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Diffuse large B-cell lymphoma in elderly: Experience from a tertiary care oncology center in South India

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Abstract

Introduction: Diffuse large B-cell lymphoma (DLBCL) is the most frequent non-Hodgkins lymphoma in the elderly. With the rising proportion of older persons in India, it is important to study current patterns and management of this disease, given that data in this regard are scarce in Indian settings. The aim of this study was to document the clinical features of DLBCL among elderly patients and their outcome over 7 years at a tertiary care oncology center. **Materials and Methods:** This was a retrospective records review of 119 DLBCL cases between January 2007 and January 2015 aged 60 years and above done at Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India. Clinical staging was done according to Ann Arbor staging as modified by Cotswold's and International Prognostic Index (IPI) calculated. **Results:** The mean age was 69.54 years (±5.44) with male: female ratio of 1.52:1. B symptoms were seen in 33% of patients. Thirty-six percent of the patients had stage II disease. The advanced stage was seen in 12% and bulky disease in 9.5%. Bone marrow was involved in 12%. The most common extranodal site was the head and neck region. The distribution according to the IPI was as follows: Low risk 38 (31.93%), low-intermediate risk 53 (44.54%), high-intermediate risk 20 (16.80%), and high risk 8 (6.72%). Among 119 patients, 98 (64.7%) received treatment with either combination of rituximab, cyclophosphamide, adriamycin, vincristine, epirubicin, and prednisolone. Overall response rate was 63.26% with a complete response rate of 38.77%. The overall survival ranged from 2 to 123 months with the median being 9.5 months. **Conclusion:** In elderly, DLBCL is common in seventh decade and most of them present in an early stage and low IPI. The incorporation of rituximab to anthracycline based chemotherapy shows a significant improvement in survival in elderly DLBCL.

Key words: Cyclophosphamide, diffuse large B-cell lymphoma, doxorubicin, India, relapse, remission, rituximab, vincristine, prednisone

Introduction

The geriatric population aged 60 years and above, is the fastest growing segment of the world's population. Diffuse large B-cell lymphoma (DLBCL) is the most frequent non-Hodgkins lymphoma (NHL), comprising more than 40% of lymphomas in the elderly.[1,2] The chance of having a DLBCL increases with age.[3,4] Older age is usually associated with multiple comorbidities, and it is a major determinant of therapeutic decisions. Hence, age is a major prognostic factor.[5] The aim of this study was to analyze the main clinical and biological features of elderly DLBCL patients and their outcome in a tertiary care oncology center in South India.

Materials and Methods

This was a retrospective records review carried out at the Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India. All cases between January 2007 and January 2015, aged ≥ 60 years, diagnosed as DLBCL by appropriate lymph node or tissue biopsy and confirmed by immunohistochemistry were included. Demographic, clinical, and treatment details were recorded and analyzed. Staging included a detailed history, physical examination, complete hemogram and serum biochemistry, including lactate dehydrogenase (LDH); human immunodeficiency virus (HIV), hepatitis B antigen, and two-dimensional echocardiography. Staging computed tomography (CT) scan or positron emission tomography-CT scan and bone marrow biopsy was done in all the patients. In relevant cases, cerebrospinal fluid (CSF) analysis was done. Patients were staged according to Ann Arbor staging as modified by Cotswold's and International Prognostic Index (IPI). The patients were treated as per the institute protocol, and responses were assessed according to International Working Group response criteria. The clinic pathological factors were statistically evaluated for survival.

Definitions

Patients with nodal or extranodal involvement with or without regional lymph nodes diagnosed as DLBCL aged ≥60 years were included. Waldeyer's ring, spleen, liver, and extensive lymph node involvement were defined as primary nodal DLBCL. Patients with DLBCL aged ≥16 years and <59 years were excluded.

Statistical analysis

Calculation of mean and median was done using Microsoft Excel, overall survival (OS) was calculated from diagnosis to the last follow-up or death due to any cause. The actuarial survival analysis was performed according to the method described by Kaplan–Meier and the univariate analysis was performed for each parameters mentioned. The values of $P \leq 0.05$ were considered to indicate statistical significance. Data were analyzed with the Statistical Package for the Social Sciences SPSS (version 16) statistical software (IBM, Bangalore).

Results

Demographic profile

Of the 628 patients diagnosed to have DLBCL in the period of study, 119 patients (18.94%) were aged ≥ 60 years. The mean age was 69.54 years (±5.44) and was 1.52 times more common in males than females. The majority of patients (40%) were in the age group of 60–70 with B symptoms in 38 (32.8%) patients [Table 1].

Staging

Most had stage II disease (36.2%) and 32 patients (26.89%) had extranodal involvement. Advanced stage with more

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Table 1: Demographic finding and pattern of diffuse large B-cell lymphoma among the study subjects and in comparison to Nehra *et al.*

Patient characteristics	Present study	Nehra *et al.*
Number of patients	119	36
Age - mean (years) (%)	69.54	-
60-65	75 (64.7)	-
65-75	39 (32.8)	24
>75	5 (2.6)	12
Gender		
Male:female	1.52:1	1:1
ECOG PS >2	31	-
Stage (%)		-
I	27.5	
II	36.2	
III	24.14	
IV	12.06	
Nodal:extranodal	2.5:1	5:1
Patients with >1 extranodal site	12.06	-
B symptoms	33	-
IPI score (%)		-
Low risk (0-1)	31.93	
Low intermediate risk (2)	44.54	
High intermediate risk (3)	16.80	
High risk (4-5)	6.72	
Treatment regimens received	CHOP, COP, R-CHOP, R-COP, CEOP, chlorambucil + prednisolone	Rituximab based: R-CHOP, R-COP, R-CEOP, RMVP, BR
ORR (%)	63.26	>60
CR (%)	38.77	60

CR=Complete response, ORR=Overall response rate, ECOG PS=Eastern Cooperative Oncology Group Performance Status, IPI=International Prognostic Index, R-CHOP=Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, R-COP=Rituximab, cyclophosphamide, vincristine, and prednisone, R-CEOP=Rituximab, cyclophosphamide, etoposide, vincristine, and prednisone

than one extranodal site (Ann Arbor IV) was seen in 14 patients (12.06%) and bulky disease in 11 (9.5%). Bone marrow was involved in ten patients (11.9%). The most common extranodal site was the head and neck region (46.87%) followed by gastrointestinal tract (32%) with stomach the most common site. Three patients had primary bone DLBCL lymphoma.

International Prognostic Index

Eastern Cooperative Oncology Group Performance Status was ≥ 2 in 31 patients and 67 patients had high serum LDH levels. CD20 was positive in all 119 cases (100%). HIV, hepatitis B, and CSF were positive in one case each. The IPI risk stratification was low risk - 38 (31.93%), low-intermediate risk - 53 (44.54%), high-intermediate risk 20 (16.80%), and high risk 8 (6.72%) [Table 1].

Co morbid conditions

Thirty-one patients had associated comorbid diseases such as diabetes mellitus, hypertension and ischemic heart disease. HIV, hepatitis B was positive in one case each.

Treatment and outcome

Of the 119 patients, 98 (64.7%) received treatment (minimum three cycles) with either combination of rituximab (375 mg/m^2), cyclophosphamide (750 mg/m^2), adriamycin (50 mg/m^2), vincristine (1.4 mg/m^2), epirubicin (100 mg/m^2), and prednisolone (100 mg/day for 5 days). The various

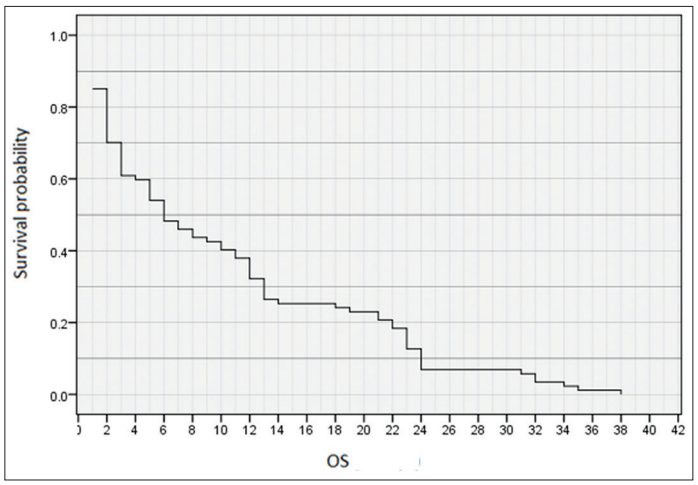

Figure 1: Kaplan–Meier graph showing overall survival in months

treatment regimens were rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (n = 15) or rituximab, cyclophosphamide, vincristine, and prednisone (COP) (n = 2) or CHOP (58) or COP (11) or cyclophosphamide, etoposide, vincristine, and prednisone (6) or chlorambucil + prednisolone.[6] Among these, 8 (6.72%) patients received involved field radiotherapy and 9 (7.56%) received surgical treatment.

Overall response rate (ORR) was 63.26% with complete response in 38.77%. Forty-nine patients were alive with no disease, eight were alive with disease, two died and 39 patients lost to follow-up at the time of data collection. Relapses were recorded in five patients (5.1%). The OS ranged from 2 to 123 months with a median being 9.5 months. The Kaplan–Meier graph depicting OS is shown in Figure 1. Among the clinic pathological factors such as age, sex, B symptoms, bulky disease, performance status, elevated LDH, stage, and IPI, only bulky disease (P = 0.034) and high IPI score ($P \leq 0.05$) was associated with statistically significant poor survival on a univariate analysis.

Discussion

DLBCL is a high grade B-cell lymphoma with varied clinical manifestations, morphology, immunophenotype, genetic, and molecular alterations.[1] In our study, the mean age was a 69.54 ± 5.44 year which was a little lower compared to another Indian study Nehra *et al*.[6] DLBCL was 1.5 times more common in males. The peak incidence for DLBCL occurs in the sixth and seventh decade, as shown in our study.[1-3] Older age is associated with poorer prognosis as reflected by the prognostic models like IPI score.[5,7] Most of our patients had low IPI scores and was an important factor to predict OS in those treated with chemotherapy. Specific clinical and biologic characteristics are described for DLBCLs arising in the elderly compared to younger individuals. Levels of interleukin 6 are higher in older patients and correlate with B symptoms, elevations of serum LDH, beta 2 microglobulin, advanced stage, bulky disease, and poor performance status predict poor survival independent of the traditional IPI risk factors.[8,9] As described earlier this study showed bulky disease and high IPI score was associated with poor prognosis.

In recent times, gene expression profiling studies have showed two distinct types of DLBCL, the unfavourable activated B-cell

phenotype (ABC) and the favorable germinal centre B-cell type (GCB). The ABC phenotype is characterized molecularly by activation of the nuclear factor Kappa β pathway and is more common in the elderly.[10-14] This maybe another reason for the poor prognosis of elderly DLBCL patients. However, due to the lack of resources we have not incorporated these parameters in our study. We are planning a further validation of these parameters in a follow-up study using the Hans criteria on IHC and classifying as ABC and GCB type.

Comorbidities such as diabetes, hypertension, and cardiovascular diseases are common in elderly patients. Almost 61% of patients ≥70 and around 85% of patients ≥80 present with coexisting comorbidity as opposed to 20% in younger patients.[12-15] DLBCL patients with comorbidities have higher risk of treatment toxicity and of death.[12,15] The hematopoietic reserve capacity is impaired with increasing age and myelotoxicity of standard dose regimens has been shown to be more severe in the elderly.[13] In our study, 31% had associated comorbid illness such as diabetes mellitus and hypertension, but they all received the normal dose intense CHOP chemotherapy regimen.

Two major randomized control trials Group d'Etude des Lymphomes de l'Adulte and RICOVER-60 have shown the addition of rituximab to CHOP given every 21 or 14 days has significantly improved the outcome in elderly patients (more than 60 years).[14,15] Similarly in our study, the best treatment regimen was rituximab + CHOP. However due to an economically poor setup, all our patients could not receive rituximab. However almost all patients received anthracycline based CHOP chemotherapy and with the proper dose intensity and growth factor support. The ORR in our study was 63.26% similar to the study by Nehra *et al*. (60%). However, the CR rates in our study was 38.77% which is slightly lower than in study by Nehra *et al*. (60%) [Table 1]. This maybe explained due to the limited use of rituximab in our elderly patients. In ricover 60 conducted by the German high grade NHL study group, 1222 patients were randomized to receive six or eight courses of CHOP14 with or without rituximab and radiotherapy to sites of initial bulky disease.[15] R-CHOP14 significantly improved 3-years event-free survival (66% vs. 47%), progression-free survival, as compared to six cycles of CHOP14 treatment.[15-17] The OS of this study is shown in Figure 1. Therefore, the standard of treatment for elderly DLBCL is rituximab based chemotherapy with addition of anthracyclines and growth factor support.

Conclusion

In elderly, DLBCL is common in seventh decade and most of them present in an early stage and low IPI. The incorporation of rituximab to anthracycline based chemotherapy shows a significant improvement in survival in elderly DLBCL. Poor outcome in elderly DLBCL patients may be related to associated comorbidities and inability to receive standard chemotherapy regimens in adequate doses. With the continuous progress made in lymphoma treatment and the usage of chemo immunotherapy, age itself should not be a justification for compromised dose intensity chemotherapy.

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Conflicts of interest

There are no conflicts of interest.

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