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ORIGINAL ARTICLE

Clinical prognostic factors of diffuse large B cell non-Hodgkin lymphoma: A retrospective study

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KEYWORDS

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Abstract *Background:* Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL in Egypt. It represents about 49% of NHL presenting to the National Cancer Institute (NCI), Cairo University. CHOP regimen is the standard treatment used for NHL since the 1970s with only 30–40% overall survival. Recently, integration of Rituximab became a standard of care for patients with DLBCL. However, its widespread use in developing countries is still limited by the lack of financial coverage. Clinical prognostic factors, as well as the pathological markers, are mandatory to individualize treatment.

Aim: The aim of the study was to evaluate the clinical risk stratification models including the age adjusted International prognostic index (aaIPI), patients profile and dose intensity (DI) of Cyclophosphamide and Doxorubicin as effective tools for predicting the outcome and prognosis of our DLBCL patients treated with first line CHOP regimen.

Patients and methods: This retrospective study included 224 patients with diffuse large B cell lymphoma who were treated with 3–8 cycles of CHOP regimen at the Medical Oncology Department, NCI, Cairo University during the time period from 1999 to 2006.

Results: One hundred and seventy-eight patients (79.5%) achieved CR after the CHOP regimen with an observation period of 51 months. The median survival time was 12 months. The OS and

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DFS at 2 years were 82% and 68.8%, respectively. The univariate analysis of predictive factors for response to treatment showed that the CR rate was significantly affected by aa-IPI and its elements (performance status, stage & LDH), extranodal lesions and DI of Cyclophosphamide and Doxorubicin. The CR rate was 96.9%, 91.2%, 73.9% and 55.6% in cases with aa-IPI 0, 1, 2 and 3, respectively ($p < 0.001$) and it was 82.4%, 81.9% versus 50% in cases with no extranodal site, one extranodal site and two extranodal sites, respectively ($p = 0.01$). As regard DI of Cyclophosphamide, with DI below or equal to the median (249 mg/m^2/week) the CR rate was 69%, while with DI above the median the CR rate was 87.7% ($p = 0.001$). For Doxorubicin, the CR rate was 72.3% with DI below or equal to the median (16.5 mg/m^2/week), however, it was 86.6% with DI above the median ($p = 0.008$). The OS rate was significantly affected by aa-IPI as it was 89.8% in cases of aa-IPI 0 + 1 versus 75.8% in those of aa-IPI 2 + 3 ($p = 0.03$). DI of Cyclophosphamide and Doxorubicin significantly influenced the OS. The OS rate was 74% with DI of Doxorubicin below or equal to the median versus 96% in cases with DI above the median ($p = 0.02$). For Cyclophosphamide the OS rate was 72.7% with DI below or equal to the median versus 96.3% in cases with DI above the median ($p = 0.01$). The tumor bulk (with a median tumor size of 5 cm) affected the OS, which was 91.23% versus 86.8% in the tumor bulk less than and more than or equal to the median, respectively ($p = 0.05$). By multivariate analysis of predictive factors for response to treatment, the CR rate was significantly affected by the number of extranodal sites and the clinical staging of diffuse large B cell lymphoma. However, OS rate was strongly associated with the bulk of the tumor and the clinical staging of diffuse large B cell lymphoma.

Conclusion: DI of Cyclophosphamide and Doxorubicin is important in the future treatment regimen plan for DLBCL especially in high risk cases. In addition to aa-IPI and its elements, extra nodal sites and bulk of the tumor proved to be significant predictors and prognostic factors for DLBCL treatment outcome.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma in western countries representing about one third of these disorders. Although DLBCL is usually considered as a specific category, the diversity in the clinical presentation, morphology, genetic and molecular alterations strongly suggests that these tumors represent a heterogeneous group of neoplasms rather than a single clinicopathological entity [1]. In fact, the biological and clinical heterogeneity of DLBCL has already been recognized in the Revised European American Lymphoid (REAL) and World Health Organization (WHO) classifications [2]. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL in Egypt. It represents about 49% of NHL presenting to the NCI, Cairo University [3]. The diffuse large cell lymphoma can be cured in more than half of the cases by conventional chemotherapy regimens. However, the other patients have tumors that are either refractory to currently available treatment or have a relapse after a period of remission; most of these patients die of the disease. The age adjusted international prognostic index (aa-IPI) takes into account factors that are mostly linked to the patient characteristics or to the disease extension and growth, for patients aged equal to or less than 60 years, lactate dehydrogenase level (normal versus high), performance status (zero or one versus two or more) and clinical stage (I, II versus III, IV). Four discrete outcome groups were identified with a 5-year overall survival ranging from 32% to 83% [4]. CHOP regimen is the standard treatment used for NHL since the 1970s, with only 30–40% overall survival. Subsequent new combinations including drugs, such as methotrexate, bleomycine or cytarabine have been employed, however, multicentre randomized trials failed to demonstrate any survival advantage of these second and third generation regimens over standard CHOP [5]. Recently, maintaining higher relative dose intensity (RDI) of chemotherapeutic drugs has become a wide-spread practice in an attempt to achieve better outcomes in the treatment of aggressive lymphoma [6]. The addition of rituximab to chemotherapy regimens has a significantly improved outcome in diffuse large B-cell lymphoma (DLBCL) [7]. However, its widespread use in developing countries is still limited by the lack of financial coverage.

Aim

The aim of the study was to evaluate the clinical risk stratification models including the age adjusted International prognostic index (aa-IPI), patient profile and dose intensity (DI) of Cyclophosphamide and Doxorubicin as effective tools for predicting the outcome and prognosis of our DLBCL patients treated with the first line CHOP regimen.

Patients and methods

This study is a retrospective analysis of 224 patients with the diagnosis of diffuse large B cell non-Hodgkin's lymphoma (DLBCL) who presented to the medical oncology clinic of the National Cancer Institute, Cairo University during the time period from 1999 to 2006. Patients included in the study were newly diagnosed with no prior chemotherapy or radiotherapy. Their ages ranged from 18 to 60 years. Standard staging work up included thoracic, abdominal, and pelvic computed tomography scans, as well as bone marrow biopsy or aspiration. We used the age adjusted international prognostic index (aa-IPI) to stratify the patients into prognostic groups [4].

Treatment plan

As initial chemotherapy, patients were planned to be treated with the standard CHOP regimen (Cyclophosphamide 750 mg/m^2 day 1, doxorubicin 50 mg/m^2 day 1 vincristine 1.4 mg/m^2 day 1, prednisone 100 mg PO for 5 days),with equal or more than three consecutive cycles. Clinical data and follow up information were obtained by reviewing the patients' medical records. Response was assessed according to conventional criteria, complete response was confirmed by the disappearance of all lesions, determined by two observations, not less than 4 weeks apart. Partial response was defined as 50% or more decrease in total tumor size that has been measured to determine the effect of therapy by two observations, not less than 4 weeks apart. No response was defined as less than 50% decrease in total tumor size, while progressive disease was reported by 25% or more increase in the size of the tumor.

Calculation of dose intensity

Dose intensity is defined as the amount of drug delivered per unit of time, expressed as milligrams per square meter per week, regardless of the schedule or route of administration. Relative dose intensity (RDI) is the amount of drug delivered per unit of time relative to an arbitrarily chosen standard single drug [8]

Dose intensity (DI) and relative dose intensity (RDI) were calculated in 224 patients who had completed their treatment at the time of evaluation. It is calculated as follows:

Dose intensity of doxorubicin in standard CHOP

$= 50\ \text{mg/m}^2 = 16.66\ \text{mg/m}^2/\text{week}\ 3$

The dose intensity of the actual dose of doxorubicin given is calculated by dividing the total dose of doxorubicin per number of weeks during which treatment was given.

Relative dose intensity of doxorubicin as compared to planned treatment is a percentage of the actual dose intensity of doxorubicin to the dose intensity of doxorubicin planned.

Dose intensity of cyclophosphamide is calculated in the same way as doxorubicin.

Dose intensity of cyclophosphamide in standard CHOP

$= 750\ \text{mg/m}^2 = 250\ \text{mg/m}^2/\text{week}\ 3$

Relative dose intensity of cyclophosphamide as compared to planned treatment is the percentage of the actual dose intensity of cyclophosphamide to the dose intensity of cyclophosphamide planned.

Statistical methods

SPSS (Statistical package for social sciences version 12.0) was used for data analysis. Chi-square and Fisher exact tests compared independent proportions. The Kaplan–Meier test estimated overall and disease free survival. The Log rank test compared survival curves. Multivariate analysis included logistic regression for response to chemotherapy (dependent variable) as affected by different prognostic factors. The entry level for the model was 0.1 and the p-value was significant at 0.05 levels. Cox regression analysis was used for multivariate analysis of overall survival. The Odds ratio and 95% confidence interval (CI) show estimated risk of no response and risk of death in the present study.

Results

Two hundred and twenty-four patients were included in the study, 120 were females and 104 were males. The median age was 47 years (range 18–60 years). The clinical characteristics of all patients are shown in Table 1. Advanced disease (stages III and IV) was reported in 56.7% of the patients and 28.6% of the patients had performance status $\geqslant 2$. LDH was above normal in 71% of the patients. Extranodal involvement was observed in 93 patients (41.5%). The distribution of extranodal sites is summarized in Table 2. The distribution of age adjusted International Prognostic Index was 0 in 32 patients (14.3%), 1 in 68 patients (30.4%), 2 in 88 patients (39.3%) and 3 in 36 patients (16%). All patients received the initial CHOP regimen with a number of cycles ranging from 3 to 8 cycles with a median of 6 cycles.

Complete remission (CR) was achieved in 178/224 patients (79.5%), while no CR (PR, SD and PD) was reported in 46 patients (20.5%). Out of 178 patients who attained complete remission, relapse was reported in 27 patients (15.2%) at a median observation period of 12 months.

Predictive factors for the response to treatment

The CR rate was correlated to different prognostic factors including: aa-IPI and its different elements (performance, stage and LDH level), in addition to extra nodal involvement, bulk of the disease and dose intensity of both Doxorubicin and Cyclophosphamide.

Table 1 Characteristics of 224 patients with DLBCL who received CHOP regimen.

Factor	Categories	No.	%
Age (years)	Range: 18–60 median: 47	224	
Sex	Female	120	53.6
	Male	104	46.4
PS	I	160	71.4
	II	58	25.9
	III	6	2.7
Stage	I	61	27.2
	II	36	16.1
	III	85	37.9
	IV	42	18.8
LDH	Normal	65	29.0
	Above normal	159	71.0
Age adjusted IPI	0	32	14.3
	1	68	30.4
	2	88	39.3
	3	36	16.0
B symptoms	Present	66	29.5
	Absent	158	70.5
Extranodal involvement	Present	93	41.5
	Absent	131	58.5
No. of extranodal lesions	1	72	32.1
	$\geqslant 2$	21	9.4

PS, performance status; LDH, lactate dehydrogenase; IPI, international prognostic index.

Table 2 Extranodal involvement in the 224 patients with DLBCL.

	No. of lesions per patient	No. of patients	%
No. of extranodal lesions	0	131	58.5
	1	72	32.1
	⩾2	21	9.4
Site of extranodal involvement	Bone/bone marrow	20	8.9
	Pulmonary	15	6.7
	Stomach	14	6.3
	Liver	11	4.9
	Intestine	8	3.6
	Skin mass	6	2.7
	Parotid mass	5	2.2
	Nasopharyngeal masses	5	2.2
	Breast	4	1.8
	CNS	3	1.3
	Abdominal soft tissue masses	3	1.3
	Renal	3	1.3
	Chest wall, soft tissue masses	2	1
	Thyroid mass	1	0.45

The CR rate was 83.1%, 72.4% and 50% with PS I, PS II and PS III, respectively ($p = 0.04$). It was 70.3% versus 83.1% for patients with PSII + III versus those with PS I, respectively ($p = 0.03$). The CR of cases with stages I + II was 93.8% versus 68.5% for those with stages III + IV ($p < 0.001$). The CR rate was 92.3% with normal LDH (= or < 500 IU/L) versus 74.2% with above normal LDH level (> 500 IU/L) ($p = 0.002$). According to the age adjusted International prognostic Index (aa-IPI), the CR rate was 96.9%, 91.2%, 73.9% and 55.6% in cases with aa-IPI 0, aa-IPI 1, aa-IPI 2, and aa-IPI 3, respectively ($p < 0.001$). The CR rate was 93.0% for cases with aa-IPI 0 and 1 versus 68.5% for cases with aa-IPI 2 and 3 ($p = 0.001$) (Table 3).

Extranodal involvement significantly influenced the CR rate. It was 82.4%, 81.9% and 50% in cases with no extranodal site, one extranodal site and two or more extranodal sites, respectively ($p = 0.01$).

The CR rate is significantly affected by the dose intensity of Doxorubicin and Cyclophosphamide. With Doxorubicin DI below or equal to the median (16.5 mg/m^2/week), the CR rate was 72.3% while it was 86.6% with DI above the median ($p = 0.008$). With relative dose intensity of Doxorubicin below or equal to the median (0.997), the CR rate was 72.3%, while it was 86.6% with RDI above the median ($p = 0.008$) (Table 4).

For Cyclophosphamide DI below or equal to the median (249 mg/m^2/week), the CR rate was 69%, while with DI above the median the CR rate was 87.7% ($p = 0.001$). RDI below or equal to the median (0.996), the CR rate was 69.6%, while it was 87.7% with RDI above the median ($p = 0.001$) (Table 4).

Overall survival and DFS with their correlation to different prognostic factors

At a maximum observation period of 51 months, the median survival time was 12 months and the OS was 82%. The disease-free survival (DFS) ranged from 1 to 45 months with a 2-year DFS of 68.8%. The OS rate was 89.8% for cases with aa-IPI 0 + 1 versus 75.8% in those with aa-IPI 2 + 3 ($p = 0.02$) (Fig. 1). The OS rate was 94.7%, 100%, 67.9% and 70% in stage I, stage II, stages III and stage IV, respectively ($p = 0.016$) Fig. 2). Combining the cases with stages I and II versus those with stages III and IV, the OS was 96.8% versus 68%, respectively ($p = 0.009$). The OS was not affected by the extranodal involvement ($p = 0.27$). However OS is affected by the tumor bulk which was 91.23% versus 86.8% in tumor bulk less than versus more than or equal to the median, respectively ($p = 0.05$) (Fig. 3).

Table 3 Correlation of aa-IPI and its elements with the CR rate in the 224 patients who received CHOP regimen.

Factors	Categories	Response to chemotherapy				*p* Value
		CR		No CR		
		No. of cases	%	No. of cases	%	
PS	I	133	83.1	27	16.9	0.04
	II	42	72.4	16	27.6	
	III	3	50.0	3	50	
Stage	I	59	96.7	2	3.3	< 0.001
	II	32	88.9	4	11.1	
	III	64	75.3	21	24.7	
	IV	23	54.8	19	45.2	
	I + II	91	93.8	6	6.2	< 0.001
	III + IV	87	68.5	40	31.5	
LDH level (IU/L)	⩽500	60	92.3	5	7.7	0.002
	> 500	118	74.2	41	25.8	
aa. IPI	0	31	96.9	1	3.1	
	1	62	91.2	6	8.8	< 0.001
	2	65	73.9	23	26.1	
	3	20	55.6	16	44.4	
	0 + 1	93	93.0	7	7.0	< 0.001
	2 + 3	85	68.5	39	31.5	

PS, performance status; LDH, lactate dehydrogenase; CR, complete remission.

Table 4 Correlation of dose intensity and relative dose intensity of Doxorubicin and Cyclophosphamide with CR and OS rate in 224 patients who received CHOP regimen.

Factor	Categories	No of patients	Response				*p* Value	OS %	*p* Value
			CR		No CR				
			No. of pts	CR %	No. of pts	No CR %			
Dose intensity of Doxorubicin	Below or equal median (16.5 mg/m^2/week)	112	81	72.3	31	27.7	0.008	74	0.02
	Above median	112	97	86.6	15	13.7		96	
Relative dose intensity of Doxorubicin	Below or equal median	112	81	72.3	31	27.7	0.008	74	0.02
	Above median	112	97	86.6	15	13.4		96	
Dose intensity of Cyclophosphamide	Below or equal median (249 mg/m^2/week)	102	71	69.6	31	30.4	0.001	72.7	0.01
	Above median	122	107	87.7	15	12.3		96.3	
Relative dose intensity of Cyclophosphamide	Below or equal median	102	71	69.6	31	30.4	0.001	72.7	0.01
	Above median	122	107	87.7	15	12.3		96.3	

CR, complete remission; OS, overall survival.

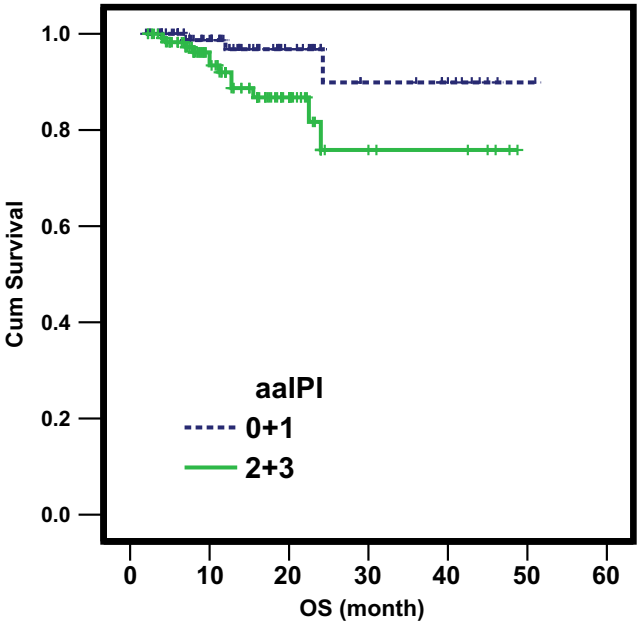

Figure 1 Overall survival in 224 DLBCL patients who received CHOP regimen according to aaIPI ($p = 0.03$).

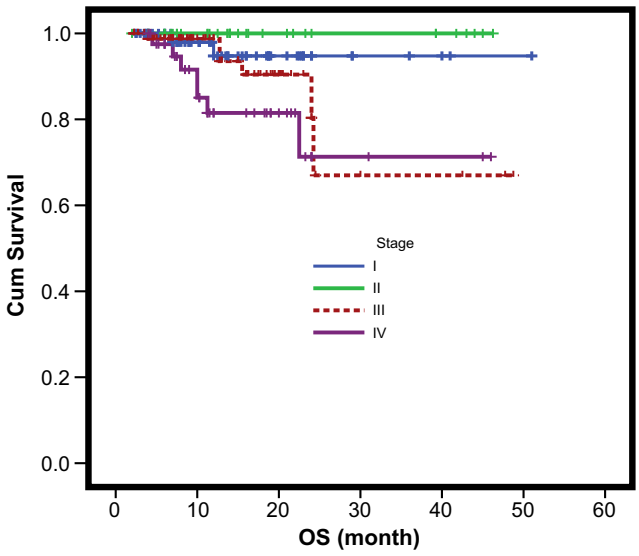

Figure 2 Overall survival in 224 DLBCL patients who received CHOP regimen according to clinical stage ($p = 0.02$).

As regards DFS, aa-IPI and its elements (performance, stage and LDH level) did not affect the DFS. The DFS rate was 71.4%,71.3%, 75% and 66.3% in cases with aa-IPI 0, aa-IPI 1, aa-IPI 2 and aa-IPI 3, respectively ($p = 0.9$).

Relation of dose intensity (DI) and relative dose intensity (RDI) of Doxorubicin and Cyclophosphamide to OS and DFS (Table 4, Figs. 4 and 5)

OS rate was significantly affected by DI and RDI of Doxorubicin and Cyclophosphamide. The OS was 74% with DI and RDI of doxorubicin below or equal to the median versus 96% in cases with DI and RDI above the median ($p = 0.02$) (Fig. 4). For Cyclophosphamide, the OS was 72.7% with DI and RDI below or equal to the median versus 96.3% in cases with DI and RDI above the median ($p = 0.01$) (Fig. 5). The DFS was not affected by DI and RDI of Doxorubicin ($p = 0.35$) or Cyclophosphamide ($p = 0.4$).

Multivariate analysis

By multivariate analysis, there was a strong association between the response to chemotherapy and the number of extranodal sites as well as the clinical stage (Table 5). The OS showed a strong association with the bulk of the tumor and the clinical staging of diffuse large B cell lymphoma by multivariate analysis (Table 6).

Discussion

DLBCL is a heterogeneous group of neoplasms in which previous morphological, phenotypic, genetic, and molecular studies have not been able to identify well-defined disease entities

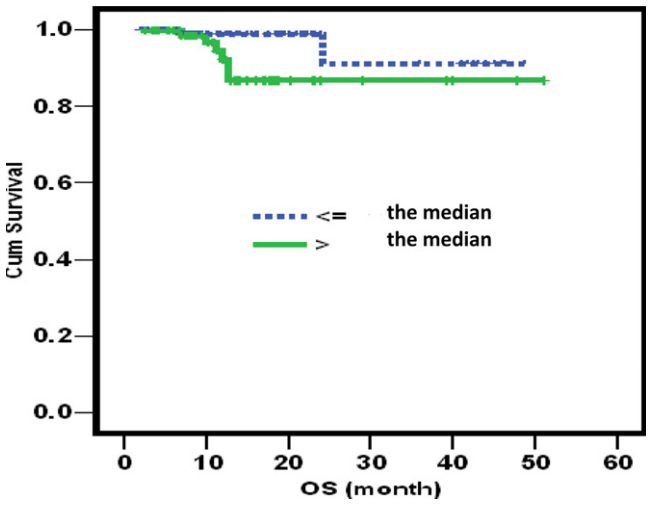

Figure 3 Overall survival in 224 DLBCL patients who received CHOP regimen according to tumor bulk at diagnosis ($p = 0.05$).

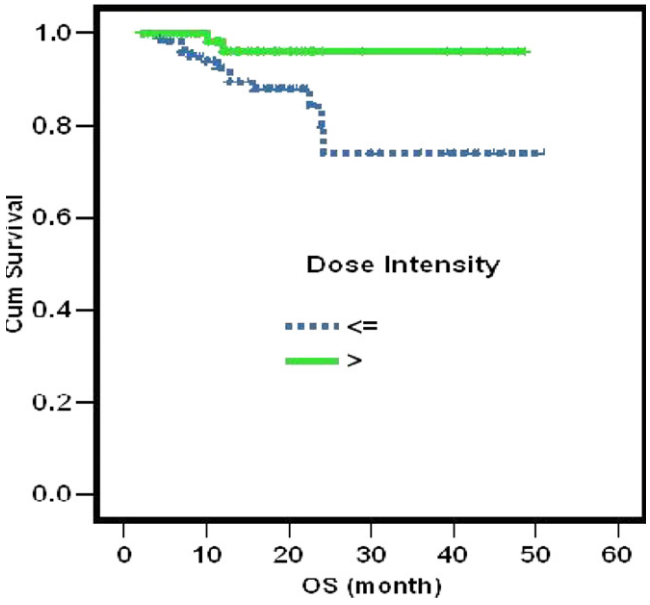

Figure 4 Overall survival in 224 DLBCL patients who received CHOP regimen according to dose intensity of Doxorubicin ($p = 0.02$).

with clinical and therapeutic relevance [9]. The IPI has been the primary prognostic model used in the management of patients with DLBCL since its publication in 1993. It has gained universal acceptance since it relies on information that is readily accessible and its predictive capacity has been validated in multiple studies [10]. The combination of cyclophosphamide, doxorubicin, vincristine, and prednisone-or-CHOP published nearly 30 years ago was the first breakthrough in the treatment of what we call today aggressive lymphomas [11]. In several studies, 5–9 cycles of CHOP achieved complete remission rates of 50–70% and 5-years survival rates of 30–50%. In the 1980s, several intensified modifications of CHOP and the concept of dose intensity, achieved complete response up to 90% and 5-year overall survival rates up to 85% in phase II trials.

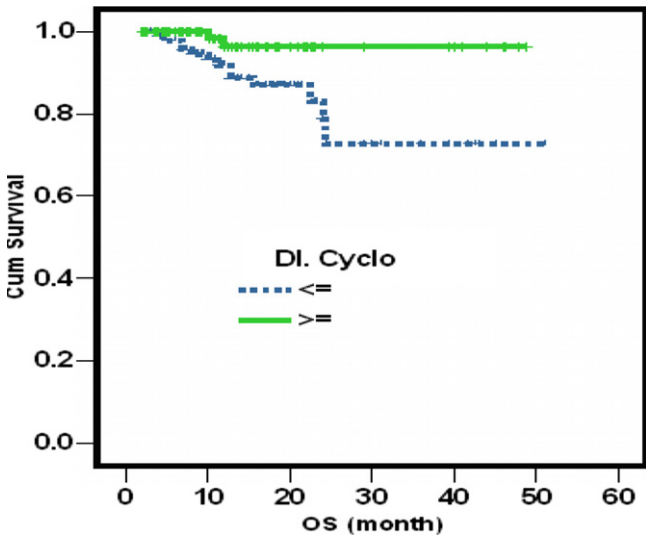

Figure 5 Overall survival in 224 DLBCL patients who received CHOP regimen according to the dose intensity of Cyclophosphamide ($p = 0.01$).

However in the pivotal trial by the American Intergroup, the intensified m-BACOD, ProMACE–CytaBOM, and MACOP-B regimens were not superior to CHOP with respect to complete response rates, event-free, or overall survival [12]. The 6-year OS for the four regimens was 33% for CHOP; 36% for m-BACOD; 34% for ProMACE/CytaBOM and 32% for MACOP-B. Retrospective subgroup analyses also did not find an advantage of the primary use of high dose chemotherapy over conventional therapy in the group of young good-prognosis patients [13]. The next series of randomized trials compared CHOP chemotherapy with R-CHOP. The GELA TRIAL, at 5 years of follow up, event free survival, progression free survival, disease free survival and overall survival remained statistically significant in favor of R-CHOP [14]. No long-term toxicity appeared to be associated with the R-CHOP combination, making this the standard of care in DLBCL [15]. There are several previous studies of the relation between the RDI of chemotherapy and survival in aggressive lymphoma. A high RDI of doxorubicin in CHOP, M-BACOD, or MACOP-B chemotherapy, a high RDI of each drug (cyclophosphamide, doxorubicin, and vincristine) and a high average RDI of these three drugs in CHOP for DLBCL reportedly had a significant positive impact on survival [16].

We reviewed two hundred and twenty four patients with diffuse large B cell lymphoma and we reported a complete remission (CR) rate of 79.5% (178 patients), while no CR (PR, SD and PD) was reported in 46 patients (20.5%). Yang et al reported a complete remission rate of 68.8% and no CR of 31.2% [17], while Colomo et al. reported a complete response rate of 57% [18]. The complete response rates were 83.1%, 72.4%, 50% with PSI, PS II and PS III, respectively while the complete response of cases with stage I + II was 93.8% versus 68.5% for those with stage III + IV ($p < 0.001$). This result matched with Yang et al. who reported that early clinical stage and performance status are significantly associated with better CR rate [17]. In our study, according to the aa-IPI, the CR rates were 96.9%, 91.2%, 73.9% and 55.6% for aa-IPI 0, 1, 2, and 3, respectively

Table 5 Significant, independent prognostic factors found to affect response to chemotherapy by logistic regression in 224 NHL patients.

Factors	B	SE	*p* Value	OR	95.0% C.I. for OR	
					Lower	Upper
No. of extra nodal sites (zero)			.038			
No. of extra nodal sites (one site)	.327	.478	.494	1.387	.543	3.540
No. of extra nodal sites (⩾2 sites)	1.379	.539	.011	3.971	1.381	11.420
Stages (3 + 4 as compared to 1 + 2)	1.467	.504	.004	4.336	1.614	11.649
Constant	−2.882	.485	.000	.056		

B, regression coefficient; SE, standard error; OR, odds ratio for no CR; CI, confidence interval.

Table 6 Significant, independent prognostic factors found to affect overall survival by logistic regression in 224 NHL patients.

Factors	B	SE	*p* Value	OR	95.0% C.I. for OR	
					Upper	Lower
Tumor bulk >5 cm compared to ⩽5 cm	1.705	.829	.040	5.500	1.084	27.916
Stages (3 + 4) compared to (1 + 2)	1.540	.834	.065	4.663	.910	23.893

B, regression coefficient; SE, standard error; OR, odds ratio for death; CI, confidence interval.

($p < 0.001$). The IPI remains predictive, but it identifies only 2 risk groups. Redistribution of the IPI factors into a revised IPI (R-IPI) provides a more clinically useful prediction of outcome. The R-IPI identifies 3 distinct prognostic groups, a group with very good prognosis with 4-year progression free survival (PFS) of 94% and overall survival (OS) of 94%, a good prognosis group with 4-year PFS of 80% and OS of 79%, and a poor prognosis group with 4-year PFS of 53% and OS of 55% ($p < .001$) [19]. In our study, aa-IPI and the clinical stage significantly influenced the OS rate. The median survival time was 12 months and the OS was 82%. The OS rate was 89.8% in cases with aa-IPI 0 + 1 versus 75.8% in those of aa-IPI 2 + 3 ($p = 0.0274$). The OS in cases with stages I + II was 96.8% versus 68% for those with stages III + IV ($p = 0.009$). The DFS rate in cases with aa-IPI 0 + 1 was 71.4% versus 66.3% in cases with aa-IPI 2 + 3 ($p = 0.8$).

Delivering less than full dose intensity in the treatment of patients with aggressive NHL is associated with poor response and overall survival rates. Reductions in average relative chemotherapy dose intensity (ARDI) compromise patient outcomes [20]. A Belgian study showed that survival for non-Hodgkin lymphoma patients receiving CHOP-21 was reduced when RDI fell below 90% as median survival was best among patients who received an ARDI of greater than 90% (7.1 years) and was poorer among patients who had an ARDI between 85% and 90% (3.1 years). Previous second and third generation therapies such as MACOP-B, m-BACOD, and ProMACE–CYTaBOM were used to improve the results of DLBCL treatment. However, dose intensity enhancement increased treatment-associated toxicity, and the treatment results did not improve. The results of this study indicated the importance of maintaining the dose intensity and relative dose intensity in the improvement of treatment results [12].

In our patient cohort, the CR rate was 72.3% with DI and RDI of doxorubicin equal to or below the median. However, with DI and RDI above median the CR rate was 86.6% ($p = 0.008$). It was also proved in our study that Cyclophosphamide DI and RDI significantly affected the CR rate, where for DI and RDI below or equal to the median, the CR rate was 69%, while it was 87.7% with DI and RDI above the median (p value 0.001). The OS rate was 74% with DI and RDI of doxorubicin below or equal to median versus 96% in cases with DI and RDI above the median ($p = 0.02$)

For Cyclophosphamide, the OS rate was 72.7% with DI and RDI below or equal to the median versus 96.3% in cases with DI and RDI above the median ($p = 0.014$). Hirakawa et al. reported the OS at 2 years to be significantly higher in patients in whom the ARDI was maintained at 70% or more, while the PFS at 2 years tended to be higher in patients in whom the ARDI was maintained at 70% or more [21], while in our study DFS was not affected by DI and RDI of doxorubicin ($p = 0.35$) or cyclophosphamide ($p = 0.386$). Terada et al. retrospectively evaluated the impact of the RDI of initial R-CHOP on outcome in newly diagnosed DLBCL patients and reported that mortality was affected by RDI of R-CHOP as the initial treatment [22].

Conclusion

This study confirmed that the DI of Cyclophosphamide and Doxorubicin is important in the future treatment regimen plan for DLBCL especially in the high risk cases. In addition to aa-IPI and its elements (performance status, stage & LDH), our study proved extra nodal sites and bulk of the tumor as significant predictors and prognostic factors for DLBCL treatment outcome.

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