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RESEARCH ARTICLE

Analysis of the Treatment of Diffuse Large B-Cell Lymphoma in Patients with Preexisting Systolic and/or Diastolic Dysfunction at Moffitt Cancer Center

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Abstract

Introduction: The treatment of choice for newly diagnosed patients with advanced Diffuse Large B Cell Lymphoma (DLBCL) is R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine And Prednisone). However older patients frequently have concomitant cardiac comorbidities that preclude the use of these agents.

Methods: A search of the Moffitt Total Cancer Care™ database identified 854 adult patients with DLBCL. We performed a retrospective chart review and identified 38 individuals with documented preexisting systolic and/or diastolic dysfunction prior to the initiation of chemotherapy.

Objectives: The primary aim was to determine the chemotherapy regimens given to patients with DLBCL and preexisting systolic and/or diastolic dysfunction, and their related outcomes.

Results: The median age was 71 years with a median follow-up time of 21 months. 24 patients (68%) received R-CHOP chemotherapy. The remainder received non R-CHOP regimens. We observed an association between the type of treatment (R-CHOP vs. non R-CHOP) and the type of heart dysfunction, with diastolic dysfunction patients being more likely to receive R-CHOP. There was a trend toward better response to chemotherapy among patients with diastolic dysfunction compared to those with systolic dysfunction. Although patients treated with R-CHOP demonstrated higher complete remission rates compared to non R-CHOP (72.2% vs. 50% respectively), this result was not statistically significant (p = 0.33), and there was no significant difference in overall survival or 2-year relapse free survival.

Conclusion: Non R-CHOP treatments seem to be better tolerated with fewer adverse cardiac events. To our knowledge this is the largest series evaluating DLBCL treatment regimens in primarily elderly patients with baseline cardiac dysfunction.

Keywords

Retrospective studies, Lymphoma, Non-Hodgkin, Cardiac dysfunction, Systolic and diastolic, R-CHOP protocol

Introduction

Diffuse Large B Cell Lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma with an incidence that increases with age from 2 cases per 100,000 at 20-24 years of age, to 45 cases per 100,000 by 60-64 years, to > 100 cases per 100,000 at 80-84 years [1]. Age is the greatest predictor of cancer. Currently 50% of all malignancies occur in individuals aged 65 and older, and by 2030 older individuals will account for 70% of all neoplasms [2].

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Hematological neoplasms do not escape this age-related increase in tumor-incidence, which holds true for non-Hodgkin's lymphomas, multiple myeloma and all leukemia subtypes, with the exception of acute lymphoblastic leukemia. In addition, the prognosis of most hematological tumors worsens with increasing age [3].

Anthracycline-based chemotherapy improves survival in patients with non-Hodgkin's lymphomas. The treatment of choice for newly diagnosed patients with advanced DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) [4]. The superiority of anthracycline-based treatment in controlling disease and prolonging survival is the case in the elderly as well [5,6].

The incidence of Congestive Heart Failure (CHF) and cardiac dysfunction increases with age [7]. In the Eindhoven cancer Registry Study, the most frequent comorbidity in elderly lymphoma patients was hypertension (22%), followed by heart and vascular disease (considered together) (19%) and then a previous history of cancer (15%) [8]. It is important to recognize that patients with concomitant cardiac comorbidities that preclude the use of anthracyclines were generally excluded from the studies proving the efficacy of chemoimmunotherapy [4,9]. For this reason treating older patients with cardiac dysfunction may be challenging for the oncologist. In this case a combination of Rituximab with Ifosfamide, Carboplatine and Etoposide (R-ICE) is frequently used with good results [10]. There are several other published regimens but no formal comparison between them [11-14].

To better understand this particular issue, we used the Total Cancer Care (TCC) ™ database from Moffitt Cancer Center to assess the treatment regimens administered to patients with DLBCL and preexisting systolic and/or diastolic dysfunction and their related outcomes.

Methods

Data source

We used the Total Cancer Care™ (TCC) database to retrieve eligible patients. TCC is one of the world's largest and most complete clinically-annotated biobanks created in 2003 by Moffitt in partnership with patients, clinicians, industry, academia and 17 hospitals around the country. It collects tumor specimens and clinical data and, to date, more than 108,000 patients have enrolled in the protocol with 400 new patients entered each week. The TransMed portal created to access the TCC data allows de-identified access to the entire cohort of patients treated at Moffitt (> 450,000 patients).

Study cohort

We searched the eligible patients using the Total Cancer Care™ database. A request was made through the TransMed portal and submitted to a TCC concierge. A cohort of 854 patients with a diagnosis of DLBCL between January 1st 2008 and December 31st 2014 and older than 18-years-old was found. After reception of the identified list of the cohort from the TCC concierge, we did a retrospective chart review of those patients using the Moffitt's electronic patient records. We identified 38 patients with documented systolic and/or diastolic dysfunction at baseline. Heart failure is a clinical diagnosis that is based upon a careful history and physical examination. However, many patients come with an outside unverified diagnosis in their chart. To have an objective criterion to select our patients, we defined cardiac dysfunction at baseline as ejection fraction less than 50% (systolic dysfunction) and/or diastolic dysfunction, prior to chemotherapy, documented either by Multiple Gated Acquisition (MUGA) scan or echocardiography. The diastolic function was not available for patients evaluated by MUGA scan. Echocardiography became progressively the standard test at Moffitt after 2008, so the most recent patients had information about diastolic function.

Data collection

Clinical data were collected at the time of diagnosis, during treatment and at follow-up. Baseline demographics, characteristics and clinical data collected were age, sex, race, weight, height, ECOG PS, ischemic or non-ischemic systolic dysfunction (cardiomyopathy), diastolic dysfunction, DLBCL subtype, stage, International Prognostic Index (IPI) or age-adjusted IPI for all patients 60-years-old and older. Major baseline comorbidities were assessed using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) and defined as CIRS-G grade 3 and 4. First-line chemotherapy regimen and completion of planned chemotherapy were recorded. Treatment-related toxicity was noted according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and further categorized in Hematological (H) and Non-Hematological (NH) toxicity. Only CTCAE grade 3 and 4 were recorded. Major cardiac events, defined as hospitalization for CHF, for cerebrovascular insult, for chest pain, for ischemic or non-ischemic cardiac events or cardiac-related deaths were recorded as well as the time related to the event. We captured the response to first-line therapy, Progression-Free Survival (PFS) as well as Overall Survival (OS). Data for OS were not always available in medical records, but provided directly from the TCC database. Other data collected were baseline Electrocardiogram (ECG) data, baseline cardiac medications and, if applicable, doxorubicine-dose per treatment, method of administration and cumulative dose per m^2.

The study was approved by the University of South Florida Institutional Review Board.

Outcomes

The primary outcome was to determine the chemotherapy regimens the patients affected with DLBCL and systolic and/or diastolic dysfunction prior to chemothera-

py received at Moffitt Cancer Center, and their related outcomes: Response, PFS, and OS. Secondary outcome was to assess the influence of these treatments on the cardiac function and the incidence of cardiac major events.

Statistical analysis

Baseline characteristics were summarized using descriptive statistics including mean, median, standard deviation and range for continuous measures and frequencies and proportions for categorical measures. The association with chemotherapy type (R-CHOP vs. non R-CHOP) was examined by the use of Fisher's exact test for categorical variables and Mann-Whitney test for continuous variables. PFS and OS were measured from the date of chemotherapy. Probabilities for RFS and OS were calculated using the Kaplan-Meier method [15]. Cumulative incidence of cardiac event was evaluated using a competing-risks approach, with death as a competing risk. The difference in time-to-event endpoints was evaluated by the log-rank test and Gray test [16]. The statistical analyses were performed using R-software (cmprsk package) and SAS version 9.4 (NC, Cary).

Results

Baseline characteristics and demographics are presented on Table 1 and Table 2.

Among 854 DLBCL patients treated at Moffitt during the period of interest, we identified 38 patients with a diagnosis of DLBCL (according to WHO classification) and preexisting systolic and/or diastolic dysfunction (prevalence of 4.7%). Three patients did not receive any treatment and were excluded from our analysis. Median age was 71 years, with the youngest patient being 21 and the oldest 93-years-old. The median follow-up time was 21 months (Table 1).

No renal comorbidities were reported in our patient cohort. A certain number of patients had a diagnosis of diabetes mellitus, but only CIRS-G grade 1 or 2, so that diabetes was not taken into account in our analysis.

Table 1: Baseline characteristics.

	N	Min	Median	Max	Range	Mean	SD
Age	35	21	71	93	72	69.4	12.9
Follow-up time (months) in censored patients	20	1.4	21.2	50.8	49.4	23.3	12.3

Table 2: Baseline demographics.

		Chemotherapy				Total		p-value
		R-CHOP (n = 24)		non R-CHOP (n = 11)				
		n	%	n	%	n	%	
Sex	Female	7	29.2	3	27.3	10	28.6	1
	Male	17	70.8	8	72.7	25	71.4	
Race	African American	2	8.3	1	9.1	3	8.6	1
	Asian	1	4.2	0	0	1	2.9	
	White	21	87.5	10	90.9	31	88.6	
ECOG PS	0	7	29.2	1	9.1	8	22.9	0.22
	1	10	41.7	5	45.5	15	42.9	
	2	6	25	2	18.2	8	22.9	
	Unknown	1	4.2	3	27.3	4	11.4	
Stage	I	2	8.3	2	18.2	4	11.4	0.32
	II	5	20.8	0	0	5	14.3	
	III	5	20.8	4	36.4	9	25.7	
	IV	12	50	5	45.5	17	48.6	
aaIPI	1	9	37.5	2	18.2	11	31.4	0.27
	2	8	33.3	3	27.3	11	31.4	
	3	6	25	3	27.3	9	25.7	
	NA	1	4.2	3	27.3	4	11.4	
DLBCL subtype	GCB	2	8.3	3	27.3	5	14.3	0.19
	NOS	15	62.5	7	63.6	22	62.9	
	Non-GCB	7	29.2	1	9.1	8	22.9	
Baseline EF	< 50%	8	33.3	11	100	19	54.3	< 0.001
	≥ 50%	16	66.7	0	0	16	45.7	
Systolic dysfunction	No	15	62.5	0	0	15	42.9	< 0.001
	Yes	7	29.2	10	90.9	17	48.6	
	Unknown	2	8.3	1	9.1	3	8.6	
Diastolic dysfunction	No	1	4.2	3	27.3	4	11.4	0.004
	Yes	15	62.5	1	9.1	16	45.7	
	Unknown	8	33.3	7	63.6	15	42.9	

GCB: Germinal Center B cell; NOS: Not Otherwise Specified; ABC: Aactivated B Cell = non-GCB (according to WHO classification 2016).

Table 3: Association type of treatment-type of cardiac dysfunction.

		Chemotherapy				p-value	OR	
		R-CHOP		non R-CHOP			Point	95% CI
		n	%	n	%			
Diastolic dysfunction	Yes	15	93.8	1	25	0.013	45	(2.2 - 937.3)
	No	1	6.3	3	75			
Systolic dysfunction	Yes	7	31.8	10	100	< 0.001	NA[1]	NA
	No	15	68.2	0	0			

[1]OR was not estimated as no systolic HF was observed in non R-CHOP arm.

Table 4: Toxicity and chemotherapy type.

		Chemotherapy				p-value
		R-CHOP		non R-CHOP		
		n	%	n	%	
Planned chemotherapy completed	Yes	13	56.5	9	90	0.11
	No	10	43.5	1	10	
Major cardiac event	Yes	6	25	2	18.2	1
	No	18	75	9	81.8	
Chemotherapy toxicity	Yes	19	86.4	8	72.7	0.38
	No	3	13.6	3	27.3	
Hematologic toxicity	Grade 0-2	13	59.1	7	63.6	1
	Grade 3	2	9.1	1	9.1	
	Grade 4	7	31.8	3	27.3	
Non hematologic toxicity	Grade 0-2	14	63.6	7	63.6	0.76
	Grade 3	4	18.2	3	27.3	
	Grade 4	4	18.2	1	9.1	

24 patients (68%) received an R-CHOP or R-CHOP like (R-EPOCH) chemotherapy. Non R-CHOP regimens were the following: R-ICE, R-MTX, R-Bendamustine, R-CVP, R-CEOP. Due to the small numbers of each individual treatment, we simplified the chemotherapy regimens as R-CHOP (or R-CHOP like) and non-R-CHOP for our analysis.

Type of treatment-type of cardiac dysfunction

We observed a statistically significant association between the type of treatment (R-CHOP vs. non R-CHOP) and the type of cardiac dysfunction, with diastolic dysfunction patients being more likely to receive R-CHOP chemotherapy (Table 3).

Response and chemotherapy type

The patients treated with an R-CHOP regimen experienced a trend towards a better response, compared to the patients treated with a non R-CHOP chemotherapy, with 72.2% of patients achieving Complete Remission (CR) vs. 50% in the non R-CHOP group. However, this result is not significant with a p-value of 0.33.

Likely in part due to the small sample size, no significant difference in overall survival was observed between patients treated with an R-CHOP regimen vs. non R-CHOP. We couldn't observe a difference in relapse free survival between the 2 groups either.

Response and type of cardiac dysfunction

Concerning the association between the response and the type cardiac dysfunction, we observed a trend for a better response achieved by the patients with a baseline diastolic dysfunction (CR in 72%, p = 1) compared to the patients with a systolic dysfunction (CR in 18% for systolic dysfunction ischemic, p = 0.37 and 25%, p = 0.48 for systolic dysfunction non ischemic).

Treatment-related toxicity

Only 56.5% of the patients treated with R-CHOP chemotherapy completed the planned treatment versus 90% (9/10) of completion in the group of patients treated with a non R-CHOP regimen. In the non R-CHOP group, the only patient who could not complete his treatment in the non R-CHOP group received R-ICE and did not experience a major cardiac toxicity (Table 4).

In the R-CHOP group, the patients treated with doxorubicin received 1 to 8 (mean 2.75) doses of 50 mg doxorubicin/m^2. They received a mean cumulative dose of 130 mg/m^2 (range 0 to 400 mg/m^2).

Although we observed more major cardiac events in the group of patients treated with R-CHOP (25%) than the non R-CHOP group (18%) the difference was not statistically significant, (p = 1).

Discussion

Although our numbers are small, this is to our knowledge the largest clinical series of DLBCL patients with preexisting cardiac dysfunction in primarily elderly patients being reported. We found in our cohort that the type of chemotherapy (R-CHOP vs. non-R-CHOP) was associated with the type of cardiac dysfunction, with diastolic dysfunction patients being more likely to receive R-CHOP chemotherapy. This result is consistent with

the current clinical practice of omitting anthracyclines in the case of baseline reduced systolic Ejection Fraction (EF), but not particularly in the case of isolated diastolic dysfunction. However, further studies are needed to better understand the impact of anthracyclines in the case of underlying diastolic failure.

We did not specify an age limit as eligibility criteria for our cohort. However we observed a median age of 71 years, consistent with the general consideration that the incidence of cardiac dysfunction increases with age [7].

Due to the small number of patients, we did not further stratify those patients with low ejection fractions, although it might be interesting to assess the subgroup of patients with an EF between 40% and 50% compared to those with an even lower EF. This could be done in a future analysis with a larger set of patients. Despite collecting the data, the small sample size also precluded analysis based on cardiomyopathy subtype (i.e. ischemic or non-ischemic). The response observed in the group of patient treated with an R-CHOP regimen is better, yet not statistically significant due to the small sample size. This is concordant with the literature, with the knowledge that anthracyclines improve the survival in patients treated for DLBCL [5,6]. However, data in the rituximab era suggest that the long-term benefit of anthracyclines may not outweigh the potential toxicity of anthracyclines in an elderly population. In a recent retrospective study done by veterans over 80 with a diagnosis of DLBCL, they described that among the 42% of those patients who received an anthracycline-based therapy, only 14% were able to complete the treatment in full intensity [17].

We observed an incidence of 25% of major cardiac events in the group of patients treated with R-CHOP, compared to 18% in the group treated without an anthracycline. A small (25 patients) recent German retrospective study assessing the same patient population with DLBCL and preexisting cardiac dysfunction who were receiving R-CHOP, reported an incidence of 36% of major cardiac events in this high-risk population [18]. Another recent retrospective study done by DLBCL patients over 65-years-old suggests that elderly patients experience meaningful PFS with anthracycline-containing regimens, but one third experienced toxicity requiring treatment modifications [19].

This study showed a trend toward a better response achieved by patients with a baseline diastolic dysfunction compared to those with a systolic dysfunction. This might be explained by the fact that they were more likely to receive anthracycline-based regimens. We might also hypothesize that the patients with diastolic dysfunction have a better prognosis, independent from the diagnosis and treatment of DLBCL than those with systolic heart dysfunction.

The major limitations of this study are the small sample size and the single center, retrospective design. However, to our knowledge, this is the largest series evaluating DLBCL treatment regimens in primarily elderly patients with baseline cardiac dysfunction. Our TCC search strategy also allowed quantifying the proportion of patients with DLBCL who present with concomitant cardiac dysfunction in a large academic center (i.e. 4.7%). This number underestimates the proportion of patients with diastolic dysfunction as systematic echocardiograms were only used since 2008. It can still provide a useful quantitative basis to design future studies in this population.

Conclusion

This study demonstrated that primarily elderly patients with DLBCL and baseline systolic dysfunction were more likely to receive non R-CHOP based regimens compared to patients with diastolic dysfunction. Non R-CHOP treatments seem to be better tolerated with a trend toward fewer adverse cardiac events. Future studies examining larger patient populations in a prospective fashion will provide more information about how to best treat DLBCL patients with cardiac impairment.

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Authorship Contributions

V. Dougoud-Chauvin and M. Extermann designed the study. V. Dougoud-Chauvin did the retrospective chart analysis and collected the data; V. Dougoud-Chauvin and M. Sehovic summarized the data, Lu Chen and Jongphil Kim performed the statistical analysis; V. Dougoud-Chauvin, M. Fradley and Martine Extermann analyzed and interpreted the data; V. Dougoud-Chauvin and Martine Extermann drafted the initial manuscript; and all authors critically reviewed the manuscript drafts, approved the final version, and made the decision to submit the manuscript for publication.

Disclosure of Conflict of Interest

All authors declare no conflict of interest.

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