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Die a Real-World Analysis of Cause of Death in Patients with Diffuse Large B-Cell Lymphoma

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1. Abstract

1.1. Background: Cause of death in diffuse large B-cell lymphoma (DLBCL) has been reported that has be diminished, but, no a real-analysis has been reported, and only retrospective studies that analysis based in statistical dates for electronic files. We report an real-world analysis in a single center.

1.2. Methods: Patients with diagnosis of DLBCL, treated in a single center, were included in a program that include a close follow-up, to detect any related cause of death and non-related.

1.3. Results: Between August 1988 to December 1918, 12860 were included. Related-cause and non-related cause were diminished, compared with most studies.

1.4. Conclusion: Follow-up of cancer survivors will be closed follow-up , to detect any complication that would be treated in an early time, to treat and limited the mortality in this special setting of patients .

2. Introduction

Diffuse large B-cell lymphoma (DLBCL)) is the most common subtype of malignant lymphomas, in our Institute represent about 44% of hematological malignancies. Greater advances have been obtained in the treatment of this disease, and most patients have a longer survival. Thus logical, the possibility that a non-related cause of death (NRCOD) has been appear in these special settings of patients. Multiple analysis has been published, but, most are retrospective , SEER analysis, and they analyzed the risks at the time of diagnosis would associated with comorbid diseases, with most emphasis in statistical tables [1-7].In our Institute when the patients achieve complete response ,the follow is performed ,during the first 5 years, remain in the Hematology Department, from 5-years until relapse, death of any cause, are performed in the Familiar Unit of our Institute, and the patients carry and program to the Familiar Doctor, with indications that continue the follow, that include the interval of cites, laboratory and R-X , studies, indications in the any abnormality is observed , the patient is resent to our Hospital , if they have any evidence of relapse , presence of a second neoplasm, cardiac, neurological, metabolic, or another medical problem , the patient remain in our Department, until resolution of the problem. Also, we have access to the electronic files of all patients of the Institute, and can detected the clinical patients. We reviewed the dates of a large and longer follow-up of our patients, and can observed in a real condition , the cause of any patient.

3. Material and Methods

We reviewed the dates of 12860 patients , that have the followed criteria : confirmed pathological diagnosis of DLBCL, age > 17-years without limit, that have a minimal of 3 years of follow-up. They have a complete clinical examination, complete blood counts, serum chemistry, serum determinations of lactic dehydrogenase (LDH), beta 2 macroglobulin (B2M), hepatitis B and C virus, immune deficiency human disease, aspirate and biopsy of bone marrow, cardiac electrocardiogram, computed tomography of neck, thorax, abdomen and pelvis.

They received initially the CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) at standard doses, from 2002 rituximab (R-CHOP) were the treatment: adjuvant radiotherapy was

administered in patients with bulky disease (nodal tumor size > 10 cm) (As mentioned, the follow-up program includes an close relationship with the familiar clinic, that if any clinical or laboratory dates are suspicious of any problem, quickly the patient is resend to the Oncology Hospital. When the patient was sent to the Familiar Clinic, clinical examination, complete blood counts, serum chemistry, serum determinations of LDH, B2M, and electrocardiogram. If the patient die, if possible, an autopsy was performed. When the patient when arrive to the Unit, signed an approval statement, thus did not approval where necessary. In the moment the treatments administered were approved by the Ethical and Scientific Committee.

4. Results

From August 1988 to December 2018 , 12860 patients fulfilled the criteria cited. (Table 1) show the clinical and laboratory studies; most patients were > 60 years, advance clinical stages, higher clinical risks, elevated levels of LDH and B2M, no differences were observed in the treatment chemotherapy regimens [9-12]. The median follow-up was 19.9 (range 5-29) years. (Table 2) show the cause of death, in the total group 3699 (28.3%) patients die secondary to disease progression, thus the overall survival of these special setting of patients as 70.3 %; infection was considered as related, but only if the infection occurs in the first three months after treatment. Only 189 deaths were related to the disease/treatment complications, the most common were complications of diabetes mellitus and degenerative neurological events, most in patients > 60 years.

Table 1: Demoghrafic characteristics

Total	< 60 years	> 60 years
12860	4126 (32.0)	8234 (65.2)
Sex : Male	2001 (48.4)	3898 (44.6)
Female	2115 (51.2)	4836 (55.3)
Age (Years) median	36.9	76.3
Bulky disease	1826 (44.2)	2390 (27.9)
Stage I-II	198 (4.7)	216 (2.4)
III	608 (11.1)	401 (4.5)
IV	3320 (81.3)	8117 (92.3)
IPI * 0,1	160 (3.8)	194 (2.2)
2,3	608 (3.8)	806 (9.2)
3,4	3358(81.3)	7734 (87.5)
DLH elevated > 2N	2712 (53.6)	7620 (87.2)
B2M elevated > 2N	2163 (52.4)	3845 (44.2)
Treatment		
CHOP	2016 (48.8)	4111 (47.0)
R-CHOP	2110 (48.8)	4623 (52.9)

International Project Index.

Table 2: Cause of death

RELATED:	Total	< 60 years No (%)	> 60 years
Relapse	3699 (28.3)	1316 (10.0)	2183 (18.5)
Infection	367 (2.8)	106 (0.8)	261(2.0)
NON -RELATED:	189 (1.4)	48 (0.37)	118 (0.9)
Second neoplasms	16 (0.12)	4 (0.03)	12 (0.09)
Cardiac disease	33 (0.28)	4 (0.03)	23 (0.17)
CHF *	21 (0.16)	1 (0.003)	20 (0.01)
MI **	11 (0.08)	1 (0.003)	10 (0.03)
Diabetes	32 (0.02)	10 (0.02)	222 (0.10)
Thrombosis	24 (0.18)	7(0.005)	17 (0.13)
Lung	2 (0.001)	1 (0.007)	1 (0.002)
Hepatic	5 (0.03)	2 (0.01)	3 (0.02)
Renal	5 (0.03)	3 (0.02)	2 (0.02)
Neurological	233 (0.17)	3 (0.02)	20 (0.15)
Accidents	16(0.12)	8 (0.06)	8 (0.06)
Suicide	2 (0.12)	0	2(0.06)
Homicide	3 (0.02)	3 (0.02)	

*Congestive heart failure ** Myocardial infarction

5. Discussion

We present the first real-world analysis that include and large number of patients and longer follow-up with an median of 19.8 (range 4 to 29 years) , we observed that related-COD the most common cause was relapse :28.5%, but these results show that > 70% of patients are alive free-disease , that is better that most of the previous studies ; the treatment appear that did not can influence, because the chemotherapy employed CHOP and R-CHOP had the same response and outcome, the addition of adjuvant radiotherapy was used only in patients with nodal bulky disease . but our analysis found that relapse was observed in 1867 patients, and 1034 were resend to the Familiar Clinic, 3 to 6 weeks after the first date of relapse, in this patients second response was achieved in 1345 (72%) , and the 522 patients that delayed the treatment second response was observed in 165(31.6) . Second neoplasms after DLBCL have been observed in multiple studies, and the prognosis is poor, because they were with advance stage, in our cases, we observed only 16 cases (0.17%), and, again, they were resent, 7 cases that were treated achieve response, and 6 are alive-free disease. Thus, it is appeared that a rapid intervention would improve the prognosis [5]. Cardiac toxicities have been considered a frequent cause of related-COD in these patients [8], in this analysis only 33 (0.28%) were a related COD, but, the presence of cardiac toxicities secondary are less frequent, we did not have any explication, inclusive in patients who received > 300 mg/m2. We considered that primary mediastinal lymphoma is different to DLBCL , radiotherapy to thorax was not employed in our patients.Although neurological and diabetes toxicities were 0.17 % and 0.02%, and were treated, we can influence in the failure .Recently Halpern et al, reported an analysis about the care of cancer survivors, and found that multiple problems difficult and adequate treatment in cases of relapse , and health [13]: delayed in the treatment of late toxicities, delayed in diagnosis, generally associated to economic causes, because patients that have private security, appear that have better prognosis. In our Institute, all patients have the same care, and as mentioned , and the communications with familiar physician is close , thus, we believe that considered that the creation of new programs that included an close follow-up, will be necessary in these special setting of patients.

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