Second Neoplasms in Diffuse Large B-Cell Lymphoma: The Role of Race

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Received: December 13, 2022
***Published*:** January 18, 2023

ABSTRACT

Aim: Patients with diffuse large B-cell lymphoma, (DLBCL) have an increased risk to develop a second neoplasm (SN). Multiple factors have been considered at risk: age, familial history, smoking, use of alkylating agents, or etoposide at increased doses, and especially radiotherapy. Moreover, most of the studies have been performed in USA and Europe countries, with a preponderance of white population. The aim of the study is analyze a large number of patients with DLBCL in a search to define the presence of SN in a Mestizo population. **Patients and Methods:** Electronic files of patients with pathological confirmed diagnosis of DLBCL, treated in our hospital between August 1988 to December 2020; age> 18 years age treated, with combined chemotherapy that were in complete response for at least 3 years. Probably factors associated were analyzed. Median follow-up were 22.4 (range 3.1 to 31.8) years. **Results:** A total of 9316 patients were evaluated, only 16 cases (0.16%) developed SN. Neither of previous mentioned risks factors: age, gender, smoking doses of chemotherapeutic drugs, alkylating agents, use of radiotherapy, advance stage, elevated International Prognostic index, history of cancer, not were associated to the development of a SN, only race were different, 98 % of our patients were mestizo race. Until now race has not been considered as a factor to be associated with the development of a SN. **Conclusion:** The unique differences in large number of cases and longer follow-up, was that the presence of an non-white populations, thus it is appear that in an Mestizo population race could have any protective possibility.

Keywords: Diffuse large B-cell lymphoma, radiotherapy, second neoplasms, race, and Mestizo race.

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is the most common hematological malignancy (HM) and considered that annually increase the incidence in most parts of the world; in United States, estimated 81560 new cases with 20 720 die secondary to the neoplasm in 2021[1]. Increased worldwide from 1990 to

DOI : https://doi.org/10.35702/cases.10009

2019 in both genders and in most geographic regions, as in East Asia.

NHL remains a substantial challenge globally and the incidence rates show marked different variation from country to country [2]. Greater improvement has been observed in the treatment of this neoplasm; based in the best knowledge of biology, identification of prognostic factors and the introduction of new therapeutic approaches. Thus, actually > 60 % of patients may be survivors at > 5-years, but longer survival has been associated with the appearance with later adverse events: cardiac dysfunction, infertility, but the most disturbing late complication is the development of a (SN); that is associated with a poor response to treatment and poor prognosis. Seemingly, the risk remains for many decades after treatment of NHL. These adverse events have been associated to various factors: age at treatment of NHL, familiar history of cancer, type and doses of cytotoxic agents, especially alkylating agents, use of radiotherapy, also other factors has been mentioned; as immunosuppressive status (not specified), family history, use of rituximab, and smoking. Moreover, most have been reported in sites of white populations: Europe and USA [3-10]; and some studies have been reported in East Asia [12-15]; and none in Latin America, or Africa that have a different ethnic population. Thus, we conducted and observational study in a Mestizo population, with homogenous histology and treatments schedules.

MATERIAL AND METHODS

From August 1988 to December 2020, patients with DLBCL who were diagnosed and treated in our institution, with at least a 3-years of follow were including according with the following criteria: age > 18 years with no upper limit, no gender differences, previously untreated, negatives for presence of acquired immunodeficiency, hepatitis B and C, treated with combined anthracycline regimen, in complete response were including. The factors that were considered were age, stage, cumulative doses of cyclophosphamide and doxorubicin, use of rituximab and radiotherapy (fields and doses), positive history of familiar cancer and smoking [1-10].

The follow-up of all patients were performed every 3 months, from the first three years, every 6 months to 3 to 5 years, and annually until the last follow-up (December 2020). The patients were evaluated with clinical examination, complete blood counts, serum chemistry, serum determinations of lactic dehydrogenase and beta 2 microglobulin, X ray of thorax, abdominal and pelvic ultrasound, if the patient report any specific sings or alteration in laboratory test, they were conducted for specific studies, to determine relapse, or SN including biopsy of the possible affected anatomic site. If SN was confirmed, they were sending to the Oncology service according to the pathological diagnosis to received specific treatment. If the patient die, autopsy was mandatory to establish the cause of death: secondary to second neoplasm or no cancer cause

Statistical Analysis

Categorical variables were expressed in terms of quantity (percentage) and were compared using the chi-square test of Fisher exact test. Survival analysis using the Kaplan-Meir method and the differences groups were compared using the Log-siting rank test. Differences between the comparative tests were significant if the two-sided p value was <0.05.

RESULTS

We found 9316 patients that fulfilled the criteria entry. Demographic at diagnosis and at the time of appearance of SN are shown in Table1, that is similar to the population all were in advanced stages (III and IV), no gender differences, 5075 (54.4%) were > 60 years old; 69.1% had higher clinical risks, no history of familiar cancer was documented and 2622 (25.8%) were smokers. They were treated with standard CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone (1988-2002); R-CHOP: CHOP + rituximab, 2002-2008) and dose-dense CHOP (2008-2017). Radiotherapy was administered to 4025 (40.4%) patients, most 3123 (77.5%) adjuvant treatment in patients with initial bulky disease at diagnosis. The doses ranged between 25 to 36 Gy.

DOI : https://doi.org/10.35702/cases.10009

Table 1: Demographics and clinical characteristics

A.-At diagnosis	
	No (%)
Number	9316 (100)
Gender	
Male	5001 (53.6)
Female	4315 (46.3)
Age (years: median)	58.9
Range	27 – 77
<60	4241 (42.4)
>60	5075 (54.4)
Stage	
III	3038 (32.6)
IV	6278 (67.3)
Familial history of cancer	0
Smokers	2622 (26.2)
Performed status	
0,1	1230 (13.2)
2	3728 (40.0)
> 2	4358 (46.7)
IPI *	
0,1	2765 (29.6)
2	4088 (42.7)
> 2	2463 (26.4)
Bulky disease (tumor mass > 10 cm)	3992 (42.8)
Treatment	
CHOP-21	2916 (31.0)
R-CHOP-21	1970 (21.0)
CHOP-14	3011 (32.3)
R-CHOP-14	1419 (15.2)
Radiotherapy	
Yes	4025 (40.4)
Total doses mg/m2	
Cyclophosphamide	
4500	5711 (61.03)
4501 – 6000	3605 (38.64)
Doxorubicine	
300	6064 (65.10)
301 – 450	3252 (34.09)

Table 2: Second neoplasms. Characteristics

Number	16 (0.17%)			
Site	Lung	Prostate	Breast	Colon
Total	6	4	4	2
Male	3	4	0	1
Female	3	0	4	1
Age (years) at diagnosis of second neoplasm				
<60	3	1	2	1
>60	3	3	2	1
Time to developed a second neoplasm (years):				
5 – 10	2	0	1	0
5.1 – 10	0	1	2	0
10.1-20	1	0	1	1
20.1-30	2	0	0	1
> 30	1	3	0	0
Smoking	1	4	3	1
Cyclophosphamide **				
4500	6	4	4	2
> 4500	0	0	0	0
Radiotherapy	1	0	1	0

Abbreviations: IPI; International Project Index; CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone, administered every 21 days) CHOP-21 (CHOP administered every 14 days), R-CHOP (rituximab + CHOP) every 21 days); R_CHOP-14 (RCHOP administered every 14 days) ** doses total of 6 cycles.

Table 2 shows the characteristics at the time of diagnosis of second neoplasms. Only 16 patients (0.17%) developed a SN, all were diagnosed in early stage, thus response was better that patients of general population Treatment for second neoplasm was well tolerated and complete response was achieved in 7 cases (49%), at the last follow-up, 6 patients remain in complete response, 10 patients died secondary to tumor progression, at death no dates of DLBCL were observed. As expected, the outcome did not show any statistical differences between patients that developed second neoplasm or not (Table 3).

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Table 3: Univariate analysis

	No (%)	p
Gender		
Male	5001 (53.6)	0.565
Female	4315 (46.3)	
Age (years)		
< 60	4241 (45.5)	0.601
> 60	5075 (54.4)	
Radiotherapy		
Yes	4025 (43.2)	0.550
Not	5291 (56.7)	
Performance status		
0 – 2	4958 (51.3)	0.425
≥ 2	4358 (46.7)	
IPI *		
Low	2765 (29.6)	0.020
Higher	6851 (72.2)	
Treatment		
Standard	4886 (52.4)	0.344
Dose-dense	4430 (46.9)	
Total doses /m2		
Cyclophosphamide		
4500 mg	4946 (52.4)	0.410
>4500 mg	4320 (46.5)	
Doxorubicin:		
300 mg	6064 (65.0)	0.889
>300 mg	3242 (35.3)	

DISCUSSION

We present the first report of patients with DLBCL in Latin America, with a prevalence of Mestizo population that has a longer follow-up. We found only 16 cases (0.16%) were diagnosed. Multiple factors have been suggested to can influence on the development of second neoplasm. Chattopadhyay et al, suggested that a familial history of previous cancers, could be associated to the risk of second neoplasms [4], in another report, they found that immune suppressed state is a key underlying mechanism in the context of second neoplasms [5]; Tao et al, observed an increased cases of second neoplasm in patients that received rituximab as induction treatment [6], and the same results were observed by Cho et al [11]. Lee et al. considered that second neoplasms are more frequent in adolescents and young adults with cancer, because response and longer survival, are common in most cancers in those age [7]; Baras et al. mentioned that the use of aggressive chemotherapy can be influence the development of this late adverse event [8]. Yin et al. found that primary sites of DLBCL, can be associated to a second neoplasm in the same anatomic site [9]. Recently, Major et al. suggested that stage and time interval since diagnostic will be considered as prognosis factor [10]. Studies performed in East Asia considered that the increase of second neoplasms is associated with the increase number of cases [12-15].

The mechanism that these group of patients with DLBCL can development an SN, are multiple and has been associated with the mentioned risks factors, buy, no clear association has been defined. We performed a retrospective analysis of the mentioned prognostic factors associated to the development of second neoplasms, and we did not find any statistical differences, inclusive in patients that received higher doses of alkylating agents, and extensive radiotherapy. The unique difference that we considered that influenced

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the development of these adverse events, was race. Our population is also a Mestrizo. Unfortunately, we did not find any reports in Latin America. We consult with hematologist of El Salvador, Guatemala, Peru, Colombia, Ecuador and they did not have any study about this association. In the other hand, diagnosis of SN: because in all cases follow-up is performed in the same hospital when these were in early stage, because in our institution, all patients the follow-up is performed in the same hospital, and when any early abnormality (clinical or laboratory), more studies are performed, and treatment began immediately if a second neoplasm is confirmed.

It is evident that several biases were observed, first, it is a retrospective analysis, it was conducted in a single people, not central pathology was performed, but the strength is that the treatment were uniform, they were a homogenous population, and a longer follow-up was observed. It is evident that studies with the same race will be available, to compare our results: thus, we hope this study may induce other hematological center to perform an analysis of this disturbing complication in the treatment of DLBCL.

CONCLUSION

We present the first study that analyzes the possibility of developed a second neoplasms in patients with DLBCL, in a Mestizo population, with a large number of cases and longer follow-up. We can no confirm that the mentioned risks factors to develop second neoplasms were similar in our cases the only difference that can considered, is that our race population is Mestizo. Most of the studies have been reported in countries (USA and Europe) with a Caucasian population. Other studies have been performed in East Asia countries (Japan and Taiwan), with different races, and the rate of second neoplasms is minor that those reports. We contact colleagues in Peru, Colombia, Ecuador, Guatemala, El Salvador, with a population similar to our country, and they mentioned that the presence of second neoplasms treated for NHL, is rare.

Data are available upon request to the corresponding author without any restrictions.

CONFLICT OF INTEREST

The author discloses no conflict of interest.

FUNDING

The manuscript did not receive any financial support and was performed with the owner resources of the Instituto Mexicano Del Seguro Social

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DOI : https://doi.org/10.35702/cases.10009