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Therapeutic Results of Rituximab Combined with CHOP-Type Chemotherapy in Diffuse Large-Cell B Lymphomas in Sub-Saharan Africa: Case of Cote d'Ivoire

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Abstract: *The addition of Rituximab with CHOP-type chemotherapy has significantly improved the survival of patients with diffuse largeB-cell lymphoma (LBDGC). The objective of the present study was therefore to evaluate the results of Rituximab associated with CHOP in LBDGCs hospitalized patient from April 2010 to February 2018, i.e. over a period of eight years through a multicenter descriptive study. The endpoints were Therapeutic Response, and Study of Survival. The mean age was 55 ± 13 years with a predominance of men. 83% of the patients presented an* ***IPI*** *score 3 and 4 therefore a poor prognosis. The complete response was 57% of cases. The mean overall survival was 15 months; The probability of overall survival at 1 year was 56.54% and 32.33% at 5 years. The probability of progression-free survival was 65% at 1 year and 36% at 5 years. Death occurred in 37%, mostly related to disease progression. 3 patients were lost to follow-up, 12 patients still alive and 4 patients in relapse.*

In conclusion, monoclonal antibodies has brought a considerable advance in the treatment of non-Hodgkin's lymphoma. Adding Rituximab to CHOP-type chemotherapy in LBDGC improves the complete response and survival of our patients. Unfortunately, very few patients have access to this therapy because of the lack of financial means of most of our patients.

Keywords: *LBDGC, Rituximab, Treatment outcomes*

1. Introduction

B lymphoproliferative pathologies are the most frequent malignant hemopathies in Africa. Among them, diffuse large B cell lymphomas represent 30% of all non-Hodgkin lymphomas [1]. The use of CHOP-type chemotherapy (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone) has long been the gold standard in the treatment of LBDGC for the past 40 years. The addition of Rituximab along with CHOP-type chemotherapy has significantly improved the survival of patients with diffuse large-cell B-cell lymphoma (LBDGC). The first randomized study comparing CHOP versus RCHOP-type chemotherapy was reported by the Adult Lymphoma Study Group (GELA) in the LNH-98.5 trial [2]. These preliminary results were obtained after a median follow-up of 2 years with significant improvement in the therapeutic response and survival of patients treated with the RCHOP protocol.Indeed, the overall survival probability at 5 years confirmed the benefit of the combination Rituximab with CHOP-type chemotherapy [3]. Several other randomized studies have demonstrated the benefit of RCHOP in the treatment of LBDGC and other subtypes of B lymphoma [4]. Despite the significant progress made by monoclonal antibodies in lymph proliferations in the West, very few studies in sub-Saharan Africa reports the contribution of rituximab associated with chemotherapy in B lymphoproliferative pathologies and particularly LBDGC. Chemotherapy using the CHOP protocol remains the standard treatment for two main reasons: the first remains the unavailability of Rituximab, and the second happens to be the high cost of this immunotherapy, the unit box of which is estimated at £ 1,800 in a country in the process of development with a modest GDP per capita (1521 USD), with an HDI index of 0.452. Note the lack of health coverage. Despite these facts, some populations have private insurance that allowed access to rituximab. The objective of the present study was therefore to evaluate the results of Rituximab associated with CHOP in LBDGC in our country.

2. Patients and Methods

This descriptive longitudinal cohort study was carried out in three centers: a public structure, the clinical hematology teaching hospital of Yopougon, and two private structures, the

Polyclinique international Sainte Anne Marie (PISAM) and the medical clinic hospital of DANGA in Abidjan. Were eligible, patients over 18 years old, with diffuse large B-cell lymphoma newly diagnosed, according to the WHO criteria (World Health Organization) [5], hospitalized from April 2010 to February 2018, i.e. for a period of eight years; treated with the combination of rituximab and CHOP-type chemotherapy. Patients with comorbidities and patients whose general condition did not allow chemotherapy to be started were excluded from the study. Also excluded were HIV positive patients and those with positive hepatitis B or C serology. The diagnosis of BDGC lymphoma was based on immunohistochemistry carried out in partnership with the Pasteur Cerba laboratory in Paris (France).All of the patients were evaluated using standard laboratory tests, computed tomography (CT) scans, along with a visual assessment. Additional information was also abstracted, including age, sex, performance status, presence of B symptoms (fever, night sweats, and weightloss), presence of extranodal disease, presence of BM involvement, International Prognostic Index (IPI) scoring system [9], serum lactate dehydrogenase (LDH). All patients were staged according to the Ann Arbor Staging classification using CT scans [10].

3. Therapeutic Conduct

Patients received Rituximab at a dose of 375 mg /m2 on Day 1 of each cycle associated with CHOP which includes 750 mg/m2 Cyclo phosphamide, 50 mg / m2 Doxorubicin, 1.4 mg / m2 Vincristine with a maximum dose of 2 mg on day 1 and 40 mg / m2 / day of Prednisone from D1 to D5 for each treatment cycle. Patients received one cycle of treatment every 3 weeks for a total of 8 cycles.

4. Evaluation

Response to treatment was assessed after 8 cycles or upon discontinuation of treatment. This assessment was based on clinical and whole-body CT examination on laboratory parameters. This assessment was done every 3 months for the first two years, then every 6 months for the next three years. The endpoints were complete remission (CR) which is the disappearance of all clinical and subclinical tumor sites. This response may be partial. At the same time, we assessed overall survival (OS), and progression-free survival. (PFS) defined according to the criteria of the International Workshop.

5. Statistical analysis

The data collected were recorded using the statistical software SAS graph generic driver 2009. The KAPLAN MEIR curve was used to express survival and the survival test made it possible to specify the probability of patient survival. Survival was based on 30 patients selected on the criteria of the existence of an inclusion date (entry date) and peak date (date of death or latest news) mentioned in days, months, years.

This study was approved by the institutional review board of our country.

6. Results

In terms of general characteristics (Table 1), the study population consisted of patients whose mean age was 55 ± 13.93 years with extremes of 27 and 76 years. Concerning sex, we note a male predominance with a sex ratio of 2. Concerning the socio-economic level, our series was marked by a predominance of patients of average socio-economic level 70%. The rest consisted of patients of high (23%) and low socioeconomic level with 7%. Concerning to The ECOG score, our study showed that 77% of the patients had an ECOG index ≥2. Clinically and biologically, the tumor location was exclusive lymph node in 37% of cases, and lymph node and extranodal in 50% of cases. The primary extranodal forms were poorly represented with 13% of cases. These attacks were mostly generalized. In fact, 77% of patients were in stages III and IV of Ann Arbor staging. We noted a predominance of clinical (80%) and biological (87%) symptoms. Overall LDH was elevated in 54.55% of cases, while beta2microglobulinemia was elevated in only 33%. From a prognostic point of view, 83% had an IPI score 3 and therefore 4 had a poor prognosis. From a therapeutic standpoint, the time taken to start treatment was mainly greater than or equal to 15 days in more than half of our patients, ie 60%. In our series, the complete response was 57% of cases (Table 2). Partial response in 13%, failure in 17%. Two patients could not be assessed. The mean overall survival was 15 months; the overall survival at 1 year was 56.54% and 32.33% at 5 years (Fig.1), and the progression-free survival was 65%at 1 year and 36% (Fig.2). In terms of side effects, a higher incidence of neutropenia is noted in 66, 67% of cases; in particular grade 3 and 4 in 36.67% and 23.33% of cases respectively. Other haematological effects were rarely observed. Nine (9) cases of anemia including 2 grade 2, 3

grade 3 and 4 grade 4 and one (1) case of grade 3 thrombocytopenia were observed in our series of patients. Regarding non-haematological effects, we observed 8 cases of reaction to Rituximab infusion like fever, pain, and rash. We observed 3 cases of renal toxicity, 2 cases of digestive and metabolic toxicity respectively, and 1 case of neuropathy. The combination of Rituximab plus chemotherapy was relatively well tolerated with side effects similar tothose seen with multidrug therapy. Regarding the outcome (Table 2), death occurred in 11 cases, or 37%. 4 patients were lost to follow-up, 12 patients still alive and 4 patients in relapse. The causes of death were mainly due to the progression of the disease in 9 patients, 2 cases of septic shock.

Table1. *Patient Characteristics*

Parameters	**effective n=30, %**
Age at diagnosis (years)	
< 30	02 (6%)
30-60	20 (67%) Mean age=55±13
≥ 60	08 (27%)
Socio-economic level	
Low	02 (7%)
Mean	21 (70%)
high	07 (23%)
Gender	
Male	20(67%)
Female	10(33%)
ECOG Scoring	
0-1	07(23%)
≥ 2	23 (77%)
Tumoral location	
Nodal	11(37%)
Nodal and extra nodal	15(50%)
Extranodal site	04(13%)
Ann Arbor staging	
I-II	07(23%)
III-IV	23(77%)
Systemic symptoms	**n %**
A	06(20%)
B	24(80%)
LDH value	
Normal	14(46%)
High	16(54%)
Beta2microglobulinea	
Normal	20(67%)
High	10(33%)
Score IPI	
1-2	05 (17%)
3-4	25(83%)

Values are presented as number (%). ECOG, Eastern Cooperation Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

Table 2. *Treatment response and evolution*

Parameters	**effective (n)(%)**
Therapeutic response	
Complète Response	17 (57%)
Partial Response	04 (13%)
Failure	05 (17%)
Non Evaluable	04 (13%)
Survival status	
Death	11 (37%)
Alive	12 (40%)
Unknown	03 (10%)
Relapse	04 (13%)

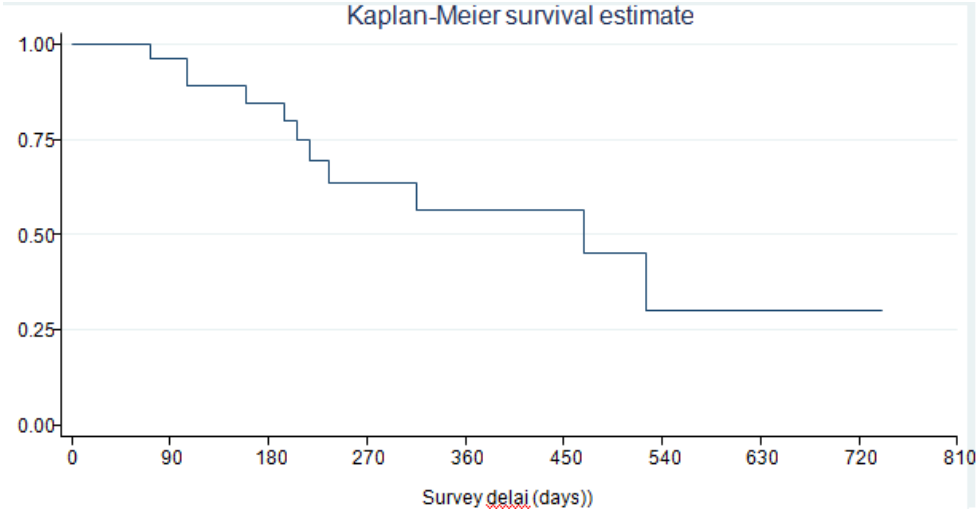

Fig1. *Overall Survival Rate*

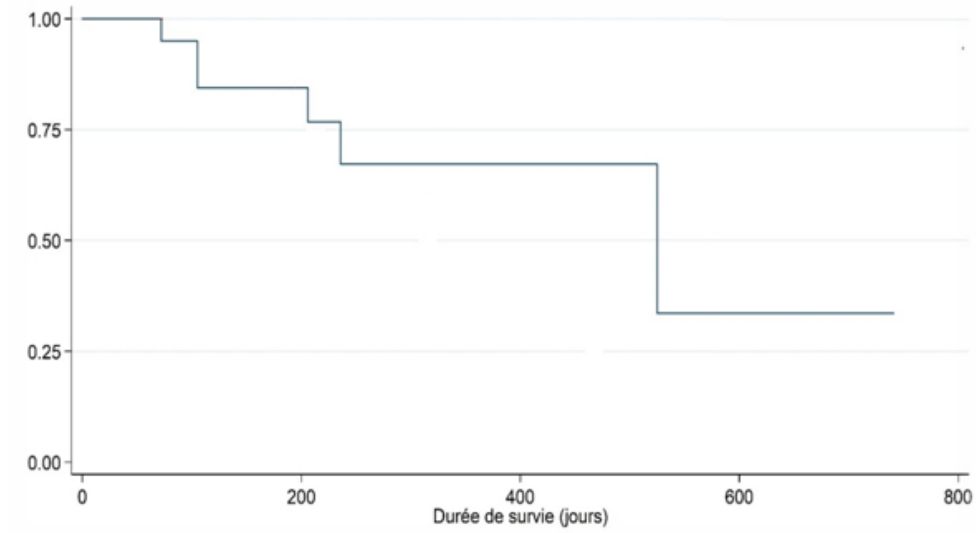

Fig2. *Progression free Survival rate*

7. DISCUSSION

From April 2010 to February 2018, 30 patients with LBDGC treated with the Rituximab protocol combined with CHOP-type chemotherapy were collected. This low number is explained by the high cost of Rituximab, which is not accessible by many patients of our country mainly in low socio-economical level. The R-CHOP regimen which combines Rituximab with CHOP is considered today as the standard first-line treatment for patients with diffuse large B-cell lymphoma. In our series, we noted an overall response of 70% of which 57% full response and 13% partial response. The failure was found in 17%. However, this response rate remains high compared to our previous study by the clinical hematology service on CHOP in BDGC IPI 3 and 4 lymphoma, achieved with a complete remission rate of 43% [6]. With a median follow-up duration of 15 months (range, 0,1 to 80.7 months) among patients who were alive at the last follow-up, the five-years OS and PFS rate was32,33% and 36%, respectively as shown in Fig. 1,and fig.2.Our results in terms of survival are better than our previous results concerning CHOP in diffuse large B cell lymphomas where we observed 18% progression-free survival at 5 years [6]. Our results nevertheless fall short of those of Western literature.

Indeed, after the first phase II studies demonstrating the benefit of rituximab alone or in combination with CHOP-type chemotherapy in relapsed or refractory LBDGC and in first-line [2, 7], several phase III studies were rapidly reported.The GELA study was the first to demonstrate the superiority of the chemotherapy arm (CHOP-21) plus rituximab compared to the chemotherapy alone arm in a prospective, randomized study in elderly patients (≥ 60 years old) with first-line LBDGC [4]. The presentation at the 2007 ASCO Congress of the

results of this study with a 7-year follow-up confirmed the maintenance of this superiority. Indeed, at 7 years, the benefit in terms of overall survival is still highly significant in favor of the arm with AcMo: OS 53% versus 36%; p = 0.0004 [8.9]. The US ECOG / CALGB study, with the participation of SWOG, also looked at the addition of rituximab to CHOP-21-type chemotherapy. The goal was failure-free survival (FFS) [10]. This prospective phase III trial in elderly patients (61-80 years) randomized rituximab for induction and for maintenance. Although different and not comparable to the French trial (double randomization, fewer cycles of rituximab), the results (based only on induction) also confirm the superiority of the rituximab-CHOP (R-CHOP) arm versus CHOP with a FFS projected at 3 years and estimated at 52% versus 39% [11]. On the other hand, the continuation of rituximab in maintenance treatment after chemotherapy of the RCHOP type does not seem to show any benefit on the maintenance of the response, with a relapse rate at 2 years of 85% in the observation arm versus 61% in the maintenance arm (p = 0.13) [12]. The comparison between these two trials finally shows similar results and above all indisputably in favor of the arm containing rituximab, with a 3-year FFS of 53% and 52% for R-CHOP (versus 35% and 35% for CHOP) and an OS of 62% and 67% for RCHOP (versus 51% and 58% for CHOP) for the GELA and ECOG / CALGB studies respectively [10]. The results of these two prospective trials were confirmed by a Canadian study [13]. Although retrospective, this compared 140 patients - median follow-up 42 months, patients treated before. The advent of rituximab with CHOP-type chemotherapy – to 152 others – median follow-up 24 month, patients who received rituximab 24 to 72 hours after treatment with CHOP. As the two groups were comparable, especially in terms of pronostic factors, OS was significantly highest in the group that received AcMo (p)**.** Compared to the western data above, our response rate is low with shorter survival in our patients with LBGDC treated with the RCHOP protocol. These results are correlated with the poor prognosis of our patients who mainly had an IPI 3 and 4 prognostic score with advances forms and long diagnostic delay. The small size of our study population could constitute a limitation in the interpretation of our results. This low number is due to the inacessibility of Rituximab whose unit cost of the box is 1800 Euro for a population mainly of unfavorable socio-economic condition.

Regarding side effects, the rituximab plus chemotherapy combination was relatively well tolerated with side effects similar to those seen with chemotherapy alone. These side effects were an haematological and non-haematological nature. From an haematological plan, a higher incidence of neutropenia was noted in 66.67% of cases, including 36.67% of grade 3 and 4. The other haematological effects were rarely observed. Regarding non-haematological effects, we observed 8 cases of reactions to the infusion of Rituximab, these were fever, pain, rash, urticaria and muscle cramp. These reactions are generally described in the literature [14, 15]. We observed 3 cases of renal toxicity and 2 cases of digestive and metabolic toxicities. The combination of Rituximab plus chemotherapy was relatively well tolerated with adverse effects similar to those observed with multidrug therapy, however, there is a higher incidence of neutropenia as reported by Markus et al [16]. Adverse effects are generally seen with Rituximab but are generally well tolerated and do not affect the quality of life of patients [17]. Eleven (11) cases of pulmonary and digestive infectious complications were observed. Regarding the evolution of our study population, we observed a death rate of 37% or 11 cases, 13 patients still alive and 3 lost to follow-up. These deaths were largely related to septic shock. It is important to emphasize that our death rate clearly shows the difficulties inherent in the management of NHL in our context of exercise in relation to the low socioeconomic level and the limitation of most of our technical platform. However, this death rate remains lower compared to a previous study by our clinical hematology service on CHOP in the LBDGC, which found 51% of deaths largely due to the progression of the disease or the toxicity of the treatment. [6]. In conclusion, the arrival of monoclonal antibodies has brought a considerable advance in the treatment of non-Hodgkin lymphoma. Rituximab, available since 2005 in our country, has become a leading therapy for the treatment of BDGC lymphomas. The effectiveness of adding Rituximab to chemotherapy gives results far above those seen with chemotherapy alone as reported in our previous studies. Unfortunately very few patients have access to this therapy because of the lack of financial means of most of our patients.

REFERENCES

[1] Harris NL, Jaffe ES, Stein H, *et al.* A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. *Blood* (1994) 84, 1361-1392.

[2] Coiffier B, Haïoun C, Ketterer N et al. Rituximab (antiCD20 monoclonal antibody) for the treatment of patients with relapsing or refractory aggressive lymphoma. A multicenter phase II study. Blood 1998; 92:1927-32.

[3] Feugier P, Van Hoof A, Sebban C, et al. Long term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-celllymphoma: a study by the Group ed'Etude] des Lymphomes de l'Adulte. *J Clin Oncol.* 2005;23(18):4117-4126.

[4] Coiffier B, Lepage E, Briere J et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large B-cell lymphoma. N Engl J Med 2002; 346:235-42

[5] Swerdlow SH. Campo E. Harris NL. Jaffe ES. Pileri SA. Stein H. et al. WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues. IARC : Lyon 2008

[6] ToloDiebkile A, Boidy K, E N'dhatz et al.Characteristics and Results of the Management of Diffuse Large B-Cell Lymphomas: The Experience of C^ote d'Ivoire. Advances in Hematology Volume 2012, Article ID 945138, 6 pagesdoi:10.1155/ 2012/945138

[7] Vose JM, Link BK, Grossbard LM et al. Phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive non Hodgkin's lymphoma. J Clin Oncol 2001;19:389-97

[8] Feugier P, Van Hoof A, Sebban C et al. Long term results of the R-CHOP study in the treatment of elderly patients with diffuse B-cell lymphoma: a study by the Groupe d'étude des lymphomes de l'adulte. J Clin Oncol 2005; 23:4117-26.

[9] Coiffier B, Feugier P, Mounier N et al. Long-term results of the GELA study comparing R-CHOP and CHOP chemotherapy in older patients with diffuse large B-cell lymphoma show good survival in poor risk patients. ASCO Annual Meeting JCO 2007;25:443s, abstract 8009.

[10] Habermann TM, Weller EA, Morrison VA et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol 2006;24:3121-7.

[11] Habermann TM. Antibodytherapy in aggressive lymphomas. Hematology Am Soc Hematol Educ Program 2007:257-64.

[12] Morrison VA, Weller EA, Habermann TM et al. Maintenance rituximab (MR) compared to observation (OBS) after R-CHOP or CHOP in older patients (pts) with diffuse large B-celllymphoma (DLBCL): an intergroup e4404/C9793 update [abstract]. Proc ASCO 2007;25:443s.

[13] Sehn LH, Donaldson J, Chhanabhai M et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-celllymphoma in British Columbia. J Clin Oncol 2005;23(22):5027-33.

[14] McLaughlin P, Grillo-Lopez AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol. 1998;16:2825–33.

[15] Ghielmini M, Schmitz S-FH, Cogliatti SB, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly _4 schedule. Blood. 2004;103:4416–23.

[16] MARCUS R., IMRIE K., SOLAL-CELIGNY P., *et al.* Phase III study of R-CVP compared with cyclophosphamide, vincristine and prednisone alone in patients with previously untreated advanced follicular lymphoma. *J Clin Oncol* (2008) 26, 4579-4586.

[17] Robat T, Dmoszynska A, Solal-Celigny P., Warzocha K, Loscertales J.,***et al.***Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukaemia. *J Clin Oncol* (2010) 28, 1756-1765.

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