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Gemcitabine and treatment of diffuse large B-cell lymphoma in relapsed or refractory elderly patients: A prospective randomized trial in Algeria

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ABSTRACT

Context: Support for non-Hodgkin's lymphoma (NHL) with large cells that is refractory or relapsed after first-line chemotherapy poses a greater therapeutic problem with bone marrow transplant therapy or when old age is a contra-indication for high-dose chemotherapy, especially among developing countries such as Algeria.

Aim: To show that the regimen, including gemcitabine, could be more effective in treating elderly patients with diffuse large B-cell lymphoma (DLBCL) in relapse / refractory, without complete remission, when compared with the ESHAP (etoposide, cisplatine, solumedrol, aracytine) regimen.

Materials and Methods: Ninety-six patients in the age group of 60-70 years were volunteers for a prospective randomized single-blind study, carried out for three years. Patients were divided into two groups by the drawing of lots. The first group (GA, n = 48, relapse; n = 27 [56.3%], refractory; n = 21 [43.7%]) received treatment with ESHAP protocol and the second one (GB, n = 48, relapse; n = 28 [58%], refractory; n = 20 [42%]) with GPD (gemcitabine, dexamethasone, cisplatine) protocol.

Results: The overall response rates and mean survival at three years were significantly higher among patients subjected to GPD treatment compared with those subjected to ESHAP treatment (63% *vs.* 55%, $P = 0.01$ and 20.5% [95% CI 16.5-24.5] *vs.* 11.8% [8.9-14.6], respectively). Additionally, three-year progression-free and event-free survival rates were 20.5% (16.3-24) and 19.7% (15.9-23.5), respectively, for the GPD regimen and 10.9% (8.2-13.7) and 11.1% (95% CI 8.5-13.7), respectively, for the ESHAP regimen. Moreover, the GPD regimen was associated with improving overall survival (RR=2.02, 95% CI 1.59-2.56; $P = 0.000$), event-free survival (2.03, 1.64-2.52; $P < 0.001$) and progression-free survival (1.86, 1.46-2.37; $P < 0.001$).

Conclusion: In cases of contra-indication for high-dose chemotherapy for elderly patients with DLBCL, without complete remission, the Gemcitabine-based therapy protocol represents a more effective and less toxic than that of ESHAP.

KEY WORDS: Diffuse large B-cell lymphoma, elderly patients, gemcitabine-based therapy, refractory, relapse

INTRODUCTION

The non-Hodgkin lymphomas (NHLs) are a heterogeneous group of malignancies of the lymphatic system,[1] resulting from an uncontrollable proliferation of B or T monoclonal lymphoid cells and also NK cells.[2-5] They develop most often in extra-ganglion territories.[6]

The classification of NHL has long been a subject of controversy. In fact, although grouped in the same nosological framework, they are different in both their molecular mechanisms and clinical presentations and evolution.[7] The histological appearances of the lymphoma cells are important elements in the classification and identification of the lymphoma type.[8]

Among the 20 identified types of NHL,[9] there are two main groups that differ depending on the aggressiveness and speed degree of the tumor evolution: the indolent NHL, with low malignancy, and aggressive NHL, with high or medium malignancy.[10] Indolent lymphomas are characterized by slow growth and have a good prognosis, with median survival as long as 10 years, and early stage (I and II) indolent NHL can be treated with radiation therapy alone. The aggressive NHLs grow faster and have shorter natural histories, however, the number of patients cured with intensive chemotherapy currently has been increasing.[11-13]

Diffuse large B-cell lymphoma is an aggressive form of NHL and is one of the most common types

of the diseases,[9] making up about 30% of all diagnosed cases.[14] It is treated with anthracycline-based chemotherapy regimens[15] that comprise a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)[3,16] or similar so-called CHOP-like regimens.[17] However, response rate to CHOP regimen is usually lower in the elderly compared with young patients.[18] The age of patients is thus a pejorative prognostic factor for NHL treatment when they are older than 60 years;[19] they constitute 40% of patients with aggressive NHL.[20,21]

A large number of new therapeutic protocols based on a combination of multi-drug chemotherapy, alone or in combination with monoclonal antibodies such us rituximab, have been introduced for the treatment of elderly patients with high-grade NHL DLBCL.[22-24] But whatever regimen is chosen, the treatment of NHL in the elderly remains complex mainly due to the frequency of concomitant diseases and poor prognosis of patients.[25] ESHAP regimens were some of the second-line regimens that have been used as a remedial treatment of relapsed and refractory high grade NHL.[26,27] Likewise, gemcitabine (2',2'-difluorodeoxycytidine)-based therapy has been shown to have a considerable potential for the treatment of both heavily pre-treated patients with Hodgkin's[28,29] and aggressive non-Hodgkin's Lymphoma.[30,31] However, using gemcitabine as a model drug has been limited in western countries and, to our knowledge, there is no consensus regarding gemcitabine as a standard therapy for elderly patients with relapsed / refractory DLBCL.

In this study, we conducted a randomized trial to compare the efficacy of gemcitabine, combined with cisplatine and dexamethasone, and ESHAP regimen in 96 Algerian relapsed or refractory patients aged over 60 years with DLBCL.

MATERIALS AND METHODS

In this prospective randomized monocentric trial, we tried to evaluate the efficacy of two regimens in single-blind, ESCHAP and GPD, in 96 volunteers (51M, 45F) with DLBCL, refractory / relapsed after first-line CHOP chemotherapy. Patients were selected based on eligibility (inclusion and exclusion) criteria from a group of 123 patients with NHL from Tlemcen and neighboring departments (Oran and Sidi-Bel-Abbes). The total number of patients was statistically determined, *a priori*, based on several factors, mainly the estimated prevalence of the disease, the desired confidence level (95%), and the margin of error (0.05). The diagnosis was confirmed by examination of biopsies according to REAL (Revised European-American Lymphoma)-World Health Organization (WHO) classification.[8,23] Histological examination and immunohistochemical analysis were complemented by a full and thorough mandatory clinical examination coupled with both expansion (imaging) and biological assessments. The study was conducted over a three-year period. The patients' age (mean ± standard deviation) at the time of recruitment was 65.8 ± 3.4 years (range: 60-70 years). The inclusion criteria were large cell NHL in relapse or refractory to conventional treatment (CHOP), all disease stages, age group - 60 to 70 years, and performance status (PS) of 0, 1 or 2. The exclusion criteria were NHL associated with another cancer, marked impairment of hepatic, metabolic, renal function, a positive Human immunodeficiency virus (HIV) serology, a history of lymphoma, indolent B-cell lymphoma, lymphoblastic lymphoma, Burkitt lymphoma, digestive lymphoma, cutaneous lymphoma, PS greater than 2, initial white blood cell (WBC) count lower than 2,500 / μL, and initial platelet count lower than 100,000 / μL. Patients were randomly divided into two equal groups. The first group (GA; n = 48, age 65.4 ± 3.6 years) receiving ESHAP protocol (Etoposide: 100 mg/m^2, day 1-4; Cisplatine: 25 mg / m^2, day 1-4; Solumedrol: 500 mg / m^2, day 1-4; Aracytine: 2 g / m^2, day 5) and the second one (GB; n = 48, age 66.2 ± 2.5) receiving GPD protocol (Gemcitabine: 1000 mg / m^2, day 1 and 8; Cisplatine: 75 mg / m^2, day 1; Dexamethasone: 40 mg, day 1-4). Treatment was administered every 28 days for three cycles. Responses to treatment were evaluated at the end of the third cycle. Patients with complete response were continued to receive one more cycle of chemotherapy. Three cycles were added in patients with partial response. The median follow-up of patients was 13 months. For dosage adaptation of drugs, some procedures were taken. Thus, if the number of neutrophils was between 500 / μL and 900 / μL and that of platelets was between 50,000 / μL and 74,000 / μL, chemotherapy doses were reduced by 25 to 50% appropriately. However, if the number of neutrophils was under than 500 / μL and that of platelet was under than 50,000 / μL, the chemotherapy cure was canceled for one week. The therapeutic evaluation was conducted at the end of the third cure, according to clinical and tomodensitometric criteria. Complete response (CR) was defined by the disappearance of all initials clinical and radiological abnormalities. A partial response (PR) was defined as a reduction in tumor volume by 50% and less than 100%. Non-responses, failures or escapements to treatment were defined as tumor regressions less than 50% or tumor growth in the original or new site. Event-free survival is defined as the survival without death and without complication of disease after chemotherapy. Progression-free survival is defined as the survival without recurrence and, therefore, without relapse and signs of progression after treatment; primary efficacy endpoint is improvement in mean survival with the use of Gemcitabine.

The overall survival, event-free and progression-free survival rates at three years was evaluated with comparison of individual survival curves. The survival curves were made using the Kaplan-Meier method[24] and differences between the survivals were statistically analyzed by the Log-Rank test using SPSS (version 16.0, SPSS Inc., Chicago, IL, USA). The Chi-square analysis was used to compare survival rates between the two groups and between the characteristics of patients, according to the disease stage, histological type, international prognostic index (IPI), and different locations. Treatment-

effectiveness response rates on survival were examined using univariate analyses. Confidence intervals were calculated by the formula of *Greenland* and *Robins*.[25] The values of $P < 0.05$ were considered significant.

This study was carried out with Good Clinical Practice Guidelines and the Helsinki declaration. This work was approved by the Local Ethics Committee of Tlemcen Medical Center University and the Scientific Council of Faculty of Medicine. All patients provided signed informed consent.

RESULTS

The characteristics of patients are summarized in Table 1.

In the period from January 1, 2005, to December 31, 2008, 96 patients with DLBCL were enrolled in this study. Of the 96 eligible patients, 48 were randomly assigned to receive three cycles of ESHAP regimen and 48 others were assigned to receive three cycles of GPD regimen.

Table 1: Characteristics of studied patients with NHL

Group	All patients (n=96)		*P*
treatment	GA (n=48)	GB (n=48)	
	ESHAP	GPD	
Mean age ± SDM (year)	65.4±3.6	66.2±2.5	NS
Gender (M/F, n)	27/21	24/24	NS
LDH > UNV (%)	56.3	54.2	NS
ECOG> 1 (%)	17	15	NS
DLBCL			
Centroblastic (%)	64	62	NS
Immunoblastic (%)	15	13	NS
Anaplastic large cell (%)	4	6	NS
Large B-cell-rich T-cell (%)	17	19	NS
NHL location			
Adenopathies (%)	86	92	NS
Splenomegaly (%)	32	25	NS
Hepatomegaly (%)	10	9.8	NS
Otorhinolaryngology (%)	17	17	NS
Mediastinal (%)	23	26	NS
Medullary (%)	25	23	NS
Anatomical stage of NHL			
Stage I (%)	20	18.5	NS
Stage II (%)	32	30	NS
Stage III (%)	26	30.5	NS
Stage IV (%)	22	21	NS
Performance status			
Sign B (%)	49	40	NS
PS >1 (%)	42	43	NS
IPI			
Low/Score 0, 1 (%)	27	33	NS
Low-intermediate/Score 2 (%)	31.3	36	NS
Score 0-2	58.3	69	NS
High-intermediate/Score 3 (%)	29.1	24	NS
High/Score 4 (%)	12.5	7	NS
Status			
Patients in relapse (%)	56.3	58	NS
Refractory patients (%)	43.7	42	NS

DLBCL: diffuse large B-cell lymphoma, LDH: lactate dehydrogenase, NHL: non-Hodgkin's lymphoma, ESHAP: Etoposide, Cisplatine, Solumedrol, Aracytine, GPD: Gemcitabine, Dexamethasone, Cisplatine, GA: group A, GB: group B, IPI: index pronostique international, NS: not significant, PS: performans status, SDM: standard deviation of mean, M: male, F: female. UNV: upper normal value

Clinical presentation and characteristics of patients at recruitment were similar between the two groups [Table 1]. In general, the histological types found were centroblastic (64% [GA] *vs.* 62% [GB]), immunoblastic (15% *vs.* 13%), anaplastic (4% *vs.* 6%), and large cells (17% *vs.* 19%).

As indicated in Table 2, Grade 3-4 haematological toxicities were a severe leucopenia in GA (63%) and thrombocytopenia in GB (41%) ($P < 0.01$ for all comparisons). Grade 3-4 non-hematologic toxicities were infection (20% *vs.* 29%, $P>0.05$) and vomiting (31.4% *vs.* 29.3%, $P > 0.05$).

For the Log-Rank test and Chi-square analysis, Figure 1 shows curves for three-year overall survival. As indicated in Table 3, all two regimens improved event-free survival. However, the overall responses rates and survival at three

Table 2: Grade 3-4 hematological and non-hematological toxicities in patients with NHL treated with ESHAP and GPD regimens

Group	All patients (n=96)				*P*
	GA (n=48)		GB (n=48)		
	ESHAP		GPD		
Disease grade	3	4	3	4	
Leucopenia (%)	19	44	12	6.2	0.001*
Thrombopenia (%)	5	6.6	29	12	0.001*
Anemia (%)	5	6.5	10	-	NS
Mucositis (%)	3.8	2	-	-	-
Infection (%)	12	8	16	13	NS
Renal (%)	-	-	-	-	NS
Vomiting (%)	21	10.4	23	6.3	NS
Diarrhea (%)	-	-	-	-	NS

*$P < 0.01$; NHL: non-Hodgkin's lymphoma, ESHAP: Etoposide, Cisplatine, Solumedrol, Aracytine, GPD: Gemcitabine, Dexamethasone, Cisplatine, GA: Group A, GB: Group B, NS: not significant

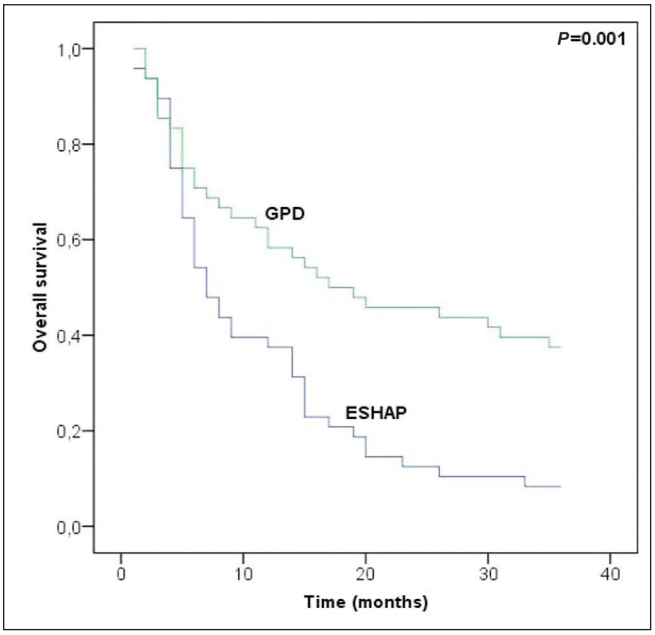

Figure 1: Overall survival Kaplan–Meier analysis in patients subjected to ESHAP and GPD regimen. (ESHAP: etoposide, cisplatine-solumedrol, aracytine, GPD: gemcitabine, dexamethasone, cisplatine)

years were significantly higher among patients subjected to GPD treatment compared with those subjected to ESHAP treatment. Thus, three-year overall survival was 11.8% (95% CI 8.9-14.6) after three cycles of ESHAP and 20.5% (16.5-24.5) after three cycles of GPD (P=0.001). The overall response rate was 63% in GB *vs.* 55% in GA (P=0.01); three-year event-free survival was 11.1% after ESHAP regimen (95% CI 8.5-13.7) and 19.7% after GPD (15.9-23.5) (P = 0.0001) [Figure 2]. Three-year progression-free survival was 10.9% after ESHAP treatment (95% CI 8.2-13.7), and 20.5% after GPD (16.3-24) (P = 0.0003) [Figure 3]. Additionally, there is a high rate of relapse in GA compared to GB (38% *vs.* 26%, $P < 0.025$).

Table 3: Therapeutic responses to ESHAP and GPD regimens and rates of relapse and death in patients with NHL

Group treatment	All patients (n=96)		*P*
	GA (n=48) ESHAP	GB (n=48) GPD	
Complete response (%)	38	29	NS
Relapse after complete response (%)	23	13	NS
Death after complete response (%)	8	6	NS
Partial response (%)	17	34	0.01*
Relapse after partial response (%)	15	13	0.01*
Death after partial response (%)	8	8	NS
Overall response (%)	55	63	0.01*
Total relapse (%)	38	26	0.025*
Total deaths (%)	92	62	0.001**
Total survival (%)	8	38	0.001**
Event-free survival (%)	2	21	0.0001***
Progression-free survival (%)	6	17	0.0003***
Patients lost to follow-up (%)	10	8	NS

*$P < 0.05$, **$P < 0.01$; ***$P < 0.001$. NHL: non-Hodgkin's lymphoma, ESHAP: Etoposide, Cisplatine, Solumedrol, Aracytine, GPD: Gemcitabine, Dexamethasone, Cisplatine, GA: group A, GB: group B, NS: not significant.

The univariate analysis showed that ESHAP regimen was not associated with overall survival (RR= 0.31, 95% CI 0.16-0.58; P=0.000) and event-free survival (0.16, 0.04-0.62; $P < 0.001$) and progression-free (0.33, 0.16-0.69; $P < 0.001$). On the contrary, GPD regimen was associated with improving overall survival (RR = 2.02, 95% CI 1.59-2.56; P = 0.000) and event-free survival (2.03, 1.64-2.52; $P < 0.001$) and progression-free (1.86, 1.46-2.37; $P < 0.001$) [Table 4].

DISCUSSION

The NHLs are hematological malignancies that account for about 3% of mortality related to cancer.[22] They usually occur in older persons (40 to 70 years of age, mean 55 years)[32] and especially in men; the sex ratio is about 1.8.[33]

The incidence rates of NHL continue to increase in many parts of the world, mainly in developed countries. It has risen by at least 100% over the past 50 years in the United States and Western Europe.[34] In the United States, in 2007, it was estimated that more than 63,190 subjects would be diagnosed with the disease.[35,36] In Europe, an estimated 72,800 new cases were diagnosed in 2006, up from 62,300 in 2004.[20] In Algeria, according to recent data from the Algerian Society of

Table 4: Univariate analysis of therapeutic responses to ESHAP and GPD regimens in patients with NHL

Treatment	EFS		PFS		Overall survival	
	RR	95% CI	RR	95% CI	RR	95% CI
ESHAP	0.16	0.04-0.62	0.33	0.16-0.69	0.31	0.16-0.58
GPD	2.03	1.64-2.52	1.86	1.46-2.37	2.02	1.59-2.56

All *P*-values for RR are inferior to 0.001. EFS: Event-free survival, PFS: Progression-free survival, NHL: non-Hodgkin's lymphoma, ESHAP: Etoposide, Cisplatine, Solumedrol, Aracytine, GPD: Gemcitabine, Dexamethasone, Cisplatine, RR: relative risk, CI: confidence interval

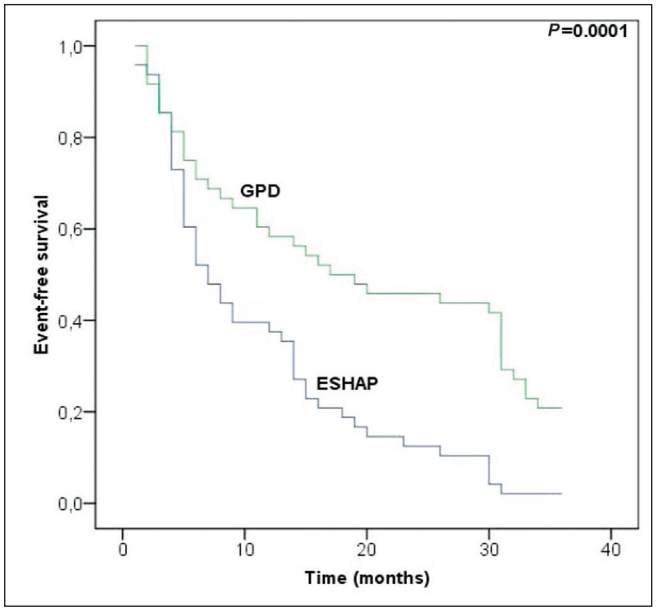

Figure 2: Event-free survival Kaplan–Meier analysis in patients treated with ESHAP and GPD regimen

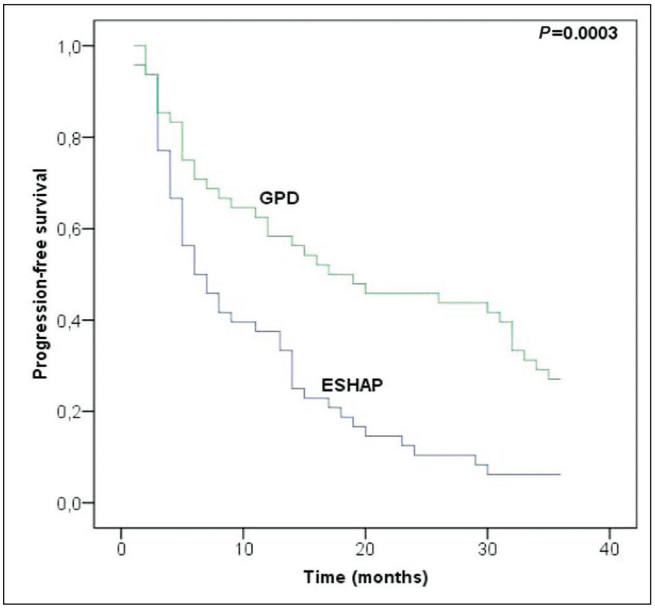

Figure 3: Progression-free survival Kaplan–Meier analysis in patients treated with ESHAP and GPD regimen

Hematology and Blood Transfusion, the NHL national incidence average is about 5 and the relative risk of developing the disease appears to be lower than Europe or USA.[37]

In the subset of aggressive NHL represented by DLBCL, the prognosis worsens with increasing age,[38] often posing problems in the choice of therapeutic procedures. In this study, it is showed that the gemcitabine-based regimen is more effective and fruitful in improving overall, event-free and progression-free survival in patients aged over 60 years with relapsed or refractory DLBCL than ESHAP regimen. Thus, three-year survival rate was 8% after three cycles of ESHAP therapy and 38% after three cycles of GPD regimen ($P = 0.001$), and three-year event-free survival was 2% after ESHAP regimen *vs.* 21% after GPD regimen ($P = 0.0001$), and three-year progression-free survival was 6% after ESHAP treatment and 17% after GPD therapy ($P = 0.0003$). Additionally, the rate of relapse was significantly greater for patients treated with ESHAP than for patients receiving GPD treatment (38% *vs.* 26%, respectively, $P < 0.025$).

Comparison of the efficacy of combination regimens with other studies remains difficult due to the treatment schedule, dosage, and cycle duration. Nevertheless, our results show moderate toxicity related to gemcitabine and are consistent with those of Fan *et al*. who have recently reported that the overall response rate of GPD regimen in patients with relapsed or refractory aggressive B- or T-cell NHL was 57% for B-cell NHL patients and 60% for T-cell NHL patients.[30] In previous studies, response rates of 20 to 43% have been reported for single-agent gemcitabine in relapsed or refractory lymphoma;[39-42] however, other data show that the activity in indolent lymphoma is limited.[39,43,44] It has been reported that the activity of gemcitabine would be even higher when combined with cisplastin.[30,45]

In conclusion, the GPD regimen shows promising activity with an acceptable toxicity profile. It is therefore necessary to know whether the GPD protocol becomes a standard protocol of treatment for elderly patients with relapsed or refractory DLBCL. Hence, the conduct of analogue and large clinical trial protocols would be useful.

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