Role of reduced dose CHOP with Rituximab plus involved field radiotherapy in treatment of early stage diffuse large B –cell lymphoma in elderly patients

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Abstract: Objective: In this research we studied the efficacy and tolerability of chemotherapy with dose reduction (80%-dose CHOP protocol) with Rituximab plus involved field radiotherapy in elderly patients with early stage diffuse large B-cell lymphoma and to study its impact on the outcome. **Method**: Between September 2012 and December 2013, 28 patients from Clinical Oncology and Nuclear Medicine Department, Zagazig University, Egypt, and Medical Oncology Department, Zagazig University, Egypt were included in this prospective study. The eligibility criteria included previously untreated patients with age ≥65 years with diffuse large B- cell lymphoma, stages IA-IIA, good PS 0-2 and received a reduced dose (80%) CHOP (cyclophosphamide 600 mg/m^2, doxorubicin 40 mg/m^2, vincristine 1.1 mg/m^2 and prednisolone 80 mg/day for 5 days),and Rituximab (which is anti- CD20 monoclonal antibody) 375mg/m^2 followed by involved field radiotherapy. Brief cycles of chemotherapy plus Rituximab (three cycles R-CHOP followed by IFRT 30-45 Gy/15-25 Fractions/1.8-2Gy/Fr) are given. The chemotherapy was given every three weeks. **Results**: Twenty eight patients with stage IA and IIA diffuse large B-cell lymphoma, were enrolled in this study, 25 patients completed full course of treatment with mean age was 69.7±2.02, 88.0% (22 patients) of the patients had complete response,8.0% (2 patients) of the patients had partial response and stationary disease presented in only one patients (4.0%). 20.0% of the patients (5 patients) had systemic relapse,12.0% of the patients (3 patients) died with a median survival was 13 month, 95% confidence interval {CI 95 % (8.706-17.294)}, 2-y OS was 88% and 2-y DFS was 80%. **Conclusion:** Elderly patients with early stage DLBCL must be treated with standard dose chemotherapy regimen plus Rituximab (R-CHOP) followed by IFRT in association with vigorous supportive care if patient can tolerate, and reduced dose intensity used in addition to Rituximab if patient cannot tolerate the full dose to get maximum benefit.

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1. Introduction

The classical definition of elderly patients is those older than 65 years, they represents more than 20% of the global population (1). Non Hodgkin's lymphoma (NHL) is the fifth most common cancer in men and the sixth in women. Diffuse large B-cell lymphoma (DLBCL) is the most frequent NHL, representing more than 40% of lymphomas in the elderly (2, 3).

Age has always affects the prognosis, because this age is associated with the presence of concomitant diseases, it clearly affects therapeutic decisions (4). Comorbidities are common in elderly patients as opposed to 20% in younger patients which leads to higher risk of treatment toxicity and death (4). Bone marrow reserve capacity is impaired and myelotoxicity of standard chemotherapy has been shown to be more severe in the elderly (5).

The comprehensive geriatric assessment (CGA) is a multidimensional diagnostic tool that evaluates risks of morbidity in elderly patients (6). Elderly patients have a decreased tolerance to chemotherapy, higher risks of treatment complications, lower treatment responses and shorter survival (6-7). Many of these patients receive suboptimal (schedule / dosing) chemotherapy (8). On the other hand, other prospective trials showed improvement of complete response rate, event free survival and overall survival for elderly patients with diffuse large B – cell lymphoma (DLBCL) (60 – 80 y) who received full dose R – CHOP (Rituximab – Cyclophosphamide – Adriamycin – Vincristine – Prednisolone) in comparison to standard full dose CHOP regimen without a clinically significant increase in toxicity. (9–10).

The study by the Grouped, Etude des Lymphomes de L' Adult recommended that R – CHOP combination should become the standard for treating these elderly patients (10). In general, patients participating in prospective clinical trials do not have severe co-morbidities and have good performance status, so it is safe to give these patients

full-dose chemotherapy (11). The gap between prospective clinical trials and clinical practice should be reduced to improve the level of clinical practice for elderly patients with NHL (11). A prospective study was done to evaluate the administration of reduced dose 80% three courses CHOP followed by involved – field radiotherapy (IFRT) 30 – 50 GY in 15 – 28 fraction for patients with localized (stage I A, or contiguous nonbulky stage II A) aggressive NHL, aged 70 – 84 years. It revealed that 3y progression free survival (3-y PFS) and 3 – years overall survival rates were 83.1% and 82.9% respectively and concluded that this regimen may be safe for elderly patients and advised to investigate the addition of rituximab to reduced dose CHOP. (12).

The aim of our study is to evaluate the efficacy and tolerability of addition of Rituximab to 80% dose CHOP plus involved field radiotherapy in elderly patients with early stage diffuse large B-cell lymphoma and to study its impact on the outcome.

2. Patients and Methods

Between September 2012 and December 2013, 28 elderly patients (≥65 years) with localized DLBCL, from Clinical Oncology and Nuclear Medicine Department, and Medical Oncology Department, Zagazig University, Egypt were included in this prospective study. The eligibility criteria included previously untreated patients with age (≥65 years), localized DLBCL with stage IA and IIA, and good (0–2) performance status according to the Eastern Cooperative Oncology Group (ECOG) classification. The exclusion criteria were past history of cancer during the previous 5 years, liver &renal impairment, human immunodeficiency virus infection, hepatitis B virus or hepatitis C virus infection, severe ischemic heart disease or cardiomyopathy. The staging procedures included clinical examination, CBC with differential count, liver function test, renal function test, LDH, ESR, computed tomography (CT) of the neck, chest, abdomen and pelvis; bone marrow biopsy, ECHO cardiography.

All patients gave a written informed consent prior to entry into the study.

Treatment

The chemotherapy was (80%-dose CHOP protocol) as follow, cyclophosphamide 600 mg/m2 (day 1), doxorubicin 40 mg/m2 (day 1), vincristine 1.1 mg/m2 (day 1) and oral prednisolone 80 mg/day (for 5 days), and Rituximab (which is anti- CD20 monoclonal antibody) 375mg/m^2 (day 1). Brief cycles of immunochemotherapy (three cycles R-CHOP) followed by IFRT. The immunochemotherapy was given every three weeks. If Grade 4 neutropenia or febrile neutropenia developed, granulocyte colonystimulating factor support was used in all the subsequent cycles.

The involved field radiotherapy was given 3 weeks after the last cycle of R-CHOP. For example unilateral or bilateral neck nodes irradiation including supraclavicular region extending from skull base to clavicle(s). Treatment of axillary, supraclavicular, and infraclavicular nodes extend from C5-C6 interspace superiorly to tip of scapula or 2 cm below most inferior node inferiorly. The medial border is ipsilateral transverse process and the lateral border is Flash axilla. The radiation dose was 30-30.6 Gy given in 15-20 Fractions over 3-4 weeks (1.8-2Gy/Fr) in patients who achieved a complete response (CR) and 40–45 Gy in 20–25 fractions (1.8-2Gy/Fr) over 4–6 weeks for those who did not achieve CR.

Response was assessed using Cheson's criteria (13). The follow up period was 2 years where clinical examination and CT neck, chest and pelvi-abdomen, CBC, LFT, KFT, ESR, LDH were done every 3 months.

Outcome Measures

The endpoints of this study were overall survival (OS), Disease-free survival (DFS) and pattern of relapse. OS rate was calculated from the date of study registration to the date of death from any cause. DFS is measured from the time of occurrence of disease-free state or attainment of a CR to disease recurrence or death as a result of lymphoma or acute toxicity of treatment. The National Cancer Institute Common Toxicity Criteria grading system, version 4.0 was used to assess the toxicity. The Kaplan–Meier method was used for calculation of OS and PFS rates. Tumor responses were classified as CR, partial response (PR), stable disease or progressive disease according to the proposed International Workshop criteria **(13).**

3. Result

Between September 2012 and December 2013 we studied 28 patients enrolled in this study with characters shown in (table 1), mean age was 69.7±2.02. Regarding the sex, male patients represent 46.0 % (13 patients) of the studied group and female patients represent 54.0 % (15 patients).PS 0-1 was the most common 25% (7 patients) of the patients While PS 2 was 75 % (21 patients) of the patients. Stage I was the majority as it represents about two thirds of studied group 68.0 % (19 patients) and 32.0 % (9 patients) of studied group was stage II. Regarding LDH, 18.0 % (5 patients) were >ULN <1.5ULN and 82.0% (23 patients) were ≤ULN. Axillary LN were the most common site followed by neck, inguinal LN, and thyroid which represent 43.0% (12 patients), 32.0% (9 patients), 21.0% (6 patients), and 4.0% (1 patient) respectively. Regarding IPI, 61.0 % (17 patients) were (IPI I), 32.0 % (9 patients) were (IPI II)

and 7.0% (2 patients) were (IPI III). 78.0% (22 patients) of the patients had size distribution less than or equal 6 cm, 11.0% (3 patients) of the patients had size distribution >6cm and < 10cm and size ≥10cm presents in 11.0% (3 patients) of the patients.

Response

Three patients did not complete the full course of therapy because of liver decompensation one patient after 1st cycle and 2 after the second cycle so they were excluded from the statistics of the results, while there was delay in receiving chemotherapy in 19 patients because of prolonged neutropenia but this was avoided by G-CSF support when needed so 25 patients complete our protocol.

A total of 88.0% (22 patients) of the patients had complete response, 8.0% (2 patients) of the patients had partial response and stationary disease presented in only one patient (4.0%). During the follow-up period 12.0% of the patients (3 patients) died one had pulmonary embolism, one died of myocardial infarction and the last one of unknown cause. 20 % (5 patients) of the studied group had systemic relapse. These systemic relapsed patients were treated with systemic chemotherapy. No local relapse was observed during follow up period (Table 2).

Table 1: Patient Characteristics:

		NO	%
Age mean ±SD	69.7±2.02	28	100
Sex	Female	15	54.0
	Male	13	46.0
PS	0-1	7	21.0
	2	21	75.0
Stage	I	19	68.0
	II	9	32.0
LDH	≤ULN	23	82.0
	>ULN <1.5ULN	5	18.0
	≥1.5 ULN	0	0.0
Site	AXILLARY LN	12	43.0
	INGUINAL LN	6	21.0
	NECK LN	9	32.0
	THYROID	1	4.0
IPI	I	17	61.0
	II	9	32.0
	III	2	7.0
Size	≤6cm	22	78.0
	≥10cm	3	11.0
	>6cm - <10cm	3	11.0

Toxicity

Regarding the toxicity all patients developed neutropenia, 64% of them were grade3-4, 12 patient had febrile neutropenia, while 60% developed thrombocytopenia, 8% were G3-4, 23 patient had anaemia, one patient was grade 3-4, Radiotherapy induced mucositis 24% (6 patients), one patient had G 3-4.

Outcome and Survival

Comparing survived and died patients regarding patient characteristics, we found no significant association between any characters and death except response (Table 3). But after comparing relapsed and non-relapsed patients in relation to patient characteristics, we found no significant association between any characters and relapse (Table 5). 2-y OS was 88% and 2-y DFS was 80%.

By using Kaplan-Meier method for overall survival, we found that median of survival was 13 month, 95% confidence interval [CI 95 % (8.706, 17.294) (figure 1) and (table 4).

Table 2: outcome:

		NO		%	
Response	CR	22		88.0	
	PR	2		8.0	
	Stationary	1		4.0	
Toxicity		Any Grade		Grades 3-4	
		NO	%	NO	%
	Neutropenia	25	100	16	64
	Febrile neutropenia	12	48	12	48
	Thrombocytopenia	15	60	2	8
	Anaemia	23	92	1	4
	Mucositis	6	24	1	4
Death	Death	3		12.0	
Relapse	local	0		0.0	
	Systemic	5		20.0	

Table 3: correlation between patient characteristics, response and survival:

		Survived patients (22)		Died patients (3)		P
		N	%	N	%	
Sex	F	12	54.54	1	33.33	0.49
	M	10	45.45	2	66.66	
Age	Mean± SD	68.7±4.3		72.1±5.3		0.06
PS	0-1	4	18.18	2	66.66	0.06
	2	18	81.81	1	33.33	
STAGE	I	15	68.18	2	66.66	0.95
	II	7	31.81	1	33.33	
LDH	≤ULN	19	86.3	2	66.66	0.7
	>ULN <1.5ULN	3	13.63	1	33.33	
	≥1.5ULN	0	0.0	0	0.0	
SITE	Axillary LN	9	40.90	1	33.33	0.86
	Inguinal LN	5	22.71	1	33.33	
	Neck LN	7	31.81	1	33.33	
	Thyroid	1	4.54	0	0.0	
IPI	I	15	68.18	1	33.33	0.19
	II	6	27.27	1	33.33	
	III	1	4.54	1	33.33	
Size	≤6cm	20	90.9	0	0.0	0.11
	≥10cm	0	0.0	2	66.66	
	>6cm - <10cm	2	9.1	1	33.33	
Response	CR	21	95.45	1	33.33	0.003*
	PR	1	4.54	1	33.33	
	Stationary	0	0.0	1	33.33	
Total		22	100.0	3	100.0	

*Sig association between response and death

Table 4: Means and Medians for Survival Time

	Estimate	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Mean	14.200	2.853	8.608	19.792
Median	13.000	2.191	8.706	17.294

Table 5: relation between patients' characteristics, response and relapse:

		No relapse(20)		Relapse(5)		P
		N	%	N	%	
Sex	Female	11	55.0	2	40.0	0.54
	Male	9	45.0	3	60.0	
PS	0-1	5	25.0	1	20.0	0.8
	2	15	75.0	4	80.0	
STAGE	I	15	75.0	2	40.0	0.13
	II	5	25.0	3	60.0	
LDH	≤ULN	18	90.0	3	60.0	
	>ULN <1.5ULN	2	10.0	2	40.0	0.1
	≥1.5ULN	0	0.0	0	0.0	
SITE	Axillary LN	8	40.0	2	40.0	0.29
	Inguinal LN	5	25.0	1	20.0	
	Neck LN	7	35.0	1	20.0	
	Thyroid	0	0.0	1	20.0	
IPI	I	13	65.0	3	60.0	0.5
	II	6	30.0	1	20.0	
	III	1	5.0	1	20.0	
Size	≤6cm	17	85.0	3	60.0	0.4
	≥10cm	1	5.0	1	20.0	
	>6cm - <10cm	2	10.0	1	20.0	
RESPONSE	CR	19	95.0	3	60.0	0.058
	PR	1	5.0	1	20.0	
	Stationary	0	0.0	1	20.0	
Total		20	100.0	5	100.0	

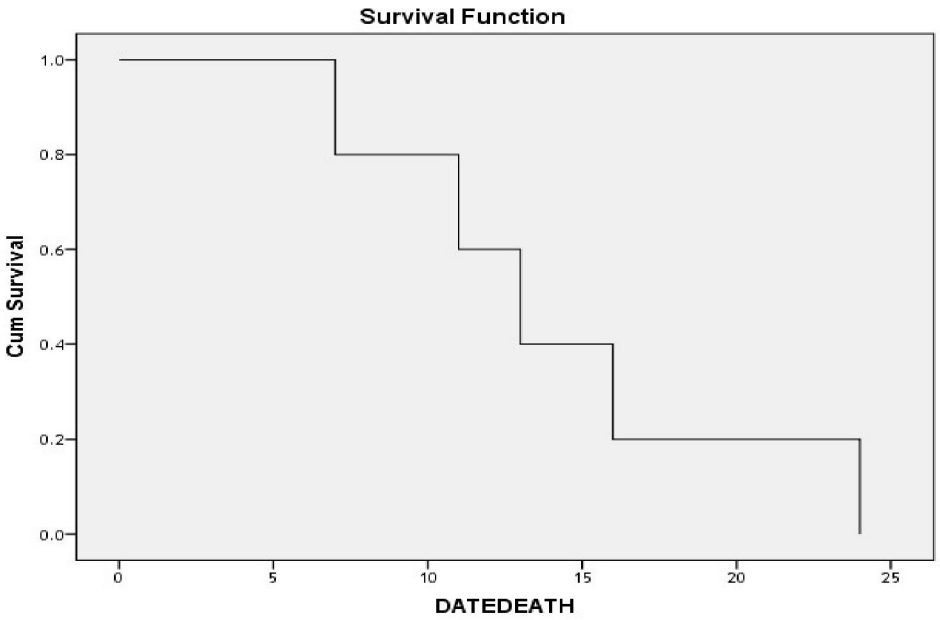

Figure 1: Kaplan-Meier for all death (overall survival)

4. Discussion

Despite more than 50% of cancer cases occur in elderly patients (>60y), they are underrepresented in clinical trials as they are excluded from most studies due to the difference in their tolerability to aggressive treatment, increased liability to toxicity due to the presence of other co morbidities in this age group, so the patients and physician prefer less toxic treatment (11).

The traditional assessment of functional status of the patients depend on the Karnofsky or Eastern Cooperative Oncology Group (ECOG) performance status, but the assessments done by a geriatrician include the assessment of ability of the elderly patients to live in the community (Activities related to Daily Living (ADLs) and instrumental activities of daily living (IADLs scale). CGA predicts survival, tolerance to chemotherapy, and mortality, independently from the PS (14).

In the past decade, the standard of care initial therapy for older DLBCL patients, as well as younger with favorable prognostic characteristics, was RCHOP (15). In the Groupe d'Etude des Lymphomes de l'Adulte (GELA) trial, treatment-naïve DLBCL patients, age 60–80 years, were randomized to RCHOP or CHOP therapy, with CR rates of 76% and 63% (P = 0.005)(16).

The GELA trial included patients aged 60–80 years with at least one other adverse prognostic factor (17). With median follow-up of 56 months, 3-year PFS did not differ by treatment (R-CHOP14, 60%; RCHOP21, 62%, *P* = 0.04), nor did 3-year OS (69% and 72%, respectively, *P* = 0.7487); side-effects were comparable (18).

In a retrospective review, 308 patients, median age 64 years, with stage I (61%) or non-bulky IIA disease received three cycles of doxorubicin-based chemotherapy followed by IFRT (19). Outcomes were similar to SWOG 8736, with 5- and 10-year PFS of 94%/89% (no risk factors), 79%/73% (1–2 factors), and 60%/50% (3–4 factors), using the Miller-modified IPI. Corresponding OS was 97%/89% (no factors), 77%/56% (1–2 factors), and 58%/48% (3–4 factors) (20).

The role of IFRT to bulky disease sites in elderly patients (age 61–80 years) was reported from the RICOVER-60 trial (21). Patients receiving six cycles of R-CHOP, followed by two additional rituximab doses, then IFRT to sites of initial bulky (≥7.5 cm) disease and extra-lymphatic involvement, were compared with those who received therapy without IFRT. EFS was superior with IFRT (P = 0.005); there were trends for superior PFS and OS in those receiving IFRT. The use of IFRT thus abrogated bulky disease as a risk factor.

In a retrospective review of 469 patients (40% stage I–II, 60% stage III–IV) who received IFRT after RCHOP, 5-year PFS (90% versus 75%) and OS (91% versus 83%) were superior with IFRT (22). In limited stage patients, 5-year PFS and OS were 82% and 92%, respectively, with R-CHOP followed by IFRT, compared with 68% and 73%, respectively, with RCHOP alone. In a SEER-based review of 13 000 limited stage patients of whom 41% received radiation therapy, improvement in DFS and OS was seen (23).

The use of IFRT improves local disease control and reduces relapses at original disease sites (24). This is confirmed in our study as recurrence was found in 20% of patients, none of them was local recurrence, so IFRT improve local control.

Our study enrolled 28 patients, 25 patients completed the designed 3 cycle of reduced dose RCHOP followed by IFRT, 88 % achieved CR. That is better than that achieved by Shikama et al., 2011 who used reduced dose of CHOP who reported 79% CR that was inferior to our results while The 7-year OS and PFS rates were 78.9% [95% confidence interval (CI), 62.3–95.5] and 65.3% (95% CI, 45.3–85.3), respectively, the improvement in response rate can be attributed to the effect of rituximab (11).

2 years Dfs was 80% that was inferior to that in Southwest Oncology Group (SWOG) trial 0014, 8736 where PFS at 2 years on S8736 (CHOP X 3 + IFRT) was 85% (95% CI, 77% to 94%) compared with 93% on S0014, respectively. For OS, the 2year estimate was 93% (95% CI, 86% to 99%) for S8736 (historical control group) versus 95% for S0014 compared to 88% in our study this may be due to the 20% reduction in the dose of the chemotherapy in our protocol (20, 25).

Regard the toxicity hematological toxicity more in our study where 100% of our patients developed neutropenia compared to 90% in S0014, with G3-4 similar in both groups 64% vs 65% in SOO14, but febrile neutropenia was more in our group where 48% of our patients compared to 15% in S0014, also thrombocytopenia 60% vs 25% in S0014 and anaemia 92% VS 65% in S0014 was because of the difference in PS also friability of our patients also we used reduced dose of CHOP as we suspect that this is the best way to tailor the therapy according to the tolerability capacity of our patients (25).

So patients in the former trials who received full dose of CHOP either with or without Rituximab had better PFS, OS than patients with reduced dose. Also the addition of Rituximab to the reduced dose improve response rate.

In this study we treated stage IA and IIA DLBCL in elderly patients with three cycles of R-

CHOP followed by IFRT the median of survival was 13 months, 95% confidence interval (95% CI 8.706-17.294). The significant association between response and death may be due to small number of patients in my study.

Conclusion:

Elderly patients with early stage DLBCL must be treated with standard dose chemotherapy regimen plus Rituximab (R-CHOP) followed by IFRT in association with vigorous supportive care if patient can tolerate, and reduced dose intensity used in addition to Rituximab if patient cannot tolerate the full dose to get maximum benefit.

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