Original Article

Non-anthracycline chemotherapy associated with a poor outcome in elderly Egyptian patients with diffuse large B-cell non-Hodgkin lymphoma

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ABSTRACT

Aim: Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) is the standard treatment for patients with diffuse large B-cell non-Hodgkin lymphoma (DLBCNHL). Nevertheless, anthracyclines are contraindicated for some patients, e.g. cardiac dysfunction, severe hepatic dysfunction, jaundice. Thus, this study assessed the effectiveness of non-anthracycline chemotherapy regimen cyclophosphamide, vincristine, and prednisone (CVP) in elderly DLBCNHL patients *vs*. the standard CHOP. **Methods:** This retrospective study included 418 DLBCNHL patients diagnosed between 2003 and 2006 and followed until March 2014. During this period of time, rituximab was not available for all patients, particularly for patients older than 60 years. **Results:** CHOP and CVP were administered to 351 (84%) and 67 (16%) patients, respectively. Older age and comorbidities, particularly cardiovascular and diabetes mellitus, were independent determinants for not receiving CHOP. Patients received more courses of CHOP treatment than that of CVP (6 *vs*. 3 courses; $P < 0.001$) and developed more toxicities (48.4% *vs*. 23.9%; $P < 0.001$), particularly fatigue, alopecia, and gastrointestinal tract toxicities. Complete response rate was higher in CHOP than in CVP (69.9% *vs*. 29.9%; $P < 0.001$). Moreover, early death was significantly higher in CVP group of patients than in CHOP (43.3% *vs*. 8.6%; $P < 0.001$). After a median follow-up of 71 months, the median overall survival (OS) and event-free survival (EFS) were significantly better in CHOP than in CVP (49.5 *vs*. 3.7 months and 32.2 *vs*. 3.5 months; $P < 0.001$ for both, respectively). Older age, poor age-adjusted International Prognostic Index scores, not receiving CHOP or consolidative radiotherapy were independent predictors of poor OS and EFS. **Conclusion:** Use of the CVP regime to treat DLBCNHL patients who were unfit to the standard CHOP treatment was associated with lower remission rates and poorer EFS and OS in this group of patients.

Key words: Non-Hodgkin's lymphoma, diffuse large B-cell, anthracycline, chemotherapy, treatment

Introduction

Non-Hodgkin's lymphoma (NHL) was the 10th most commonly diagnosed cancer and the 9th cause of cancer mortality in the world in 2012.[1] In Egypt, NHL was the 4th most common cancer in males and 5th in females and the 5th cause of cancer mortality.[1,2] NHL is a diverse group of malignancies with different clinical and biological features.[3] Diffuse large B-cell NHL (DLBCNHL) is the most common NHL type in the world, accounting for 30% of NHL and 80% of its aggressive subtypes.[4] In Egypt, DLBCNHL accounts for 44.5% of lymphoid malignancies in a population-based cancer registry[5] and 50% of NHL subtypes at the Egyptian National Cancer Institute.[6] DLBCNHL treatment mostly relies on multi-agent combination chemotherapy.[7] The addition of the anti-CD20 monoclonal antibody rituximab to the chemotherapy combination dramatically improved overall survival (OS).[8,9] Anthracyclines, particularly doxorubicin are an integral component of these combination chemotherapy regimens, e.g. cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP); procarbazine, methotrexate, doxorubicin, cyclophosphamide, etoposide-cytarabine, bleomycin, vincristine, methotrexate; methotrexate-bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone; methotrexate, doxorubicin, cyclophosphamide, vincristine, dexamethasone, bleomycin, and many others.[10] Intensive chemotherapy with more agents failed to show additional benefit, and the CHOP regimen was concluded to be the best available for patients with intermediate and high-grade NHL, including DLBCNHL.[7] Reductions in dose intensity clearly determine treatment efficacy.[11] However, patients with older age, comorbidities, particularly cardiovascular, and expected higher morbidity and mortality may hinder the use of an anthracycline.[12,13] Compared to

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anthracycline-containing regimens, the 3-year OS is almost halved when a non-anthracycline-containing regimen is used with an absolute survival reduction of 23%.[12]

Thus, the aim of this retrospective study was to investigate the effectiveness of non-anthracycline chemotherapy regimen on elderly DLBCNHL patients by mainly focusing on geriatric organ dysfunction, frailty and comorbidities *vs*. suboptimal treatment with the cyclophosphamide, vincristine, and prednisone (CVP) *vs*. the standard CHOP to assess the factors that impact the regimen choice.

Methods

Study population

This retrospective clinical study included 418 patients with a confirmed DLBCNHL diagnosis at Tanta Cancer Center, Gharbiah, Egypt between 2003 and 2006. Diagnosis of DLBCNHL was based on histology and immunohistochemical data on CD19, CD20, and CD 22 expression. Patients were treated with either CHOP chemotherapy regimen (cyclophosphamide 750 mg/m^2 intravenous (IV) on day 1, doxorubicin 50 mg/m^2 IV on day 1, vincristine 1.4 mg/m^2 (maximum 2 mg) IV on day 1 and prednisone 100 mg p.o. for 5 days) or CVP regimen (same as CHOP without doxorubicin) and followed-up until March 2014 via phone conversation. Response to therapy was assessed using the response criteria developed by the lymphoma International Working Group.[14] OS is calculated from the date of diagnosis to the date of death from any cause or last follow-up. Event-free survival (EFS) was calculated from the date of starting treatment to the date of relapse, progression, death or last follows up.[14] Clinicopathological data were extracted from patients' medical records. This study was approved by the Institutional Review Board of the Egyptian National Cancer Institute.

Statistical analyses

Statistical analyses were performed using IBM SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA). Nominal and categorical variables were compared using the Chi-square or Fisher's exact test. Numerical variables were compared using *t*-test or Man-Whitney's test. Multivariate logistic regression was used to describe the use of CHOP or CVP, controlling for patient covariates. Unadjusted survival was estimated using the Kaplan-Meier method and groups were compared using the log-rank test. Stepwise Cox regression hazards model was used for calculating adjusted survival for each treatment, controlling for patients covariates. A probability $P \leq 0.05$ was considered statistically significant. The primary endpoint was OS. The secondary endpoint included EFS, complete response (CR) rate, and treatment-related toxicities.

Results

Patients' characteristics

CHOP and CVP were administered to 351 (84%) and 67 (16%) patients, respectively. Compared with those receiving CVP, patients receiving CHOP were significantly younger, having less comorbidity, better performance status (PS), fewer B-symptoms, and lower International Prognostic Index-risk (IPI-risk) categories [Table 1]. Logistic regression analysis assessed the impact of different baseline characteristics on the likelihood to receive CHOP or CVP. Only age and comorbidities were independent determinants of the regimen received [Table 2]. Older patients had 10.5 odds of not receiving CHOP compared to the younger patients (95% confidence interval (CI): 4.6-23.6; $P < 0.001$). Patients with comorbidities had 37.2 odds of not receiving CHOP compared to those with no comorbidities (95% CI: 12.6-109.6; $P < 0.001$).

Table 1: Characteristics of 418 DLBCNHL patients

Characteristic	Subgroup	*n* (%)		*P*
		CHOP	CVP	
n		351	67	
Age	Mean ± SD	48.6 ± 13.3	69.7 ± 8.8	< 0.001
	< 70	334 (95.2)	29 (43.3)	
	≥ 70	17 (4.8)	38 (56.7)	< 0.001
LDH	≤ Normal	78 (22.2)	12 (17.9)	
	> Normal	273 (77.8)	55 (82.1)	0.431
Gender	Female	176 (50.1)	30 (44.8)	
	Male	175 (49.9)	37 (55.2)	0.421
Comorbidity	No	289 (82.3)	4 (6.0)	
	Yes	62 (17.7)	63 (94)	< 0.001
Bulky disease	Yes	40 (11.4)	6 (9.0)	
	No	311 (88.6)	61 (91.0)	0.673
PS grouping	0-1	221 (63.0)	21 (31.3)	
	2-4	130 (37.0)	46 (69.7)	< 0.001
Extra-nodal disease	No	232 (66.1)	44 (65.7)	
	Yes	119 (33.9)	23 (34.3)	0.946
Stage	1	68 (19.4)	16 (23.9)	
	2	128 (36.5)	20 (29.9)	
	3	119 (33.9)	23 (34.3)	
	4	36 (10.3)	8 (11.9)	0.701
B symptoms	A	191 (54.4)	27 (40.3)	
	B	160 (45.6)	40 (59.7)	0.034
IPI risk category	Low	85 (24.2)	3 (4.5)	
	Low intermediate	150 (42.7)	15 (22.4)	
	High intermediate	86 (24.5)	18 (26.9)	
	High	30 (8.5)	31 (46.3)	< 0.001
aaIPI groups	0-1	90 (25.6)	17 (25.4)	
	2-3	261 (74.4)	50 (74.6)	0.963

DLBCNHL: Diffuse large B-cell non-Hodgkin's lymphoma; CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP: Cyclophosphamide, vincristine, and prednisone; SD: Standard deviation; LDH: Lactate dehydrogenase; IPI: International prognostic index; aaIPI: Age-adjusted international prognostic index; PS: Performance status

Patients with diabetes mellitus, hypertension, and cardiovascular diseases (e.g. myocardial infarction, heart failure, cerebrovascular stroke) were significantly more common in the CVP group [Table 3]. Among different comorbidities, cardiovascular diseases, and diabetes mellitus were the most significant ones that guided regimen selection. The odds of not receiving CHOP were 125 times higher in patients with cardiovascular diseases compared to those without cardiovascular diseases (95% CI: 48-327; $P < 0.001$). The odds of not receiving CHOP was 9 times higher in patients with diabetes mellitus compared to those without diabetes mellitus (95% CI: 3-28; $P < 0.001$).

Table 2: Multivariate analysis of the factors that impact not receiving CHOP treatment

Variables in equation	OR (95% CI)	*P*
Age (≥ 60 *vs*. < 60 years)	10.5 (4.6-23.6)	<0.001
Comorbidity (yes *vs*. no)	37.2 (12.6-109.6)	<0.001

CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisone; CI: Confidence interval; OR: Odds ratio

Table 3: Comorbidities among DLBCNHL patients receiving CHOP or CVP

Comorbidity	Sub-group	*n* (%)		*P*
		CHOP	CVP	
Diabetes mellitus	No	330 (94.0)	43 (64.2)	
	Yes	21 (6.0)	24 (35.8)	<0.001
Hypertension	No	345 (98.3)	60 (89.6)	
	Yes	6 (1.7)	7 (10.4)	0.002
Cardiovascular	No	340 (96.9)	15 (22.4)	
	Yes	11 (3.1)	52 (77.6)	<0.001
Renal impairment	No	347 (98.9)	64 (95.5)	
	Yes	4 (1.1)	3 (4.5)	0.085
Liver disease	No	331 (94.3)	64 (95.5)	
	Yes	20 (5.7)	3 (4.5)	1.000
Others*	No	343 (97.7)	61 (91.0)	
	Yes	8 (2.3)	6 (9.0)	0.014

*Include bronchial asthma, chronic obstructive airway disease, thyroid dysfunction, ulcerative colitis, rheumatoid arthritis, and systemic lupus erythematous. DLBCNHL: Diffuse large B-cell non-Hodgkin's lymphoma; CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP: Cyclophosphamide, vincristine, and prednisone

Treatment responses and toxicities

Patients with CHOP treatment received more chemotherapy cycles than those treated with CVP (median 6 and 3 cycles, respectively; $P < 0.001$; Table 4). CR rate was higher in CHOP-treated patients than in CVP-treated patients (69.9% *vs*. 29.9%; $P < 0.001$). More patients received radiotherapy after CHOP treatment achieved CR than CVP-treated patients (22.2% *vs*. 3%; $P = 0.001$; Table 3). Compared to CVP, CHOP was associated with significantly higher toxicities (48.4% *vs*. 23.9%; $P < 0.001$), particularly fatigue, alopecia, and gastrointestinal tract toxicities. However, early deaths following one or two chemotherapy courses were significantly higher in patients with CVP treatment than with CHOP treatment (43.3% *vs*. 8.6%; $P < 0.001$).

Overall survival and event-free survival

The median EFS was 22 months (range: 1.0-104.7 months; 95% CI: 16.7-27.4 months) in these patients [Figure 1]. The 2- and 5-year EFS rates were 47.8% and 30.4%, respectively. However, compared to CVP, CHOP was associated with significantly better EFS (median of 32.2 *vs*. 3.5 months; $P < 0.001$). After 5 years, no CVP-treated patients were event-free compared to 36% of CHOP-treated patients [Table 5]. The EFS was also significantly better in patients who were younger than 60 years, females had no comorbidities or B symptoms, good PS, lower stages, or lower IPI scores or those who received consolidative radiotherapy. Multivariate analysis showed that age > 60 years old, poor age-adjusted IPI (aaIPI) scores, and not receiving CHOP or radiotherapy were independent predictors for poor EFS [Table 6].

The median follow-up period of time was 71 months (range between 1.0 and 111.7 months;

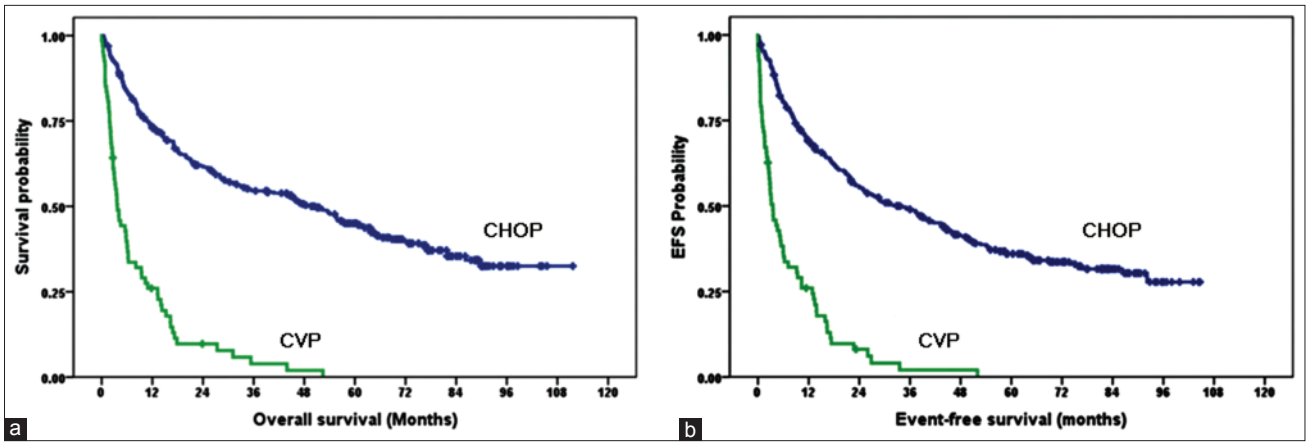

Figure 1: Kaplan-Meier curves of overall survival (OS) and event-free survival stratified by CHOP and CVP regimes. (a) OS of DLBCNHL patients after receiving CHOP or CVP treatment; (b) event-free survival of DLBCNHL patients after receiving CHOP or CVP therapy. CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCNHL: Diffuse large B-cell non-Hodgkin lymphoma; CVP: Cyclophosphamide, vincristine, and prednisone

Table 4: First-line treatments administered to DLBCNHL patients according to their age

Characteristic	Sub-group	*n* (%)		*P*
		CHOP	CVP	
No cycles 1st	Median (range)	6 (1-9)	3 (1-8)	<0.001
Toxicity	No	181 (51.6)	51 (76.1)	
	Yes	170 (48.4)	16 (23.9)	<0.001
Early death*	No	321 (91.4)	38 (56.7)	
	Yes	30 (8.6)	29 (43.3)	<0.001
Fatigue	No	230 (65.5)	61 (91)	
	Yes	121 (34.5)	6 (9)	<0.001
Alopecia	No	230 (65.5)	62 (92.5)	
	Yes	121 (34.5)	5 (7.5)	<0.001
Anemia	No	333 (94.9)	67 (100.0)	
	Yes	18 (5.1)	0 (0)	0.092
Neutropenia	No	317 (90.3)	63 (94.0)	
	Yes	34 (9.7)	4 (6.0)	0.486
Thrombocytopenia	No	343 (97.7)	67 (100)	
	Yes	8 (2.3)	0 (0)	0.365
GIT*	No	319 (90.9)	67 (100.0)	
	Yes	32 (9.1)	0 (0)	0.005
Skin	No	346 (98.6)	67 (100.0)	
	Yes	5 (1.4)	0 (0)	1.000
DVT	No	345 (98.3)	67 (100.0)	
	Yes	6 (1.7)	0 (0)	0.595
Liver	No	345 (98.3)	67 (100.0)	
	Yes	6 (1.7)	0 (0)	0. 595
Response group	CR	245 (69.8)	20 (29.9)	
	No CR	106 (30.2)	47 (70.1)	<0.001
Radiotherapy	No	273 (77.8)	65 (97.0)	
	Yes	78 (22.2)	2 (3.0)	0.001

*Early death after 1-2 courses of chemotherapy (response was not assessed). DLBCNHL: Diffuse large B-cell non-Hodgkin's lymphoma; CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP: Cyclophosphamide, vincristine, and prednisone; CR: Complete remission; PR: Partial remission; SD: Stable disease; GIT: Gastrointestinal toxicity in the form of either: mucositis, diarrhea or constipation; DVT: Deep venous thrombosis

95% CI: 66.3-75.0 months) [Figure 1]. At the last follow-up, 263 patients were deceased (199 in the CHOP group and 64 in the CVP group). The median OS rate was 28.6 (95% CI: 17.0-40.2) for this cohort of patients. However, the median OS rate was significantly longer in CHOP-treated patients than that of CVP-treated patients (49.5 *vs*. 3.7 months; $P < 0.001$; Table 5). The median OS rate was also significantly longer in young patients without comorbidities, bulky disease or B symptoms, good PS, lower stages, and IPI or aaIPI scores or patients who received consolidation radiotherapy. The multivariate analysis showed that age > 60 years, poor aaIPI scores, and not receiving CHOP or radiotherapy were independent predictors of poor OS [Table 6].

Discussion

Since its development in the late 1960's, doxorubicin has been firmly established as the most effective single agent in the treatment of malignant lymphoma.[15,16] The CHOP regime was invented in the late 1970's and after its efficacy in NHL was established, it became the standard of care as it produced high CR rate and durable effects.[15,17] Its known adverse effects mainly affect the cardiovascular system.[15,16,18] Reduction of inter-treatment intervals (CHOP-14) and the addition of rituximab (R-CHOP) were shown to improve treatment outcomes.[16] CHOP-14 does not appear to be superior to CHOP-21 when given with rituximab, but associates with increased toxicities, including an increased risk of Pneumocystis Jiroveci Pneumonia. Use of R-CHOP-21 is recommended rather than R-CHOP-14. This is primarily due to decreased need for growth factor support, and a lack of data showing the superiority of one regimen over another in the rituximab era. More intensive chemotherapy or additional agents have failed to show additional benefit.[7] However, elimination of anthracycline from the treatment regimen reduced the CR rate, duration of response and disease stabilization, and OS.[12,13]

In the current study, 16% of DLBCNHL patients (67/418) did not receive anthracycline, whereas other studies showed a higher percentage (20-67%) as they only included patients aged 66 years or older.[12,19,20] However, Link *et al.*[18] reported a lower percentage in an older population. Different studies in the different period of time and inclusion criteria may explain this variance. The rate of anthracycline use in the treatment of DLBCNHL did not vary with time, that is, between the pre-rituximab era and the post-rituximab era.[18] Furthermore, similar to other studies,[18,19,21] our current study showed that older age and comorbidities were strong indictors of treatment regimen selection without doxorubicin in addition to cardiovascular diseases and diabetes mellitus but the lower relevance of kidney and liver disease.[19] Pre-therapy heart disease, diabetes, hypertension, and older age were reported to be independent predictors of cardiotoxicity and subsequent death from the same cause.[22-24] Our results also concur with those of van de Schans *et al.*[25] and Peters *et al.*[26] regarding the impact of poor PS and estimated short survival on the likelihood of treatment regimens without anthracycline. We showed that early death, that is, following 1-2 chemotherapy courses was encountered more in the non-anthracycline group (43.3% *vs.* 8.6%). Expected higher toxicities are another important reason. While this is difficult to assess quantitatively before therapy is given, it was confirmed by the higher rates of toxicities in the CHOP compared to the CVP group (48.4% *vs.* 23.9%).

The lower response rate with the CVP regimen without anthracycline than anthracycline-containing CHOP regimen confirms the established fact that anthracycline is the most active single agent in the treatment of lymphoma.[12,13,15,16] In the current study, doxorubicin contributed almost 40% of the CRs exceeding the

Table 5: EFS and OS of 418 DLBCNHL patients

Group	*n*	EFS				OS			
		Median	2-year rate	5-year rate	*P*	Median	2-year rate	5-year rate	*P*
All	418	22.0	47.8	30.4		28.6	53.3	37.9	
First line chemotherapy									
CHOP	351	32.2	55.3	36.0		49.5	61.8	45.0	
CVP	67	3.5	8.1	0	<0.001	3.7	9.7	0	<0.001
Age (years)									
< 60	297	39.4	59.6	39.9		57.4	67.0	49.6	
≥ 60	121	6.3	18.2	5.7	<0.001	6.0	19.0	6.3	<0.001
Gender									
Male	212	17.8	43.6	25.0		25.0	50.0	35.6	
Female	206	26.8	52.2	35.9	0.032	43.0	56.7	40.3	0.188
Comorbidities									
No	293	35.2	56.0	36.2		53.7	63.3	46.4	
Yes	125	7.2	28.4	16.4	<0.001	8.0	28.8	16.7	<0.001
Bulky disease									
Yes	46	13.9	34.8	24.6		17.0	43.5	31.2	
No	372	23.9	49.5	31.1	0.178	31.1	54.6	38.8	0.407
B symptoms									
A	218	28.8	54.7	36.4		46.2	60.0	42.8	
B	200	16.0	40.2	32.6	0.002	18.0	45.8	32.6	0.003
PS									
0-1	242	41.2	59.7	38.6		55.9	67.0	48.8	
2-4	176	9.7	31.2	18.9	<0.001	10.6	34.2	22.7	<0.001
Extra-nodal									
No	276	22.9	48.8	29.7		31.1	55.2	38.4	
Yes	142	18.0	45.8	31.8	0.738	21.8	49.5	37.1	0.376
Stage									
1.0	84	76.7	63.0	52.2		NR	68.1	5.6	
2.0	148	20.6	45.3	29.2		28.0	52.4	36.8	
3.0	142	19.1	44.4	21.3		25.6	50.3	32.8	
4.0	44	6.9	39.5	19.1	<0.001	8.8	41.9	21.9	<0.001
Stage-group									
1-2	232	26.0	51.6	37.4		44.2	57.3	43.4	
3-4	186	16.3	43.2	20.7	0.001	21.3	48.3	30.7	0.006
IPI-group									
Low	88	NR	72.0	57.6		NR	79.1	65.4	
Low intermediate	165	28.9	54.1	31.3		45.6	62.3	42.2	
High intermediate	104	14.1	39.3	21.3		16.3	42.5	27.2	
High	61	4.6	9.2	0	<0.001	4.6	10.7	0	<0.001
aaIPI									
0-1	107	52.0	62.4	84.2		NR	68.3	54.7	
2-3	311	17.8	42.8	24.1	<0.001	20.5	46.5	32.1	<0.001
Radiotherapy									
No	338	17.2	43.5	26.6		20.0	47.9	32.9	
Yes	80	50.7	66.1	46.0	<0.001	72.5	77.5	58.8	<0.001

EFS: Event-free survival; OS: Overall survival; DLBCNHL: Diffuse large B-cell non-Hodgkin's lymphoma; CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP: Cyclophosphamide, vincristine, and prednisone; PS: Performance status; IPI: International prognostic index; aaIPI: Age adjusted international prognostic index; NR: Not reached

combination of cyclophosphamide, vincristine, and prednisolone (from 29.9% to 69.9%) in DLBCNHL treated solely by chemotherapy. Achieving CR is crucial for long-term survival and cure.[27] Our current study clearly shows that patients are failing to achieve CR only had a median OS of 4.4 months compared to 76.8 months in those who achieved CR with almost 11-fold higher relative risk of death. CHOP-produced CR rates is comparable to those reported by Khaled *et al.*,[28] Burton *et al.*,[29] Hallack Neto *et al.*[30] [Table 7]. However, a large Egyptian study by Abdelhamid *et al.*[6] reported a 10% higher CR rate. This latter study only included younger patients with a maximum age of 60, better PS, and lower aaIPI scores. In contrast, our current

study included older patients with a maximum age of 82, poorer PS, and higher aaIPI scores. Patients that are older and have poor PS frequently received reduced doses or interrupted and delayed therapy. This reduced dose intensity is a key determinant of CR and survival.[6,31]

In the current study, removal of the anthracycline doxorubicin from the CHOP regimen significantly reduced the median OS (unadjusted from 49.5 to 3.7 months, i.e. 45.8 months and adjusted from 44 to 9 months, i.e. 35 months) and the 3-year OS (unadjusted from 54.5% to 3.9% i.e. 50.5% and adjusted from 52% to 19% i.e. 33%) with an increase in the hazards of death by 4 times. This is similar to Tien *et al.*[12] and Link *et al.*[18] who showed a 22% and 16% decline in 3-year OS, respectively [Table 7]. The difference in our study (33%) may be due to the poorer outcome of patients receiving non-anthracycline-containing regimens (19%) compared to that in the mentioned studies (29% and 33%). This may be due to the more developed health care system in the US than Egypt as the former ranks 37th and the latter ranks 63th in overall health system performance.[33] A high performing health care system is capable of providing better supportive therapies for patients that are elderly, having comorbidities and progressing on inadequate anti-lymphoma therapy.

OS with CHOP treatment (52% at 3 years) in the current study is comparable to the 49-57% figure reported by many authors [Table 7],[6,9,12,18] but was lower than the 60-70% OS reported by Habermann *et al.*,[32] Burton *et al.*,[29] and Khaled *et al*.[28] All of these studies performed prospective trials where patients were carefully selected and generally fit to tolerate therapy. It is understandable that results from phase III studies do not always translate into corresponding outcomes in the general population.[18]

Similar to CR and OS, our current data showed that removal of doxorubicin from the CHOP regimen significantly reduced EFS. We could not easily find information on the use of CVP in DLBCNHL to compare our EFS with the studies that comparison of anthracycline-containing regimens to non-anthracycline-containing regimens only showed OS.[12,18] The EFS rate of CHOP treatment in our current study is similar to Sehn *et al.*[9] and Habermann *et al.*[32] However, it was lower than that of Khaled *et al.*[28] and Burton *et al.*[29] This may be explained by the difference in study settings between the well-controlled environment of a clinical trial and the community practice environment. The disease-free survival of our study (75.9% at 2 years) was similar to that of Abdelhamid *et al.*[6] (68.8%) who used a similar setting to our study. It was higher than that reported by Hallack Neto *et al.*[30] This retrospective Brazilian study reported on a relatively small number of

Table 6: Multivariate analysis of EFS and OS in DLBCNHL patients

Variables in equation	EFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (≥ 60 *vs.* < 60 years)	2.1 (1.6-2.9)	< 0.001	2.5 (1.8-3.0)	< 0.001
First line chemotherapy (non-CHOP *vs*. CHOP)	2.6 (1.9-3.7)	< 0.001	2.6 (1.8-3.8)	< 0.001
aaIPI (score 0-1 *vs*. 2-3)	1.8 (1.3-2.5)	< 0.001	2.0 (1.4-2.7)	< 0.001
Radiotherapy (no *vs*. yes)	1.8 (1.3-2.5)	< 0.001	2.1 (1.5-3.1)	< 0.001

DLBCNHL: Diffuse large B-cell non-Hodgkin's lymphoma; CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP: Cyclophosphamide, vincristine, and prednisone; EFS: Event-free survival; OS: Overall survival; HR: Hazard's ratio; CI: Confidence interval; aaIPI: Age-adjusted international prognostic index; IPI: International prognostic index

Table 7: Comparison of treatment outcomes in DLBCNHL patients

Authors	Regimen	*n*	Age	CR (%)	2-year (3-year) EFS/PFS (%)	2-year (3-year) OS (%)
Our current study	CHOP	251	17-82	69.8	55.3 (46.0)	58.0 (52.0)
	CVP	67	45-87	29.9*	18.0 (12.0)*	25.0 (19.0)*
Tien *et al.*[12]	ACR	1090	≥ 66			(52)
	Non-ACR	267	≥ 66			(29)*
Link *et al.*[18]	ACR	2346	≥ 66			59 (49)
	Non-ACR	460	≥ 66			40 (33)*
Abdelhamid *et al.*[6]	CHOP	224	18-60	79.5	2-year DFS: 68.8	57 (57)
Hallack Neto *et al.*[30]	CHOP	77	< 60	68.8	2-year DFS: 61.3	5-year OS: 72.8
Habermann *et al.*[32]	CHOP	279	> 60		(46)	(60)
Sehn *et al.*[9]	ACR	140	19-86		51% (46%)	52 (50)
Khaled *et al.*[28]	CHOP	40	19-75	67	54 (54)	82 (71)
Burton *et al.*[29]	CHOP	105	22-66	70	4-year PFS: 56	4-year OS: 65
	CIOP	106	25-67	52	4-year PFS: 40*	4-year OS: 56#

*$P < 0.05$, #$P \geq 0.05$. EFS: Event-free survival; PFS: Progression-free survival; DFS: Disease-free survival; CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP: Cyclophosphamide, vincristine, and prednisone; ACR: Anthracycline containing regimen; CIOP: Cyclophosphamide, idarubicin, vincristine, and prednisone; CR: Complete response; DLBCNHL: Diffuse large B-cell non-Hodgkin's lymphoma

patients (n = 77) with many poorer prognostic factors than ours.

DLBCNHL is potentially curable after treated with anthracycline-containing regimens; however, a significant proportion of patients do not receive anthracyclines, particularly doxorubicin for various reasons, e.g. older age, expected poor tolerance or significant comorbidities. These patients present an unmet medical need.[12] Measures that may decrease toxicity and improve anthracycline tolerance includes adequate supports (e.g. hematopoietic growth factors), dose reductions, increase in infusion time, the addition of cardio-protectants (e.g. dexrazoxane).[16,18,26,34,35] An alternative less-toxic and more tolerable anthracycline may be considered if feasible, e.g. liposomal doxorubicin,[36,37] epirubicin,[38] mitoxantrone[39] or pixantrone.[40] In case an anthracycline cannot be used, substitution with other agents, e.g. etoposide or gemcitabine may better than omission.[41] Addition of the immunotherapy agent like rituximab to non-anthracycline-containing regimens significantly improves the outcomes and should be considered.[18] Non-anthracycline-containing regimens with the addition of rituximab produced equivalent outcomes to anthracycline-containing regimens.[12,18,19]

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