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Safety and Preliminary Effect of the Anti-CD20 Monoclonal Antibody 1B8 in B Cell Non-Hodgkin's Lymphoma: Results of An Expanded Access Program

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ABSTRACT

Introduction: The expanded access program with the anti-CD20 monoclonal antibody (mAb) offered treatment for patients with CD20+ B cell non-Hodgkin's lymphoma not eligible for the Phase I/II clinical trial carried out in Cuba, or without any other better possibility of treatment. The aim was to explore the mAb safety profile in these patients. Method: Prospective, multicenter, open, uncontrolled and non-randomized study. The 81 patients who received at least one doses of the mAb previously untreated, relapsed or refractory, were included in this analysis. The mAb was administered according to Mabthera® standards. Were determined the occurrence of adverse event, the seriousness, the severity and the causality relationship. In addition, the objective response, and the Bayes Factor as a measure of the benefit-risk balance. Results: 58.0% of patients presented some adverse event. There were 245 adverse events reported, most of the related were mild and moderate. The severe and very severe events appeared in 19.8% of the patients, the serious in 6.8%, but only 6 of them were related. The most frequent AE were anemia, neutropenia, leucopenia, and eosinophilia. Treatment with the mAb induced an objective response in 85.4% (62.5% complete remission + 22.9% partial remission) of the patients evaluated at the end of the induction phase. The benefit of the treatment is seven times greater than the risk of developing a related and serious adverse event (Bayes Factor = 7.28). Conclusion: The anti-CD20 monoclonal antibody was safe in patients with CD20+ B cell NHL treated in the expanded access program.

Key points

The anti-CD20 monoclonal antibody 1B8 was safe for the patients treated in this expanded access program.

The use of the product in these patients shows a favorable benefit-risk relation.

Compliance with ethical standards

- Disclosure of potential conflicts of interest: Yaimarelis Saumell and Patricia Lorenzo-Luaces are employees of the Center of Molecular Immunology. The other authors declare that they have not conflict of interest.

- Informed Consent: All participating patients provided a signed informed consent for the administration of the drug before enrolment in the expanded access program.

- The study was approved by the research ethics committees of all the participating institutions, and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and is later amendments.

INTRODUCTION

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative neoplasms. These are the most prevalent hematologic neoplasms, representing approximately 4% of all cancer diagnoses and occupying the seventh place among all neoplasms, with a marked increase in the last four decades. [1]

In Cuba, the National Cancer Registry in relation to the incidence of NHL in the year 2013 reported 895 new cases, with a predominance of the male sex. Were diagnosed 500 cases in the male sex (9.0 gross rate and 6.2 of rate adjusted by 100000 inhabitants); and 395 cases in the female sex (which represented 7.1 of gross rate and 4.4 of rate adjusted by 100000 inhabitants). [2]

Currently in the treatment of patients with NHL is included the monoclonal antibody chimeric anti-CD20 rituximab (Rituxan, Genentech, Inc., South San Francisco, CA, USA; Mabthera, Roche, Switzerland). ThismAbbinds specifically to the CD20 membrane antigen, which is expressed in more than 95% of all B-cell NHL. [3]

Rituximab has proven to be effective both as a simple agent and in combination with chemotherapy against malignant disorders originating in B cells. [4-6] The administration of this mAb concurrent with the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) scheme or others chemotherapy regimens has become a new standard of treatment regardless of the subtype of NHL. [7] It has been found that the combination prolongs overall survival in patients with follicular lymphomas, [8-11] diffuse large-B cell lymphoma [12-16]and Burkitt lymphoma. [17]In clinical trials with marginal zone lymphomas rituximab has been demonstrated that there is a benefit in the control of the disease but not with respect to the survival. [18]

The anti-CD20 mAb 1B8 (registered later as CIMABior®, a rituximab biosimilar) was developed in Cuba by the Center of Molecular Immunology (CIM), transfected with genetic construction for the expression of a chimeric antibody. It recognizes the CD20 molecule and contains the constant regions of human immunoglobulins (subtype IgG1) and the variable regions corresponding to the anti-CD20 mAb.[19] The Cuban regulatory sanitary agency (CECMED) approved in April 2017 the use of this mAb for the treatment of CD20 positive NHL: as monotherapy for low-grade NHL (follicular or small lymphocytic who are chemo-resistant or in their second or subsequent recurrence after chemotherapy). Also was approved as monotherapy for maintenance treatment in patients with low-grade NHL (small follicular or lymphocytic) who have responded to the induction treatment, or in combination with chemotherapy for patients with follicular NHL stages III-IV who have not been previously treated and, in combination with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisolone) in patients with diffuse large CD20 positive NHL.

The expanded access program (EAP) started when the mAb was not approved yet. It was developed for placing the mAb at the disposition of those patients with indolent NHL who were not eligible for the ongoing phase I/II clinical trial (RPCEC00000138). [20] Also for those chemo-resistant or relapsing patients who have less chance of responding to chemotherapy alone, or patients with aggressive B cell CD20+ NHL, a life-threatening, long-lasting and seriously debilitating illnesses, which cannot be treated satisfactorily with any currently authorized therapies in our country. We explored the safety profile of the anti-CD20 mAb 1B8 in patients treated in the EAP, the clinical response to the treatment and the benefit-risk relation.

METHOD

The prospective, open, uncontrolled study was conducted at six centers across Cuba between February 2016 and December 2017. Were included all patients who met histologic confirmation of the diagnosis of B-cell CD20+ NHL and attended onco-hematology consultation of the six participating hospitals from the program starting until the sanitary registry of the product was obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki [21] and the applicable regulatory standards.[22]

All patients who met the diagnostic criteria and attended in the six participating hospitals were evaluated for the EAP, from the program started until the sanitary registry of the product was obtained. Those subjects who have given their consent to participate in the study were included, older than 18 years, with ECOG ≤2 and who have Hemoglobin ≥ 100 g/ L, CTL ≥ 3.0 x 109 / L, CAN ≥ 1.5 x 109 / L, platelet count ≥100 x 109 / L, transaminase ≤ 2.5 times the normal upper limit, creatinine and bilirubin ≤ 1.5 times the normal upper limit and negative values of hepatitis B and C antigens. Patients were excluded if they had evidence of NHL dissemination to the central nervous system; pregnancy or lactation period, uncontrolled intercurrent diseases, previous history of demyelinating or inflammatory diseases of the central nervous system or peripheral, positive serology to human immunodeficiency virus (HIV) or active infections due to hepatitis C or B virus. Also were excluded patients with previous malignancies (except in situ carcinoma of the cervix or non-melanoma skin cancer correctly treated), acute allergic states or history of severe allergic reactions or allergy attributed to compounds of chemical or biological composition similar to the monoclonal antibody.

The mAb was integrated into the standardized treatment regimens (immunotherapy + chemotherapy or as monotherapy), taking into account whether at the time of inclusion in the program the patient was previously untreated, was in relapse or was refractory to pre-treatment. Were administered 375 mg/m2 of anti-CD20 mAb1B8 intravenously (IV) diluted in 0.9% sodium chloride, at a concentration of 1 mg/ml. During the first infusion, the initial velocity was 50 mg/h and, after the first 30 minutes, it could be increased, in increments of 50 mg/h every 30 minutes, to a maximum of 400 mg/h. In subsequent infusions, it was possible to start with a speed of 100 mg/h and increase, in increments of 100 mg/h every 30 minutes, to a maximum of 400 mg/h. To reduce the incidence of events related to the infusion, patients

previously received 8 mg of intravenous dexamethasone, acetaminophen oral, as well as 40 mg of diphenhydramine.

The treatment standards for the original product were considered.[23] In the induction phase were administered 4 cycles if monotherapy and 6 to 8 cycles were administered if was indicated the immunotherapy concurrently with chemotherapy. Then, depending on the response to the induction treatment, the histological variety, and its treatment standards, 12 doses were indicated in the maintenance phase, 1 every 2 months. Exceptionally, the maintenance regimen was included directly, every two months and until no more than two years in those cases that, at the time of inclusion in the program, had reached an objective response to a 1st line (within a period no longer than 4 months after reached the remission), with schemes that did not contain monoclonal antibodies due to their non-availability, or with the original product Rituximab but it was not available to continue the maintenance stage.

It was determined the occurrence of adverse event in all the subjects treated, the seriousness of AE, the severity, and causality relationship. The seriousness and the causal relationship were assessed according to the criteria of the International Conference on Harmonization (ICH).[24]Serious AE were defined as any adverse event that results in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, resulted in a congenital abnormality or birth defect, or other medically important. The severity was graded according to the Common Toxicity Criteria for Adverse Events (version 4.0) from the U.S. National Cancer Institute´s Cancer Therapy Evaluation Program. [25]The causality relationship was determined with the algorithm of World Health Organization by using the categories: certain/very probable, probable, possible, unlikely and unclassified. [26]All enrolled patients who took at least one dose of the anti-CD20 mAb were evaluable for safety. All AEs, regardless of drug attribution, were recorded from the first dose of the mAb until 60 days after treatment discontinuation.

The effect was measured through the clinical response, in accordance with the standards of the onco-hematology Cuban services, and was assessed 4-6 weeks after the end of the last cycle of treatment in patients treated with the mAb as monotherapy. In patients treated with the mAb in combination with chemotherapy, the clinical response was evaluated at the end of the 4th cycle if 6 cycles were indicated, or at the end of the 6th if 8 cycles were indicated. The response was classified according to the standardized criteria for NHL in: complete

remission (CR), partial remission (PR), stable disease (SD) or progressive disease (PD). [27]The antitumor therapeutic effect was evaluated considering the objective response (OR): CR+ PR. The effect was analyzed in the 48 patients who received the induction treatment scheme (at least 4 doses of the mAb) and it was possible to perform the response evaluation.

All the information of the patients, general data, AEs and response to treatment was described by the researcher in each patient's clinical history and by the clinical research coordinator in the electronic patient's collection form, using the XAVIA_Clinic as software platform.

As a measure of the benefit-risk balance was estimated the Bayes Factor (BF: likelihood ratio between benefit and risk) [28] by estimating a difference between two proportions using the EPIDAT program. The BF ≥1 expresses evidence in favor of the benefit. It was considered as a benefit the objective response, and as risk, the occurrence of some serious AE first, and in a second analysis, the occurrence of some serious and related AE.

RESULTS

Patient characteristics

Between February 2016 and June 2017were treated with the anti-CD20 mAb 87 patients with the diagnosis of B-cell CD20+ NHL, at one of the six Cuban centers in the EAP. Of these 81 received at least one doses. (Figure 1)

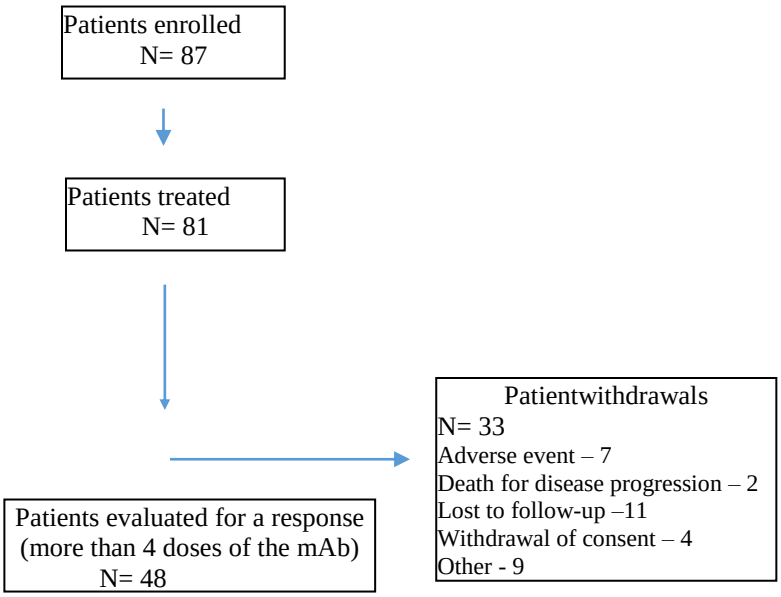

Figure 1. Overview of the EAP patient's population

Baseline characteristics are provided in Table 1. In the treated population were similar the number of men and women, with an average age of 61.0. The 57.9% of patients included in the program had a diagnosis of aggressive LNH and 56.1% of these were diffuse LNH of large B cells. (Table 1)The majority of the analysis patients received the combined treatment. The most used schemes included CHOP and its variants (38.7%).

Table 1. Baseline characteristics of the study population

Characteristic		Anti-CD20 mAb		Anti-CD20 mAb +CT		Total	
		No.	%	No.	%	No.	%
N		19	100,0	62	100,0	81	100,0
Sex	Men	8	42,1	34	54,8	42	51,9
	Women	11	**57,9**	28	45,2	39	48,1
Age (years)	*Mean ± SD*	*63,19±13,9*		*58,32±12,85*		*59,64±13,25*	
	Range	*28-79*		*23-82*		*23-82*	
Degree of malignancy	Aggresive	*8*	*42,1*	*34*	*54,8*	*42*	*51,9*
	Indolent	*11*	*57,9*	*28*	*45,2*	*39*	*48,1*
Histological subtypes	Diffuselarge B cells	***5***	***26,3***	***18***	***29,0***	***23***	***28,4***
	NHL of mantlecells	*0*	*,0*	*6*	*9,7*	*6*	*7,4*
	NHL of intermediate cell	*2*	*10,5*	*6*	*9,7*	*8*	*9,9*
	NHL intermediate and large B cells	*0*	*,0*	*2*	*3,2*	*2*	*2,5*
	NHL of marginal zone	*1*	*5,3*	*1*	*1,6*	*2*	*2,5*
	Follicular NHL	***5***	***26,3***	***11***	***17,7***	***16***	***19,8***
	Small cell lymphocytic lymphoma	***4***	***21,1***	***12***	***19,4***	***16***	***19,8***
	Lympho plasmacytic NHL	*0*	*,0*	*2*	*3,2*	*2*	*2,5*
	NHL without other specification	*1*	5,3	*4*	6,5	*5*	6,2
	Chronic linfocitic leukemia	*1*	*5,3*	*0*	*,0*	*1*	*1,2*
Ann Arbor	Ia	*1*	*5,3*	*7*	*11,3*	8	*9,9*
	Ib	*1*	*5,3*	*0*	*,0*	*1*	*1,2*
	IIa	*2*	*10,5*	*4*	*6,5*	*6*	*7,4*
	IIb	*1*	*5,3*	*3*	*4,8*	*4*	*4,9*
	IIIa	*4*	*21,1*	*8*	*12,9*	*12*	*14,8*
	IIIb	*1*	*5,3*	*11*	*17,7*	*12*	*14,8*
	IVa	***5***	***26,3***	***18***	***29,0***	***23***	***28,4***
	IVb	*4*	*21,1*	*11*	*17,7*	*15*	*18,5*
Status of the disease at the inclusion in the program	Previously untreated	***10***	***52,6***	***33***	***53,2***	***43***	***53,1***
	Refractory	*1*	*5,3*	*9*	*14,5*	*10*	*12,3*
	Relapse	*4*	*21,1*	*20*	*32,3*	*24*	*29,6*
	Response to 1st line of treatment	*4*	*21,1*	*0*	*0,0*	*4*	*4,9*

Characteristic	Anti-CD20 mAb		Anti-CD20 mAb +CT		Total	
	No.	%	No.	%	No.	%
N	19	100,0	62	100, 0	81	100, 0
Total	*19*	*100,0*	*62*	*100,0*	*81*	*100,0*

Adverse events

In 47patients (58%) some AEwere reported: 11patients belong to the group who received the mAb 1B8 as monotherapy and 36 belong to the group who received the mAb + CT (Table 2).

A total of 245 adverse events of 75 different types were recorded (36 in the mAb group and 209 in the mAb + CT Group). The severe and very severe AE were reported in the 18.0% of patients who presented some AE. 156 treatment-related AE(63.7%) were recorded in 19.8% of patients. Only appears SAE treatment-related in 8 patients (3.8%) of those treated with the combination.

Table 2. General Information of Adverse Event

Categories of patients and adverse events (AE)	T Received treatment		Total N=81
	Anti-CD20 N= 62	Anti-CD20 + CT N= 19	
	N (%)	N (%)	N (%)
Patients with some adverse event	11 (57.9)	36 (58.1)	47 (58)
Patients with some treatment-related AE	10 (52.6)	27 (43.5)	37 (45.7)
Patients with some severe or very severe AE	3 (15.8)	13 (21)	16 (19.8)
Patients with some severe or very severe treatment-related AE	2 (10.5)	7 (11.3)	9 (11.1)
Patients with some serious treatment-related AE	0 (0)	6 (9.7)	6 (7.4)
Total of AE	36 (100)	209 (100)	245 (100)
Treatment-related AE	32 (88.9)	124 (59.3)	156 (63.7)
Severe or very severe AE	3 (8.3)	41 (19.6)	44 (18)
Severe or very severe treatment-related AE	2 (5.6)	18 (8.6)	20 (8.2)
Serious treatment-related AE	0 (0)	8 (3.8)	8 (3.3)

The 80.2% of the patients presented fourth or fewer AEs, predominant this characteristic in both groups (89.5% of those treated with monotherapy and 77.4% of those treated with the combination).

In general, the most frequently AE appeared were anemia (8.2%), hyperglycemia (7.8%), fever (7.3%), neutropenia (6.1%), leucopenia (5.7%), eosinophilia (5.3%), diarrhea (2.9%), weight loss (2.9%) and hypotension (2.9%). Figure 1 shows the 10 most frequent adverse events and their causal relationship with the product, highlighting among these those that were also classified as severe or very severe according to the severity.

<Figure 1. The ten most frequent adverse events appeared in the EAP and their causal relation with the mAb. Supplementary material>

In general, were registered 17 (8.1%) SAE, none in the group treated with the mAb as monotherapy. (Table 2)

The majority of the AEs were classified as mild (40.7%) and moderate (45.7%). The 43.3% of the AEs were classified as a possible relation with the administration of the mAb.There are no significant differences between the groups in the intensity of the AEs found.

Table 2. Adverse events evaluation criteria

Evaluation criteria	Received treatment				Total		p-value
	Anti-CD20		Anti-CD20 + CT				
	No.	%	No.	%	No.	%	
Seriousness							
Serious	0	0	17	8.1	17	6.9	0.012
Non-serious	35	97.2	192	91.9	227	92.7	
Severity							
Mild	11	30.6	88	42.1	99	40.4	0.126
Moderate	21	58.3	79	37.8	100	40.8	
Severe	3	8.3	35	16.7	38	15.5	
Very severe	0	0	2	1	2	0.8	
Death	0	0	4	1.9	4	1.6	
Causality							
Certain	7	19.4	13	6.2	20	8.2	0.002
Very probable	0	0	2	1	2	0.8	
Probable	5	13.9	23	11	28	11.4	
Possible	**20**	**55.6**	**86**	**41.1**	**106**	**43.3**	
Not related	3	8.3	84	40.2	87	35.5	

Treatment effect

As a result of the overall analysis of the response in the evaluated patients were reached 85.4% of objective response (62.5% of CR + 22.9% of PR) and 93.5% of disease control (Table 3). The greatest response benefit was obtained in the subgroup that received treatment

with the anti-CD20 mAb 1B8 combined with CT (87.5% of OR, 65.0% CR + 22.5% PR)(Table 3)

Table 3: Distribution of patients assessed according to the clinical response reached.

Response evaluation	Anti-CD20 mAb group		Anti-CD20 mAb + CT group		Total	
	No.	%	No.	%		
Complete remission (CR)	4	50,0	26	65,0	30	62,5
Partial remission (PR)	2	25,0	9	22,5	11	22,9
Stable disease (SD)	0	0,0	4	10,0	4	8,3
Progressive disease (PD)	2	25,0	1	2,5	3	6,3
Total	8	100,0	40	100,0	48	100,0
Objective response (OR= CR+PR)	6	75,0	35	87,5	41	85,4
Disease Control (DC= CR+PR+SD)	6	75,0	39	97,5	45	93,7

In the aggressive NHL stratum (rapid growth) the previously untreated patients reached 90.9% of OR, while in the subgroup of refractory/relapsed aggressive (population of worst prognosis) reached objective response the 66.7% of the patients evaluated. For the NHL of Indolent course was reached 100% of ROin the subgroup of refractory/relapsed while 88.9% in previously untreated patients. (Table 4)

Table 4: Objective response achieved according to the degree of malignancy and the disease status.

Degree of malignancy	Status of the disease	Objective response (CR+PR)	No.	%
Aggressives (N=28)	Previously untreated	CR+PR	17	89,5
		SD + PD	2	10,5
		Total	19	100
	Refractory/ Relapsed	CR+PR	5	55,5
		SD + PD	4	44,5
		Total	9	100
Indolents (N=20)	Previously untreated	CR+PR	11	100
		SD + PD	0	0,0
		Total	11	100
	Refractory/ Relapsed	CR+PR	8	88,9
		SD + PD	1	11,1
		Total	9	100

In the subgroup of aggressive refractory/relapse patients, OR was reached in 55.5% of the patients, whereas in patients with indolent refractory/relapse disease 88,9% of OR was reached.

When evaluating the benefit-risk relationship considering the possibility of presenting a serious adverse event, it was found that the benefit of receiving the treatment was 4 times greater than the risk of presenting a serious adverse event (BF = 4.25).

When evaluating the risk of presenting serious adverse events related to the administration of the mAb, it was found that the benefit of receiving the treatment is 7 times greater than the risk of developing a related serious adverse event (BF = 7.28).

DISCUSSION

Safety analysis

The safety profile analyzed showed that the anti-CD20 mAb was safe during the EAP, and the reactions were very similar to the original rituximab.

In general, the incidence in the program of infusional reactions related to the administration of the anti-CD20 mAb was very low. The fever, one of the highest incidences of AE, is usually reported as a symptom related to perfusion, as well as chills and transient hypotension; although the latter appears less frequently. [14] These infusional reactions are due to the activation of complement and consequent release of cytokines produced by the action of rituximab. [15]

The absence of infusion-related symptoms that were considered serious events in the series of patients treated with the mAb in the program might be is due to the knowledge of the product's management (the product was used low strict conditions and using the indicated premedication).No other serious infusional reactions such as anaphylaxis and allergic reactions were reported, which are the most common serious AE associated with the administration of rituximab in approximately 80-90% of the clinical trials published to date. [29]

Anemia, a related event that appeared most frequently in the program, is also reported among the most frequent events for the reference product, as well as other alterations of the hemolymphopoietic system, such as neutropenia, leukopenia, and thrombocytopenia.

However, the fact that these four events have appeared in more than 90% of the cases of the group treated with the monoclonal concurrent with chemotherapy, suggests that, as stated in the medical literature, cytopenia is generally more common in patients treated with chemotherapeutic agents that induce myelosuppression. It has not been shown if these cytopenia have clinical implications. [29, 30] Similarly, although combined therapy can cause leukopenia and/or essentially lymphopenia, the risk of developing serious infections is not conclusive either. On the one hand, the number of patients considered is not enough to assess the risk of the appearance of these events in the studies carried out so far. On the other hand, as with other products, the degree of induced immunosuppression does not necessarily correlate with the predisposition to develop a serious infection. [31]

Although studies have shown an increased frequency of infectious complications with rituximab up to one year after the completion of the treatment, most infections either resolved or were treated without significant sequelae. According to Mabthera registry information, of 356 patients with NHL treated with the product, 31% developed bacterial infections, 10% developed viral infections, and 1% developed fungal infections. [32]

In this program only two cases of pneumonia were reported and three other respiratory infections, one herpes zoster and one cutaneous mycosis. None of these belongs to the group treated with the antibody as monotherapy and only one case of pneumonia was classified as severe and related to the product.

It has been described that there is a dose-dependent increase in the frequency of infections in patients treated with rituximab, and although elderly patients have a higher risk of developing severe infectious complications, such infections are rarely fatal. [33]

The eosinophilia was another frequent AE reported in the program, all the cases with possible or probable causal relationship.

There is no evidence of the appearance of eosinophilia as an isolated event in patients treated with Mabthera. However, eosinophilia has been identified as part of a picture of hypersensitivity pneumonitis after the administration of rituximab, which yields after stopping treatment and administering steroids. This picture is reported in the literature as a rare event and presents with hypoxemia, dyspnea and pulmonary infiltration. [34]

But it should be taken into account that, independently of the situations in which eosinophils and their precursors are properly affected in the bone marrow, peripheral eosinophilia can

occur in other diseases in which there is eosinophilopoietic cytokine release, as is the case of non-Hodgkin lymphomas. According to the literature, moderate eosinophilia occurs in 5% of patients affected by this disease. Even in B-cell lymphomas. [35]

Only two serious AE whose cause the death of patients were attributed to the investigational product (one septic shock and one acute myocardial infarction). Both were classified as possible, mainly addressing the temporal relationship between the administration of the product and the occurrence of the AE. The rest of the serious AEs that caused the death were classified as not related to the administration of the product.

All the safety results were very similar to those reported previously by Fernández in a similar compassionate use number of cases. [36]

Effect analysis

Although the program does not have a methodological design to confirm efficacy, and the number of patients per subgroup is small, the heterogeneous nature of the treated population adds external validity to the result, since it is closer to the usual medical practice where different histological varieties of CD20 + B-cell NHL are treated. [29] On the other hand, most of the CD20 + B-cell NHL included in the program belong to the 4 subtypes of NHL identified as the most common (diffuse large-cell NHL, follicular NHL, lymphocytic NHL small and LNH of the mantle). [1]

The analysis of the clinical response for this program was made in the population that met the minimum treatment scheme indicated (4 cycles of the mAb). This behavior, together with the fulfillment of elementary ethical aspects, and the rigor and quality in obtaining the data of the patients of the program, contributed confidence to the results although it does not constitute first level of evidence.

The rate of OR, and the predominance of complete responses in the subgroup treated with the anti-CD20 mAb 1B8 concurrent with CT, ratifies the numerous evidence of greater benefit of rituximab combined with chemotherapy. [29, 30]In spite of the limited number of cases of each histological subtype, preliminary clinical observations, as well as other studies, suggested the superiority of R-CHOP.

Although aggressive NHL has a shorter evolution, more than 50% of patients can be cured with intensive combined CT regimens. The guide of the National Comprehensive Cancer

Network recommends that patients with this type of disease, given their high morbidity and mortality, be enrolled in clinical trials as soon as possible, by looking for better treatment options. [1]

Indolent NHL have a better prognosis because of their slow growth rate, however, in advanced clinical stages they are not usually curable. In this program, patients included with indolent NHL were mainly from the small lymphocytic NHL and follicular NHL varieties.

In Cuba, the medical needs of availability of rituximab for patients with lymphomas are not covered and the acquisition of this product in the international market is hindered by the high price, being impossible to meet the demands. The possibility of having a Cuban biosimilar would significantly improve the clinical response of these patients to the treatment and influence a better survival of Cuban patients, as well as saving important resources for the country.[36]

Practical aspects

We recognized that this was an analysis of data from an EAP that was not designed to compare efficacy outcomes between patient subgroups. The overall survival will be estimated at two, three and five years of having included the last patient in the program so; this outcome and the progression-free survival (PFS) were not considered in this preliminary analysis.

Results from Cuban health institutions may have also been influenced by national patient management trends. Notwithstanding the EAP provided an important opportunity to assess a situation closely resembling real world clinical practice. After de culmination of the ongoing phase IV clinical trial with the product in the same indication, future research should focus on assessing another real-life outcomes and increasing the number of patients who benefit with the treatment.

CONCLUSION

The product was safe and well tolerated by the patients treated in the program. The anti-CD20 mAb (CIMABior®) showed some evidence of an effect on the clinical response of patients with aggressive or indolent B-cell CD20+ NHL and the benefit of using the product was greater than the risk of developing a serious adverse event related to the use of the product.

Authors' contributions

CH, YS, JDF, and PL were involved in designing the study and statistical analysis. All the authors were responsible for the data acquisition, data analysis and interpretation. All the authors contributed to the preparation, editing, and review of this manuscript. All authors read and approved the final manuscript.

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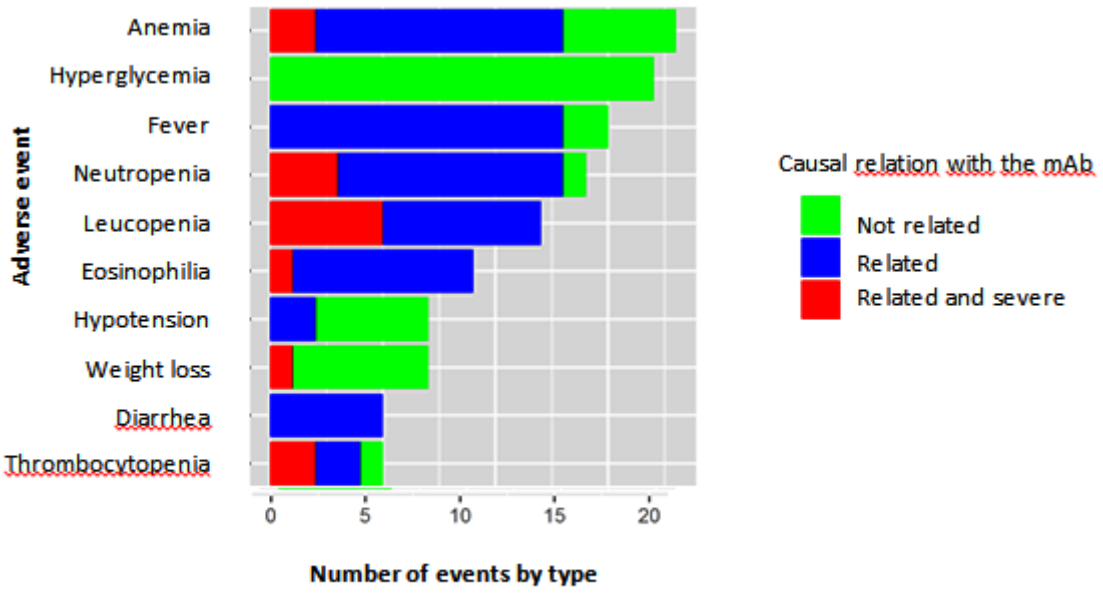

Figure 1 The ten most frequent adverse events appeared in the EAP