Haematologica 1998; 83:317-322 original paper

Effects of recombinant granulocyte colony-stimulating factor (G-CSF) in patients treated with ProMACE-CytaBOM for HIV-related non-Hodgkin's lymphoma (NHL)

Giuseppe Rossi, Alessandra Donisi,* Salvatore Casari,* Alessandro Re, Roberto Stellini,° GianPiero Cadeo,° Giampiero Carosi*

*Sezione Ematologia, III Divisione Medicina Generale; *Cattedra e Divisione Malattie Infettive e Tropicali, Spedali Civili, Università degli Studi; °Divisione Malattie Infettive, Spedali Civili, Brescia, Italy*

Abstract

Background and Objective. **The use of hematopoietic growth factors in association with chemotherapy in human immunodeficiency virus (HIV)-related non-Hodgkin's lymphoma (NHL) has been recommended, but few studies have evaluated its cost-effectiveness.**

Design and Methods. **The effects of recombinant granulocyte colony-stimulating factor (G-CSF) were analyzed in 33 consecutive patients with HIV-related NHL treated at a single institution with the same chemotherapy program, ProMACE-CytaBOM, with G-CSF, in 21 cases diagnosed after December 31, 1991, or without G-CSF, in 12 cases diagnosed earlier. Pearson's chi-square analysis and the two-sided Student's t-test were used for statistical comparisons. The method of Kaplan-Meyer and the log-rank-test were used for survival analyses.**

Results. **G-CSF support significantly reduced the frequency of day-1 drug dose reductions ($p<0.001$) and of chemotherapy delays ($p<0.001$), and improved the actual delivered doses of adriamycin, cyclophosphamide and etoposide ($p<0.02$). In patients with a $CD4^+$ count $< 0.1\times10^9$/L, chemotherapy could be given at full doses in 90% of cycles with G-CSF compared to only 20% without it. G-CSF affected neither the frequency and duration of fever and hospitalization nor the complete remission and survival rates after stratification according to the $CD4^+$ count.**

Interpretation and Conclusions. **G-CSF support significantly improved dose-intensity in patients with HIV-related NHL treated with aggressive chemotherapy, particularly in the subgroup with a $CD4^+$ count $< 0.1\times10^9$/L, but it did not improve their clinical outcome.**

Key words: granulocyte-colony-stimulating factor, HIV, non-Hodgkin's lymphoma, ProMACE-CytaBOM, chemotherapy

Correspondence: Giuseppe Rossi, MD, Sezione Ematologia, Spedali Civili, 25121 Brescia, Italy.
Phone: international +39-30-3995262 • Fax: international +39-30-3700852.

Non-Hodgkin's lymphoma (NHL) of aggressive histology is a well recognized complication of human immunodeficiency virus (HIV) infection.[1] Its incidence is increasing, particularly in patients with severe immunodeficiency who survive for years with antiretroviral therapy.[2] The prognosis of HIV-related NHL is worse than that of NHL occurring in HIV negative individuals. The response rates range from 33-64% and median survivals from 5 to 9 months.[3,4]

The aggressive clinical features only partially account for the poor prognosis of HIV-related NHL. The underlying HIV infection also plays a major adverse prognostic role,[5,6] both by predisposing patients to recurrent opportunistic infections and by impairing hematopoietic function. Consequently, though aggressive chemotherapy has also proven clearly effective in HIV-related NHL,[4] it is frequently complicated by systemic toxicity and severe myelosuppression, that lead to treatment delays and to drug dosage reductions, thereby reducing dose intensity and possibly affecting clinical outcome.

Hematopoietic growth factors (HGF) have recently become available and have proven effective in reducing the toxicity of systemic chemotherapy in various clinical studies. To better define their cost-effectiveness, the *American Society of Clinical Oncology* developed evidence-based guidelines for the use of HGF.[7] In HIV-related NHL, it was concluded that the primary administration of HGF seems warranted. This was primarily based on the results of a single controlled study on the use of granulocyte-macrophage colony stimulating factor (GM-CSF) in patients treated with cyclophosphamide, adriamycin, vincristine and prednisone (CHOP) combination chemotherapy.[8] The use of GM-CSF significantly reduced the mean nadir and the duration of neutropenia, the number of episodes of febrile neutropenia, and allowed less frequent reductions in chemotherapy dosages and delays in chemotherapy administration. However, the response rate and survival duration did not change significantly compared to controls. Of concern, the levels of HIV antigen

showed a significant, albeit transient, rise after GM-CSF administration.

No controlled study had thus far evaluated the effects of granulocyte colony-stimulating factor (G-CSF), which is frequently used in association with chemotherapy in the treatment of HIV patients with NHL. In this study we retrospectively compared the clinical outcome of two consecutive cohorts of patients with HIV-related NHL, which were treated at a single center with the same third-generation chemotherapy regimen, ProMACE-CytaBOM,[9] with or without the addition of G-CSF.

Materials and Methods

Thirty-three HIV-seropositive individuals with previously untreated systemic NHL were studied. All had biopsy-proven NHL of intermediate- or high-grade histology according to the Working Formulation.[10] They represented all consecutive patients with HIV-related systemic NHL treated with combination chemotherapy at our Institution up to December 1995, with the exception of three patients who were enrolled in multicenter studies and received chemotherapy regimens other than ProMACE-CytaBOM.

The same team of hematology and infectious disease specialists followed the patients over the entire period of the study. They were staged according to Ann Arbor criteria.[11] Staging procedures included cranial, thorax and abdominal computed tomography, bone marrow biopsy and cerebral spinal fluid examination. Other examinations were performed when clinically indicated. Patients were treated with a slight modification of the original ProMACE-CytaBOM regimen in which prednisone was given only from day 1 to day 8 of each cycle.[12] The treatment plan included 4 cycles of chemotherapy followed by involved-field radiotherapy for stage IA patients, and 6 to 8 cycles of chemotherapy for all other patients. Meningeal prophylaxis with intrathecal methotrexate was routinely added to combination chemotherapy. All patients actually received the intended treatment, with the exception of one stage IA patients who was treated with 6 chemotherapy cycles and did not receive irradiation. Modifications in the dosages of cytostatic agents due to hematological toxicity were done in accordance to published guidelines.[9] Whenever possible, treatment was given on an outpatient basis. Response to treatment was assessed at the end of chemotherapy by complete reevaluation of all initial sites of the disease using standard oncologic criteria. Toxicity grading was defined according to WHO. Patients did not receive routine antibacterial prophylaxis. No antiretroviral therapy was given during NHL treatment.

Patients diagnosed after January 1, 1992 also received G-CSF as part of their treatment, at a dose of 300 ug/daily by subcutaneous administration beginning from day 9 and stopping at day 20 of each cycle. G-CSF could be stopped earlier when the absolute neutrophil count (ANC) was above 1.5×10^9/L for more than three days.

Statistical analysis was conducted using BMDP software. Pearson's chi-square analysis, with or without Yates' correction, and the two-sided Student's t-test were used for comparisons between the two groups. Survival curves were estimated using the Kaplan-Meyer method and compared using the log-rank test.

Results

Patients characteristics

Of the 33 patients, 30 were males, 28 were intravenous drug users, 2 were homosexuals, and 3 were heterosexuals. The median age was 29 years (range 21-47). At NHL diagnosis, 14 patients belonged to CDC group 2, 12 to CDC group 3, 7 to CDC group 4. The median $CD4^+$ cell count was 0.097×10^9/L (range 0.002-1.21). The NHL Ann Arbor stage at presentation was I in 5 patients, II in 3 patients, III in 2 patients, and IV in 23 patients (70%). NHL involvement of extranodal sites at diagnosis occurred in 27 cases (82%). Lactic dehydrogenase (LDH) levels were > 1N in 22/31 cases (71%). According to the *International Prognostic Index*,[13] 5 patients belonged to the low risk group, 4 to the low-intermediate, 11 to the high-intermediate, and 13 to the high risk group. NHL histology according to WF was as follows: group G, 13 cases; group H, 6 cases; group J, 7 cases; high-grade not classifiable, 5 cases; others, 2 cases.

Of the 33 patients, 12, diagnosed before December 31, 1991, did not receive G-CSF, which was not available at that time, and served as control group. Conversely, all 21 patients diagnosed after December 31, 1991, received G-CSF in adjunct to ProMACE-CytaBOM. The pretreatment characteristics of the two groups are shown in Table 1. The underlying HIV disease was more advanced in the G-CSF treated group whose $CD4^+$ cell count was more frequently $< 0.1\times 10^9$/L (71% vs 17%; $p < 0.003$). It also had a significantly lower WBC count (3.84 vs 6.66×10^9/L; $p < 0.03$). Two patients, one in each group, died during the administration of the first chemotherapy cycle and were excluded from further analyses.

Chemotherapy cycles and effects of G-CSF treatment

The mean number of chemotherapy cycles administered to the G-CSF treated group and to the control group was 4.2 and 6.0 respectively ($p=0.02$) (Table 2). The reasons for patients not receiving the intended number of cycles were progressive disease in 8 cases, progressive disease and hepatic toxicity in 1, death due to infectious complications in 2, and mucosal toxicity in one.

As summarized in Table 2, there was a significant reduction in the percentage of cycles given at reduced dose on day 1, from 37% of cycles in controls to 8% of cycles in G-CSF treated patients ($p<0.001$). The

Table 1. Characteristics of the two groups of HIV-seropositive patients with NHL, treated with ProMACE-CytaBOM, with or without the addition of G-CSF.

	G-CSF treated	Controls	p value
No. of patients	21	12	
Median age (years)	29	29	
Male/female	20/1	10/2	
HIV risk group			
intravenous drug users	20	8	
homosexuals	0	2	
heterosexuals	1	2	
CDC group			
II	8	6	
III	7	5	
IV	6	1	
$CD4^+$ count < 0.1×10^9/L	5	10	< 0.003*
NHL stage			
I-II	6	2	
III-IV	15	10	
extranodal presentation	17	10	
NHL pathology (WF)			
G	10	3	
H	4	2	
J	2	5	
others	5	2	
LDH (U/L) (mean)	1416	1095	
Hematologic values			
WBC count/mL (mean)	6.66	3.84	< 0.03°
PLT count/mL (mean)	178	172	
Hb level (g/dL) (mean)	12.0	11.8	
NHL prognostic index			
low	3	2	
low-intermediate	2	2	
high-intermediate	6	5	
high	10	3	

**Chi-square analysis with Yates' correction; °Student's t-test.*

frequency of treatment delay of at least 7 days was also significantly reduced by G-CSF treatment, from 56% to 9% (p<0.001). The proportion between the actually delivered and the scheduled drug dosage was significantly increased with G-CSF for adriamycin, cyclophosphamide and etoposide (p<0.02). G-CSF treatment did not affect dose reduction and relative dose intensity of drugs scheduled on day 8 of ProMACE-CytaBOM, but, as mentioned above, it was given only from day 9 of each cycle. The occurrence of fever as well as the number and the duration of hospital admissions did not change between the two groups. Since patients were treated predominantly on an outpatient basis, blood cell counts were not routinely monitored between cycles, so the mean nadir ANC and the duration of severe neutropenia could not be assessed.

Major opportunistic infections during NHL treatment occurred in 3/12 controls and in 6/21 G-CSF treated patients and caused the death of 1 patient in each group. Extrahematological toxicity was moderate, leading to treatment interruption in 1 patient in each group. It included 2 episodes of mucosal toxicity WHO grade 3 and 4 among controls, 1 episode of peripheral nerve toxicity grade 3 and 1 of hepatic toxicity grade 4 among G-CSF treated patients. The presence of serum HIV p24 antigen was evaluated before and after chemotherapy in 12 patients. Three control patients were negative at NHL diagnosis and 1 became positive after therapy. Of 9 G-CSF treated patients, 4 were negative before treatment and 2 of them became positive after treatment; five were positive before treatment and one of them became negative.

Table 2. Chemotherapy dosing, episodes of fever and of hospital admission in patients receiving G-CSF and in control patients.

	G-CSF treated	Controls	p value
No. evaluable chemotherapy cycles	85	52	
No. cycles/patient (mean)	4.2	6.0	0.02°
No. cycles with dose reduction (%)			
day 1	7 (8%)	19 (37%)	< 0.001°
day 8	34 (40%)	26 (50%)	
No. cycles with >7 days delay (%)	8 (9%)	29 (56%)	< 0.001°
Actually delivered drug dose (%)			
adriamycin	96.5	83.4	< 0.02*
cyclophosphamide	96.5	83.3	< 0.02*
etoposide	97.1	87.9	< 0.02*
cytarabine	82.3	76.6	
vincristine	96.7	95.8	
bleomycin	97.3	95.8	
methotrexate	91.7	94.8	
Fever > 38.5°C			
No. of episodes/patient (mean)	0.9	1.7	
No. of days/patient (mean)	5.5	5.3	
Hospitalization for febrile neutropenia			
No. of episodes	5	4	
Days in hospital/patient (mean)	63.3	64.3	

**Student's t-test; °Pearson's chi-square analysis.*

The outcome of NHL treatment was better in the control group compared to the G-CSF treated group. Complete remission (CR) was obtained in 9/11 controls (82%) and in 8/20 G-CSF treated patients (40%) (p<0.05). Five G-CSF treated patients achieved good partial remission (PR), so the overall response rate to ProMACE-CytaBOM treatment did not significantly differ between the two groups (82% vs 65%, respectively). NHL relapse occurred only in 1 patient in the control group. Death occurred in 7 controls (64%) and in 16 G-CSF treated patients (80%). NHL as a cause of death was less frequent in the control than in the G-CSF treated group (18% vs 55%, respectively; p<0.05). Opportunistic infections or other HIV-related conditions were the cause of death in 9 patients, 5 control and 4 G-CSF treated. They occurred during chemotherapy in 2 cases and during continuous CR lasting 1-74

months in 7 cases. Nine patients, 4 in the control and 5 in the G-CSF treated group, are currently alive in continuous CR after a median follow-up of 64 months (range 47-101) and 16 months (range 7-26), respectively. The median survival is better in the control group [53.5±24.7 months; confidence interval (CI) 95%] compared to the G-CSF treated group (6.9±1.8 months; CI 95%) (p=0.025). However, of the 9 surviving patients, 7 had a $CD4^+$ cell count > 0.1×10^9/L at NHL diagnosis, a condition which, as noted above, was significantly more frequent in controls than in G-CSF treated patients.

Since differences in the severity of the underlying HIV disease might be responsible for the survival differences observed between control and G-CSF treated patients, we have compared the two groups after stratification according to the $CD4^+$ lymphocyte count at NHL diagnosis. Results are shown in Table 3. In patients with a $CD4^+$ cell count >0.1×10^9/L, G-CSF support significantly reduced the frequency of delay in chemotherapy administration form 46% to 9% of cycles (p<0.01), but it did not significantly affect chemotherapy dosage reductions. Conversely, in patients with a $CD4^+$ cell count <0.1×10^9/L), the doses of both day 1 and day 8 drugs were reduced in 80% and 89% of cycles, respectively, in the control group, compared to 10% and 50% of cycles in the G-CSF treated group (p<0.001 and p<0.05, respectively). Also, cycles were delayed in 80% of cases in controls compared to 10% in G-CSF treated patients (p<0.01). There were no significant differences in the clinical outcome of patients. Median survival was not reached among G-CSF treated patients with CD4+ cell count > 0.1×10^9/L compared to 75 months (±20 months; CI 95%) among controls (p=0.98). Among patients with $CD4^+$ cell count < 0.1×10^9/L, it was 6.4 months (±1.6 months; CI 95%) in G-CSF treated and 32 months in the two control patients (p=0.17).

Discussion

This study shows that the addition of G-CSF significantly increased the actual dose intensity of the aggressive combination chemotherapy regimen Pro-MACE-CytaBOM, delivered to patients affected by systemic HIV-related NHL. The frequency of day-1 drug dose reductions and of delays in chemotherapy administration were significantly reduced by G-CSF and the actual delivered total doses of adriamycin, cyclophosphamide, and etoposide were significantly increased. Of note, these effects were obtained in a group of patients which had worse prognostic features compared to controls, particularly more advanced HIV disease, and significantly lower WBC count at NHL diagnosis.

Other investigators have described the use of hematopoietic growth factors in HIV-related NHL. GM-CSF was used in pilot studies with variable results,[14,15] and in a randomized trial in which an increase in dose intensity was obtained by GM-CSF addition from day 4 to day 13 of CHOP regimen, resulting in fewer chemotherapy dosage reductions and chemotherapy administration delays.[8] More recently, GM-CSF failed to reduce significantly the cumulative hematologic toxicity of intensive chemotherapy and zidovudine when compared to historical controls treated with the same chemotherapy regimen without zidovudine and GM-CSF.[16] Results with the use of G-CSF were reported in abstract form. A reduction in the mean delay between chemotherapy cycles but not in the number of cycles given at

Table 3. Chemotherapy dosing, episodes of fever and of hospital admission in patients receiving G-CSF and in control patients, subdivided according to their $CD4^+$ cell count at NHL diagnosis.

	$CD4^+$ > 0.1×10^9/L		*$CD4^+$ < 0.1×10^9/L*	
	G-CSF		*G-CSF*	
	yes	*no*	*yes*	*no*
No. evaluable chemotherapy cycles	23	37	62	15
No. cycles with dose reduction (%)				
day 1	1 (4%)	7 (19%)	6 (10%)	12 (80%)*
day 8	3 (13%)	13 (35%)	31 (50%)	13 (89%)§
No. cycles with >7 days delay(%)	2 (9%)	17 (46%)^	6 (10%)	12 (80%)*
Fever > 38.5°C				
no. episodes/patient (mean)	0.6	1.0	0.9	3.0
days/patient (mean)	1.4	3.0	6.8	9.5
Hospitalization for febrile neutropenia				
no. episodes	1	1	4	3
days/patient (mean)	43.6	58.5	69.9	81.5

*Chi-square analysis with Yates's correction; *p<0.001; §p=0.02; ^p=0-007.*

reduced dose was reported in patients treated with different types of combination chemotherapy[17] and a reduction in the frequency of neutropenic fever and of hospital admission was noted after CHOP chemotherapy.[18]

The increase in chemotherapy dose intensity was obtained in our study with no significant additional toxicity attributable to G-CSF administration, whereas the benefits of GM-CSF support were obtained at the expense of an increase in fever, fatigue and diarrhea.[8] Moreover a transient increase of serum HIV p24 antigen levels was noted in patients treated with GM-CSF. In our study, serum HIV p24 antigen levels were not monitored closely. We observed a trend towards an increase in serum HIV p24 antigen detection after chemotherapy, but G-CSF did not appear to play a role in such changes. However, the number of cases studied was to small to allow definite conclusions.

The reduction in the number of episodes of neutropenia and fever and of related hospitalization days, which was reported in the randomized trial on GM-CSF addition,[8] was not documented in our study using G-CSF. However, our patients receiving G-CSF had more advanced HIV disease compared to those treated with GM-CSF, as documented by their lower $CD4^+$ cell count (median 50×10^9/L vs 230×10^9/L). It should be emphasized that in patients with very advanced HIV disease, both fever and hospitalization days are very difficult end points to evaluate because they may be biased by their poor clinical conditions as well as by concomitant diseases related to the HIV infection rather than to chemotherapy or NHL.

Considering patients survival, no published study could as yet show a benefit from the addition of any hematopoietic growth factor to chemotherapy for HIV-related NHL. Indeed, in the present study, control patients actually showed a better survival when compared to patients treated with the addition of G-CSF. However, the difference in the stage of the underlying HIV disease between the control and the G-CSF treated group largely accounted for this result. When the two groups were subdivided according to a $CD4^+$ cell count cut-off of 0.1×10^9/L, there were no significant survival differences between the subgroups.

In patients with $CD4^+$ count > 0.1×10^9/L, the clinical outcome was similar to that of HIV-negative patients with NHL. Both the G-CSF treated group and the control group had good response rates and prolonged disease free survival, as it was reported in non-severely immunodeficient patients with HIV-related NHL treated with aggressive combination chemotherapy.[4] In this subgroup of patients in our study, the only significant effect of the addition of G-CSF was a reduction in the frequency of chemotherapy administration delay from 46% of cycles without G-CSF to 9% of cycles with G-CSF ($p<0.01$).

Also, in patients with a $CD4^+$ count < 0.1×10^9/L the clinical outcome also did not differ between controls and G-CSF treated patients, but the statistical power of the analysis was limited by the little number of controls.This was not due to a different selection of patients eligible for aggressive combination therapy in different time periods, since the percentage of consecutive patients with HIV-related NHL which received aggressive chemotherapy at our institution was 60% before, and 62% after the introduction of G-CSF support. It was noteworthy that in this subgroup of severely immunodeficient patients, the scheduled dose intensity of ProMACE-CytaBOM could be actually delivered only with G-CSF support. However, in spite of the significant increase in chemotherapy dose intensity in the subset of severely immunodeficient patients, no clinical benefit could be demonstrated. This result may be related not only to the small number of patients studied, but also to the characteristics of NHL developing in the setting of advanced HIV disease. It has been shown that this type of HIV-related NHL markedly differs from that occurring among less severely immunodeficient patients, both on pathological, etiopathogenetic and molecular grounds.[19-21] Clinical studies did not demonstrate a clear advantage for the use of aggressive chemotherapy in HIV-related NHL[3] except in patients without severe immunodeficiency.[4] Indeed, in a recent randomized trial, the use of half-dose chemotherapy in association with antiretroviral agents was as effective as full-dose chemotherapy in a group of patients with a median $CD4^+$ count of 100×10^9/L.[22] It must also be considered that intensive chemotherapy may have serious adverse effects other than bone marrow depression in patients with malignant lymphoma, in particular in those who also are HCV- or HBV-positive.[23,24]

In conclusion, in patients with advanced HIV disease, it remains to be demonstrated whether the increase in the actually delivered chemotherapy dose, which can be achieved only with G-CSF support, will ultimately result in a significant therapeutic benefit.

Contributions and Acknowledgments

GR was the principal investigator; he was responsible for NHL and G-CSF treatment, analyzed the data with AD and AR and wrote the paper. AD, SC, RS, GPC and GC were responsible for the clinical care of the patients and reviewed the manuscript.

The names appear in an order corresponding to the importance of the contribution of the authors to the study, with the exception of GPC and GC who equally contributed to the study as heads of the Infectious Disease Divisions.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

Manuscript processing

Manuscript received September 17, 1997; accepted January 7, 1998.

References

1. Ziegler JL, Beckstead JA, Volberding PA, et al. Non-Hodgkin's lymphoma in 90 homosexual men. N Engl J Med 1984; 311:565-70.
2. Pluda JM, Venzon DJ, Tosato G, et al. Parameters affecting the development of non-Hodgkin's lymphoma in patients with severe human immunodeficiency virus infection receiving antiretroviral therapy. J Clin Oncol 1993; 11:1099-107.
3. Gill PS, Levine AM, Krailo M, et al. AIDS-related malignant lymphoma: results of prospective treatment trials. J Clin Oncol 1987; 5:1322-8.
4. Gisselbrecht C, Oksenhendler E, Tirelli U, et al. Human immunodeficiency virus-related lymphoma treatment with intensive combination chemotherapy. Am J Med 1993; 95:188-96.
5. Levine AM, Sullivan-Halley J, Pike MC, et al. Human immunodeficiency virus-related lymphoma. Prognostic factors predictive of survival. Cancer 1991; 68: 2466-72.
6. Kaplan LD, Abrams DI, Feigal E, et al. AIDS-associated non-Hodgkin's lymphoma in San Francisco. JAMA 1989; 261:719-24.
7. American Society of Clinical Oncology (ASCO). American Society of Clinical Oncology recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. J Clin Oncol 1994; 12:2471-508.
8. Kaplan LD, Kahn JO, Crowe S, et al. Clinical and virologic effects of recombinant human granulocyte-macrophage colony-stimulating factor in patients receiving chemotherapy for human immunodeficiency-virus associated non-Hodgkin's lymphoma: results of a randomized trial. J Clin Oncol 1991; 9:929-40.
9. Miller TP, Dahlberg S, Weick JK, et al. Unfavorable histologies of non-Hodgkin's lymphoma treated with ProMACE-CytaBOM: a groupwide Southwest Oncology Group study. J Clin Oncol 1990; 8:1951-8.
10. The Non-Hodgkin's Lymphoma Classification Project. National Cancer Institute sponsored study of classification of non-Hodgkin's lymphoma: summary and description of a Working Formulation for clinical usage. Cancer 1982; 49:2112-35.
11. Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging. Cancer Res 1966; 26:1311.
12. Rossi G, Mariano MR, Arcangeli G, et al. A phase II trial of ProMACE-CytaBOM in previously untreated non-Hodgkin's lymphoma of intermediate- or high-grade histology. Hematol Oncol 1991; 9:147-55.
13. The International non-Hodgkin's Lymphoma Prognostic Factor Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329: 987-94.
14. Hahn S, Pluda J, Shay L, et al. Treatment of AIDS-related non-Hodgkin's lymphoma with chemotherapy, AZT and GM-CSF. Proc Am Soc Clin Oncol 1992; 11:45.
15. Walsh C, Wernz JC, Levine A, et al. Phase I trial of m-BACOD and granulocyte-macrophage colony stimulating factor in HIV-associated non-Hodgkin's lymphoma. J Acquir Immune Defic Syndr 1993; 6:265-71.
16. Gabarre J, Lepage E, Thyss A, et al. Chemotherapy combined with zidovudine and GM-CSF in human immunodeficiency virus-related non-Hodgkin's lymphoma. Ann Oncol 1995; 6:1025-32.
17. Tirelli U, Errante D, Vaccher E, et al. Treatment of HIV-related non-Hodgkin's lymphoma (NHL) with chemotherapy (CT) and G-CSF: reduction in the days of hospitalization and toxicity with concomitant overall reduction in the cost. Proc Am Soc Clin Oncol 1993; 12:53.
18. Navarro JT, Ribera JM, Gomez J, et al. The effect of G-CSF after CHOP chemotherapy in patients with human immunodeficiency virus (HIV) infection with non-Hodgkin's lymphomas. Br J Haematol 1996; 93 (suppl.2):93.
19. Hamilton-Dutoit SJ, Pallesen G, Franzmann MB, et al. AIDS-related lymphoma. Histopathology, immunophenotype, and association with Epstein-Barr virus as demonstrated by *in situ* nucleic acid hybridization. Am J Pathol 1991; 138:149-63.
20. Ballerini P, Gaidano G, Gong JZ, et al. Multiple genetic lesions in acquired immunodeficiency syndrome-related non-Hodgkin's lymphoma. Blood 1993; 81: 166-76.
21. Rossi G, Cadeo GP, Stellini R, et al. Incidence and clinicopathological heterogeneity of HIV-related non-Hodgkin's lymphoma. Haematologica 1990; 75:235-42.
22. Kaplan LD, Straus DJ, Testa MA, et al. for the National Institute of Allergy and Infectious Disease AIDS Clinical Trials Group. Low-dose compared with standard-dose m-BACOD chemotherapy for non-Hodgkin's lymphoma associated with human immunodeficiency virus infection. N Engl J Med 1997; 336:1641-8.
23. Luppi M, Torelli G The new lymphotropic herpesviruses (HHV-6, HHV-7, HHV-8) and hepatitis C virus (HCV) in human lymphoproliferative diseases: an overview. Haematologica 1996; 81:265-81.
24. Faggioli P, De Paschale M, Tocci A, et al. Acute hepatic toxicity during cyclic chemotherapy in non Hodgkin's lymphoma. Haematologica 1997; 82:38-42.