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Impact of a federal program on response rate & survival, in a cohort of patients with diffuse large B-cell lymphoma. Analysis in a single national reference institution in México

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ABSTRACT

The actual standard of care of diffuse large B-cell lymphoma (DLBCL) includes rituximab in combination with chemotherapy, with response rates up to 76%. However, this treatment may not be accessible to many patients, particularly in developing countries, where most of the treatment must be paid from the pocket of patients or their families. In México, since 2011 a federal program has fully covered this treatment of patients with DLBCL. At the Instituto Nacional de Cancerología (INCan) in Mexico City, 214 new cases with this disease were treated without cost with the standard of care in 20 months. The mean age at diagnosis was 56.7 ± 15.9 (22-91). This series of cases was compared with a retrospective analysis of cases with DLBCL attended at the INCan between 2006-2009. A total of 264 cases were retrospectively analyzed. No differences were found in demographic and clinical characteristics at time of diagnosis. However a clear positive impact was found in the group that received full treatment thanks to this new social coverage by this new social security program. The follow-up and completion of treatment was 99 %. In contrast; from 264 in the retrospective group (79%) were treated, but only 29 (10.9%) were able to receive an optimal treatment, including rituximab. These differences in treatments had a clearly impact on the response rate: 66.8 *vs.* 50.7% global response (full treatment *vs.* retrospective group, respectively). These results demonstrate the importance of social programs that may accessible standard treatment options in countries with limited resources.

Key words. Non-Hodgkin lymphoma. Diffuse large B-cell Lymphoma (DLBCL). Treatment of lymphoma.

Impacto de un programa federal en la respuesta y supervivencia en una cohorte de pacientes con linfoma difuso de células grandes B. Análisis en una institución de referencia en México.

RESUMEN

El tratamiento estándar actual del linfoma difuso de células grandes B (DLBCL) incluye rituximab en combinación con quimioterapia y ofrece tasas de respuesta hasta de 76%. Sin embargo, este tratamiento no es accesible a muchos pacientes, particularmente en países en desarrollo, donde el costo de los medicamentos debe cubrirse con recursos familiares. En México, en 2011, inició un programa federal que ha cubierto este tratamiento a pacientes con DLBCL. En el Instituto Nacional de Cancerología (INCan) de México se trataron 214 casos nuevos con esta enfermedad, con apoyo del manejo estándar en un periodo de 20 meses. La edad promedio al diagnóstico fue de 56.7 ± 15.9 (22-91) años. Esta serie de casos se comparó con un análisis retrospectivo de 264 casos con diagnóstico de DLBCL atendidos en el INCan entre 2006-2009. No se encontraron diferencias demográficas o en las características clínicas al momento del diagnóstico. Sin embargo, sí se documentó un impacto positivo en el grupo de pacientes que recibió el tratamiento completo con la cobertura de este programa de seguridad social, ya que se logró completar tratamiento y seguimiento en 99% de los casos. Por el contrario, de 264 pacientes del grupo retrospectivo, 79% se trataron y solamente 29 casos (10.9 %) recibieron un tratamiento óptimo, incluyendo rituximab. Estas diferencias en el tratamiento administrado impactaron en la tasa de respuesta global: 66.8 vs. *50.7% (pacientes con programa de apoyo* vs. *grupo retrospectivo, respectivamente). Estos resultados demuestran la importancia y la necesidad de programas sociales que permitan el acceso de tratamientos estándares en pacientes con recursos limitados.*

Palabras clave. *Linfoma no Hodgkin. Linfoma difuso de células grandes B. Tratamiento de linfoma.*

INTRODUCTION

Non-Hodgkin lymphoma (NHL) constitutes a malignancy that has increased in the lasts years, with an actual incidence of 2.8 x 100,000 inhabitants.[1] Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHL, accounting for about 25% of all lymphoid neoplasms.[2] The actual standard of care of this malignancy includes the monoclonal antiCD20 antibody rituximab in combination with chemotherapy, in most Cancer Centers the CHOP-R (cyclophosphamide/doxorrubicine/vincristine/prednisone/rituximab) is an acceptable regimen for these patients. The addition of this antibody increased the response rate from 63% up to 76% in DLBCL patients,[3-5] including elderly population;[6] although the development of this monoclonal antiCD20 antibody clearly improved the response rate & prognosis of patients with DLBCL, this treatment may not be accessible to many patients because of limited economical resources, particularly in developing countries, where the treatment must be paid with patient's-, or family's resources, which frequently allows an unoptimal treatment without the antiCD20 antibody rituximab. In México, since 2011 a federal program covered the full treatment of such patients, which has allowed not only the whole diagnostic tests, but also the free access of chemotherapy & rituximab to all patients. We considered of interest to show the impact of this program on DLBCL patients attended at a single national reference center [Instituto Nacional de Cancerología (INCan)] in Mexico City, in terms of treatment adherence, proportion of patients achieving an optimal treatment, as well as response rate & survival.

MATERIAL AND METHODS

Two groups with hystologically documented DLBCL were compared. Group A consisted of a serie of cases which included adult patients with this diagnosis, who were treated at INCAn during the period 2011-2012 and were benefited from a federal program. This social program supported a complete diagnosis approach, including pathology study with immunohistochemistry, determination of viral serologies (HIV, HBV, HCV), blood chemistry evaluation, a cost free treatment with CHOP-R regimen and follow up during 5 years. Patients treated within this group received 6-8 cycles with 21-days CHOP-R regimen: cyclophosphamide 750 mg/m^2/day 1, doxorubicine 50 mg/m^2/day 1, vincristine 1.4 mg/m^2/day 1, rituximab 375 mg/m^2/day 1 (maximal total dose: 600 mg), prednisone 100 mg/day/5 days. Follow-up included physical examination, chemistry & blood tests every three months and computed tomography (CT) every six months. All patients were treated by the same attending physician (MC), when they did not attend in a period of 1 month, they were contacted by a social worker.

Group B is a retrospective group of adults with hystologically DLBCL diagnosis treated at the same Institution within the years 2006-2009. This retrospective group supported diagnosis studies, treatment and follow-up, with patient –or family– economical resources. Follow-up evaluation in the retrospective patients was done according with physician's criteria.

Both groups were compared in terms of demographic characteristics, including gender, age, clinical stage, presence of Bulky disease, B-symptoms, number of cycles received and proportion of patients treated with a whole schema, including rituximab.

Since most of the retrospective group was treated without rituximab, prognostic at diagnosis was evaluated according to IPI (International Prognostic Index) scale,[7] in preference of R-IPI scale.[8] Histological diagnosis & subclassification of DLBCL was done according to Hansnomogram.[9] Treatment: In the retrospective group, CHOP or CHOP-R was administered, according with patient's economical resources. Optimal treatment was evaluated and defined as the proportion of patients receiving the schema that was recommended by attending physicians.

Treatment adherence was also evaluated, as the proportion of patients that received the whole number of cycles of treatment prescribed. Response was assessed according with the International Workshop criteria[10] by the treating physician and was defined as the proportion of patients with complete remission for all patients evaluable for response. Progression-free survival (PFS) was defined as time to progression during treatment, relapse, or death from any cause; additional treatment was censored for this endpoint. Overall survival (OS) was defined as time to death from any cause. Data for patients without an event in progression-free or overall survival were censored at the last day of having valid information for that endpoint.

Statistical analysis

Main analysis included all diagnosed patients within each period (by intention to treat). Demographic and clinical characteristics were compared

Table 1. Demographic characteristics in both treatment groups.

	A: patients within the social program n (%)	B: retrospective group n (%)	p
Patients	214	264	–
Gender			
Female	132 (61.6)	128 (48.4)	ns
Male	82 (38.3)	136 (53.5)	
Age, mean ± SD (range)	56.7 ± 15.9 (22-91)	56.4 ± 16.7 (20-90)	ns
Clinical stage			
I	21 (9.8)	46 (17.4)	
II	49 (22.8)	56 (21.2)	ns
III	50 (23.3)	47 (17.8)	
IV	94 (43.9)	115 (43.5)	
ECOG			
0	3 (1.4)	98 (37.1)	
1	133 (62.1)	95 (35.9)	
2	50 (23.3)	42 (15.9)	ns
3	28 (13.08)	20 (75)	
4	-	9 (3.4)	
B symptoms			
Yes	134 (62.6)	155 (58.7)	ns
No	80 (37.4)	109 (41.2)	
Bulky disease			
Yes	103 (48.1)	119 (45)	ns
No	111 (51.9)	145 (55)	
Extranodal disease sites (n)			
0	85 (39.7)	89 (33.9)	
1	94 (43.9)	119 (45)	ns
2	21 (9.8)	48 (18.1)	
3	8 (3.7)	8 (3)	
4	6 (2.8)	0 0.004	
Basal DHL			
Normal	105 (49)	129 (48.8)	
Increased	109 (51)	134 (51.2)	ns
Basal beta2microglobuline			
Normal	115 (53.7)	114 (43.4)	
Increased	99 (46.3)	133 (50.6)	ns
Not known	—	16 (6)	
HIV status			
Positive	18 (8.4)	17 (6.4)	ns
Negative	195 (91.6)	170 (64.3)	
Not known	—	76 (29.3)	
HBV status			
Positive	7 (3.2)	5 (1.9)	ns
Negative	207 (96.8)	56 (21.2)	
Not known	—	203 (76.9)	
International prognostic index			
Low	37 (17.2)	93 (35.1)	
Intermediate-low	57 (26.7)	55 (21)	ns
Intermediate-high	66 (30.9)	68 (25.9)	
High	54 (25.2)	48 (18)	

Table 2. Treatment administered and response rate.

	A: patients within the social program n (%)	B: retrospective group n (%)	p
Patients	214	264 (100)	–
Treatment			
CHOP-R	204 (95.3)	29 (11.2)	
CHOP	10* (4.7)	180 (68)	
0-2 cycles**	–	55 (20.8)	0.001
Response (all patients)			
Complete	124 (58)	103 (39)	0.001
Partial	19 (8.8)	31 (11.7)	
Stable disease	0 –	11 (4.1)	
Progressive	29 (13.5)	24 (9)	
Not evaluable, lost of follow up	–	95 (36)	
Relapse rate (%)	43 (20)	93 (35)	0.0001

*7 patients did not received rituximab because of HBV & 3 HIV positive had < 100 absolute CD4 counts. **Patients who abandoned treatment because of reduced economical resources.

by χ^2. Response and progression during treatment were compared by Fisher's exact test. Progression-free, and overall survival were done according with Kaplan-Meier methodology. Cox regression analysis was used to evaluate factors influencing on relapse rate & survival. Differences between groups were regarded as significant for p values < 0.05.

RESULTS

Demographic characteristics

- *Group A.* Serie of patients included in the social program from 2011 till December 2012: two hundred and fourteen patients (61% female) were treated within this period. Mean age was 56.7 + 15.9 (22-91) (Table 1). In all patients viral serologies (HIV, HBV, HCV) were documented, from this group, 18 cases (8.4%) were HIV positive; in the same direction, HBV & HCV serologies were done in all cases and chronic HBV was documented in seven patients (Table 1).
- *Group B.* Retrospective group (2006-2009): two hundred and sixty four patients were attended at the INCan in Mexico City, none predominance for gender either was documented (Table 1). Within this period, a clearly incomplete evaluation of viral comorbidities influencing on response & determining treatment was done, since 76.9% of patients didn't have a HIV status determination, and in the same direction, HBV & HCV serologies were absent in most of patients (Table 1).

Other demographic & clinical prognostic factors were similar in both groups, as age, clinical stage, IPI distribution, presence of bulky disease or B symptoms, as shown in table 1.

Treatment

- *Group A.* Patients treated: from 214 patients, ten cases received only CHOP regimen because of comorbidities that clearly contraindicated the administration of rituximab (in seven cases chronic HBV & three HIV with $< 100/\mu$L total CD4 cells). In the rest of the group CHOP-R regimen was indicated. In these terms, all patients received the medically indicated regimen, which allows a 100% optimal treatment.

All were treated with at least 2 cycles of chemothe rapy. From them, 209 (98%) received all programmed treatment, which shows and adherence of 98%.

- *Group B.* Patients treated: from 264 cases, 209 (79 %) were treated, but only 29 (10.9%) were able to receive an optimal treatment, including rituximab. This means, that within this group, 79% were suboptimally treated and only 10.9% were optimally treated, mainly because of limited

Table 3. Comparision of HIV positive & negative population in group A.

Characteristic	HIV (+)	HIV (-)	P
Number	18	196	
Female/male (n)	3/15	126/70	0.001
ECOG: 1/2/3	13/4/1	131/46/26	0.22
Bulky: yes/no	07/11	100/96	0.07
B symptoms: yes/no	14/4	124/72	0.31
Ann Arbor I/II/III/IV	0/2/1/15	22/49/50/75	0.007
IPI			
Low	0	39	0.28
Intermediate low	6	55	
Intermediate high	7	60	
High	5	42	
Response rate (CR + PR)	55.5	75%	0.03

economical resources. Adherence treatment: fifty five patients (20.8%) received < 2 chemotherapy cycles and only 188 completed all programmed cycles, which shows an adherence of 71.2%.

These differences in treatment received & adherence had a clearly influence on response rate, as follows: 66.8 % global response in the group A, in comparison with 50.7 % global response in group (Table 2). However, response rate in the 29 cases from group B, receiving CHOP-R was 65% similar to group A. In the same direction, patients from group A thad did not receive rituximab (because of medically it was contraindicated) had a 52% global response, similar to those patients in group B.

Table 4. Comparison of both AIDS population between groups.

	A: patients within the social program n (%)	B: retrospective group n (%)
Patients	18	15
Regimen		
CHOP-	3 (16.6)	10 (66.6)
CHOP-R	15 (83.4)	3 (21.7)
COP	-	1 (5.8)
EPOCH	-	1 (5.8)
Response		
Complete	8 (44.4)	5 (33.3)
Partial	2 (11.1)	5 (33.3)
Stable disease	5 (27.7)	1 (6.6)
Progressive	3 (16.6)	4 (26.6)

After analyzing both whole groups, we decided to evaluate & compare response rate in HIV positive and negative population treated in group A, in terms of clinical characteristics & response rate. As shown in table 3, a higher proportion of males, as well as advance stage disease were documented in HIV population. In the same direction, the response rate was lower in these cases (55 *vs.* 75% in HIV positive & negative, respectively, $p = 0.03$).

Thereafter, HIV population was compared in both groups. As shown in table 4, three patients from group A did not receive rituximab because of a low CD4 count, the rest received CHOP-R. In group B, two patients did not receive treatment and only 15 cases were treated with regimens summarized on table 4. A higher proportion of patients with access to the monoclonal antibody (group A), achieved a higher complete response rate, although the global response (CR + PR) was not different between both groups.

Survival

Disease free survival (Figure 1) and overall survival (Figure 2) were also significantly better (78 *vs.* 58% to two-years of follow up) in group A. Mean (follow-up + SD in groups A & B was 11.45 + 6.7 & 16.7 + 17.7 months, respectively).

At this follow-up, 37 patients (17.2 %) have died in group A & 46 (17.4 %) in group B. Mortality rates secondary to infectious complications were similar in both groups, 7.2 and 7.9% in groups A & B, respectively. As expected, progressive disease predominated in the group B.

After Cox regression analysis, only the administration of an optimal treatment was a predictor

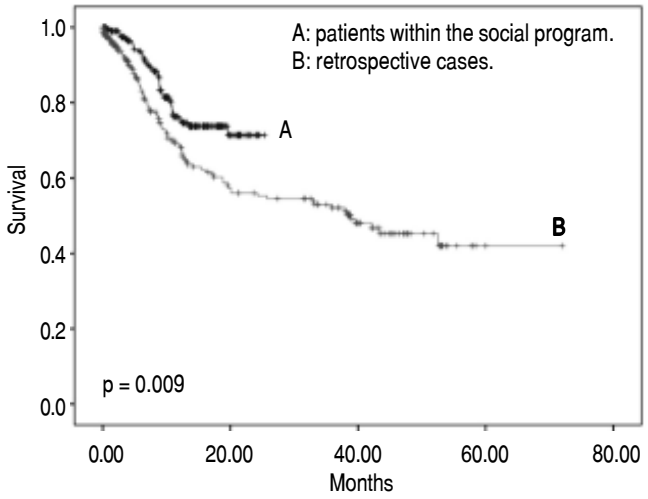

Figure 1. *Disease free survival comparison between both groups.*

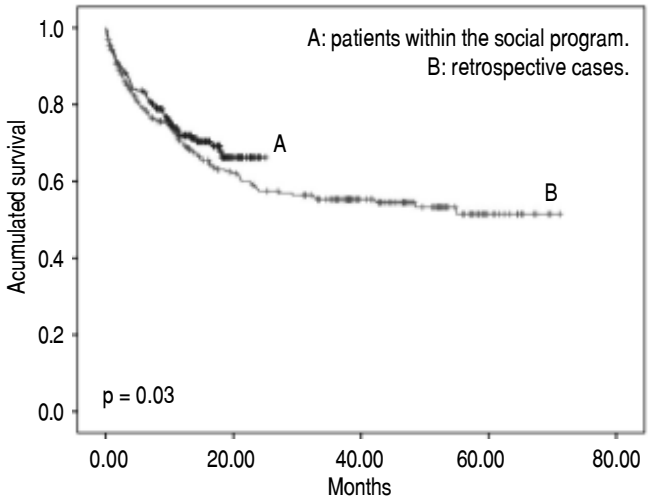

Figure 2. Overall survival comparison between both groups.

factor influencing on disease free & overall survival. Otherwise, when this analysis was done only in the group that had the federal support, the presence of Bulky disease, B symptoms, relapse, HIV positive patients, intermediate high & high risk according with IPI scale were factors influencing on overall survival (Tables 5 and 6).

DISCUSSION

The development in new drugs has allowed a better response in many diseases, including malignancies. The introduction of rituximab in past decade, and its combination with classic CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy has greatly improved patients outcome[11-12] and has been set as standard of care,[13-14] either patient's age. Results from three prospective randomized studies undertaken in elderly population (aged 60-80 years) established immune-chemotherapy as standard of treatment. In GELA[2,6] and US Intergroup study,[15] rituximab was administered with classic CHOP 21 (3-week cycle). In the German Recover-60 study,[16] rituximab was added to dose-dense CHOP 14 (2-week cycle), since previous work showed that CHOP14 (without rituximab) was associated with improved progression-free and overall survival compared with CHOP 21 in elderly population with untreated diffuse large B-cell lymphoma. All these studies concluded that the addition of rituximab was able, improved response without adding significant toxicity in elderly population and must be considered a standard therapy. In the same direction, young patients with DLBCL will be benefited with the addition of this monoclonal antibody, the study of the MabThera International Trial (MInt) Group[4] demonstrated two major benefits: an increase of the rate of complete remissions and a decrease of the rate of progressions during treatment, which resulted in improved event-free, progression free, and overall survival after 6 years of follow-up. However, the addition of monoclonal antibodies

Table 5. Cox regression analysis of factors influencing on disease free survival & overall survival.

Factor (considering patients from groups A & B)	Disease free survival (p)	Overall survival (p)
Group A/B	0.009	0.03
Ann Arbor	0.79	0.93
B symptoms	0.71	0.84
IPI	0.69	0.50
Bulky disease	0.90	0.84
HIV positive*	n.e.	n.e.

n.e.: not evaluable, since most of cases had none result of this laboratory test within group B.

Table 6. Cox regression analysis of factors influencing on disease free survival & overall survival, analyzing only patients in group A.

Factor	Overall survival (p)
Relapse	0.0001
B symptoms	0.001
IPI	0.05
Bulky disease	0.001
HIV positive*	0.008
Ann Arbor	0.93

increases the cost of treatment an some authors[17] in México have suggested that the addition of rituximab increased 26- fold treatment costs and had only a mild positive impact in OS in patients with DLBCL, although they included a total of 74 patients with this diagnosis, from them 32 receiving RCHOP had an OS of 87% at 80 months, in comparison with 84 % at the same time in 42 cases with CHOP regimen. This OS was superior to that achieved in this institution, which may be explained because we had a higher proportion of patients with intermediate & high-risk DLBCL. In this institution the coverage of full treatment with a social program allowed to access an optimal treatment with similar results to those obtained worldwide in these prospective trials, and disease free survival to 2 years was 78%, significantly better than 58% in the retrospective group, which demonstrates that the addition of rituximab is mandatory in most of patients with untreated DLBCL. The addition of rituximab to other schemas, as CEOP has also been evaluated by different authors[18] within randomized clinical trials and only a mild benefit has been documented, either in young & elderly population.[18-19]

The benefit of adding rituximab in response rate has also been documented in at least three clinical trials including HIV associated lymphoma. Results obtained initially[20,21] demonstrated similar response rates to that achieved in this series of cases. However, a French phase 2 study[22] achieved a CR rate of 77% and 2 year-survival rate of 75%, confirming that rituximab was beneficial and could be given to this group of patients. Thereafter, results of the EPOCH regimen in this population were very promising, and the randomized patients to receive concurrent *vs.* sequential rituximab with EPOCH.[23,24] Additionally these authors found that concurrent rituximab was not associated with increased infectious deaths. Results from the comparision between EPOCH-R with CHOP with or without rituximab showed a 75% CR for EPOCH-R.[25] In the same direction, Dunleavy, *et al.*[26] involved a second-generation EPOCH regimen termed Short Course-EPOCHRR, which is designed to address the dual challenge of achieving excellent tumor control while preserving immune integrity; with 5-years of follow-up, the PFS- and OS of SC-EPOCH-RR are 84 and 68%. These new regimens are clearly superior to those obtained in HIV patients in this series of cases, and other schemas, as EPOCH-R or SC-EPOCH-RR may be considered for such patients.

Optimal treatment of hematological malignancies is desirable in whole population. However, in middle-income and low-income countries health-care systems face many challenges for such patients, as inequitable distribution of resources and services, inadequate funding; inadequate numbers, training, and distribution of health-care personnel and equipment; lack of adequate care for many populations based on socioeconomic, geographic, ethnic, and other factors. Recently, Goss P, *et al.,*[27] suggested that prompt and deliberate actions must be taken to avoid this scenario and increasing efforts are required to reduce suffering and mortality from malignancies. This Federal support program for patients with DLBCL allowed not only a complete basal clinical evaluation, including determination of viral serologies for HIV, HBV, HCV, but also a complete treatment with monoclonal antibody, which was reflected in a higher complete rate and overall survival.

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