade 3/4 anemia. Of the nonhematologic toxicity, mucositis was the most significant toxicity, 6 (33.3%) patients developed grade 3/4 mucositis. The other nonhematologic grade 3/4 toxicity was diarrhea (15%) and transaminitis (5%).

Survival

The median event-free survival (EFS) and OS were not reached in our cohort. One-year EFS and OS was 76% and 81.1%, respectively, with a median follow-up of 15.6 months (2.5–49.2 months) [Figures 1 and 2]. The estimate 2-year EFS and OS are 68.4% and 73%, respectively. Bone marrow involvement ($P = 0.01$) and female gender ($P = 0.01$) was associated with poor OS.

Discussion

This is the first case series describing the treatment outcome of the patients of BL using a uniform protocol from India. In our series, the median age of patients was 38 (19–64), while 2/18 (11%) patients were elderly (age >60 years). The patients were predominantly male (3.5:1). These findings are consistent with other case series.^[3-5] In some series, a higher median age (44–58 year) has also been reported.^[6,7] Two earlier studies from India have reported the median age of presentation to be 22 years and 6.5 years with BL comprising 3.5% and 3% of all NHL, respectively.^[8,9] However, in these two studies, pediatric BL cases were also included in this study.

In the present study, the patients have a higher frequency of B-symptoms (66.6%), a higher proportion of advanced disease (77.8%), bone marrow involvement (50%), and Burkitt leukemia (22%) subtype. CNS involvement was not seen in our case series. The majority of the patients in our study were high risk (94.5%) and bone marrow being the most common extranodal site (50%) followed by GI tract (44.4%). Studies have reported bone marrow and central nervous system (CNS) involvement in 30%–38% and 13%–17% of adults, respectively.^[3,10,11]

In our study, all 18 patients received CODEX-M/IVAC regimen out of them, 12 received rituximab. The ORR and CR rate in our population was 75% and 66.6%, respectively. The 1-year EFS and OS was 76% and 81.1% respectively with a median follow-up of 15.6 (2.5–49.2) months. It is interesting that all patients who achieved CR at the end of treatment are disease free and surviving till the last follow-up. This supports the fact that though BL is an aggressive disease, once patients successfully complete treatment the long-term outcomes are good. The results of our study are comparable to the outcome of other studies using this protocol^[3,4,12,13,17] [Table 3]. All of these trials used a risk-adapted approach. Two-year EFS and OS varied from 64%–92% and 67%–73%, respectively in these studies. The Dosing of CODEX-M/IVAC has varied slightly between these studies. Other regimens such as Cancer and leukemia Group B, HyperCVD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone), Rituximab-HyperCVD, Lymphomes Malins B (LMB) reported 2-year EFS and OS varied from 61% to 74% and 49% to 78%, respectively.^[6,7,14] Dunleavy *et al.* reported a freedom from progression of 95% and OS of 100% at a median follow-up 86 months with DA-EPOCH regimen with rituximab.^[15] The impact of rituximab has not been well studied in BL. Few studies reported 3-year EFS and OS in the rituximab-containing arms at 74%–76% and 77%–82%^[16-18] [Table 4].

Bone marrow involvement ($P = 0.01$) and female gender ($P = 0.01$) were significantly related to poor OS. The association of poor OS with female gender could be a chance association in view of a small sample size and relatively shorter follow-up. The grade 3/4 myelosuppression was universal CODEX-M/IVAC regimen, and

Table 3: Regimens and outcomes for the upfront therapy of Burkitt lymphoma

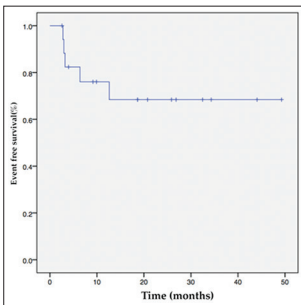
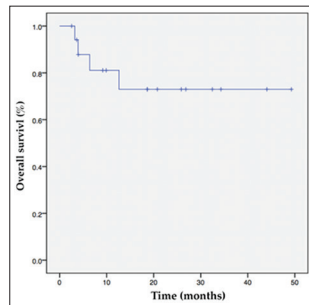
Reference	Regimen	n	Median age (years)	Risk	TRM	EFS/PFS	OS
Mead <i>et al.</i> ^[3]	CODOX-M/IVAC	52	35	High risk 77%	5	2 years EFS 65%	2 years OS 67%
Mead <i>et al.</i> ^[4]	CODOX-M/IVAC	53	37	High risk 79%	9	2 years EFS 64%	2 years OS 67%
Magrath <i>et al.</i> ^[12]	CODOX-M/IVAC	41	25	High risk 83%	0	2 years PFS 92%	NA
Lacasce <i>et al.</i> ^[13]	CODOX-M/IVAC	14	47	High risk 78%	0	2 years EFS 64%	2 years OS 71%
Barnes <i>et al.</i> ^[17]	CODOX-M/IVAC		46	High risk 84%	NA	3 years PFS	3 years OS
	With R	40				74%	77%
	Without R	40				61%	66%

EFS=Event free survival, PFS=Progression free survival, OS=Overall survival, CODOX-M/IVAC=Cyclophosphamide, vincristine, doxorubicin, methotrexate, ifosfamide, etoposide, cytarabine, NA=Not available, TRM= treatment related mortality, R= rituximab

Table 4: Other regimens and outcomes for the upfront therapy of Burkitt lymphoma

Author	Regimen	n	Median age (years)	Risk	TRM	EFS/PFS	OS
Rizzieri <i>et al.</i> ^[6]	CALGB regimen	105	44	IPI ≥ 3 , 47%	7	2-year EFS 74%	3-year OS 58%
Thomas <i>et al.</i> ^[7]	Hyper CVAD	26	58	High LDH 70%	5	3-year CCR 61%	3-year OS 49%
Diviné <i>et al.</i> ^[14]	LMB regimen	72	33	High LDH 60%	0	2-year EFS 65%	2-year OS 70%
Dunleavy <i>et al.</i> ^[15]	DA-EPOCH	19	25	High LDH 37%	0	EFS 95%**	OS 100%**
Ribrag <i>et al.</i> ^[16]	LMBA regimen					3-year EFS	3-year OS
	With R	128	47	High LDH 75%	9	75%	83%
	Without R	129			7	62%	70%
Thomas <i>et al.</i> ^[18]	R-hyper CVAD	31	46	High LDH 100%	1	3-year EFS 80%	3 years OS 89%

**Median follow-up 86 months. EFS=Event-free survival, PFS=Progression-free survival, OS=Overall survival, CALGB=Cancer and leukemia Group B, R-hyper CVAD=Rituximab-hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, DA-REPOCH=Dose-adjusted rituximab, etoposide, vincristine, cyclophosphamide, doxorubicin, LDH=Lactate dehydrogenase, TRM = Treatment related mortality, IPI = International prognostic index, CCR = continuous complete response, LMB= Lymphomes Malins B

**Figure 1: Event-free survival in Burkitt lymphoma****Figure 2: Overall survival in Burkitt lymphoma**

it was the most common toxicity in our series. However, despite significant toxicity related to this regimen, the protocol completion rate in our series was 83.3%, which is comparable with western literature.^[12,18] There were no toxic deaths in this case series.

A large proportion of our patients were diagnosed of having BL based on morphology and immunohistochemistry. The molecular evidence through FISH was available in only five (27%) patients. In our resource-limited setting, the availability of FISH for MYC rearrangement hampers adequate molecular diagnosis of these patients.

Our study is limited by its small sample size, short follow-up, and retrospective study design. Despite, of these limitations, it gives us a window of opportunity to see the outcomes and toxicity of our patients who are treated with aggressive chemotherapy protocol like CODOX-M/IVAC.

Conclusion

Our patients of BL treated with CODOX-M/IVAC protocol are able to complete treatment despite significant toxicity. The outcomes of these patients are comparable to those in the western population. The bone marrow involvement at baseline was found to be a poor outcome predictor in our series which needs verification in larger series.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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