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High dose idarubicin-based regimen for diffuse large cell AIDS-related non-Hodgkin's lymphoma patients: a pilot study

ROBERTA GASTALDI,* PIETRO MARTINO,* GIUSEPPE GENTILE,* ARTURO CAFOLLA,* IOLE CORDONE,* GIACOMO GIANNINI,° CONCETTA TORROMEO,* LUCIA PALMISANO,° VINCENZO PICARDI,* MAURO ANDREOTTI,° GIUSEPPE AVVISATI,* FRANCO MANDELLI*

*Ematologia, Dipartimento di Biotecnologie Cellulari ed Ematologia, University "La Sapienza" of Rome, Italy; °Laboratorio di Virologia, Istituto Superiore Sanità, Rome, Italy

Correspondence: Roberta Gastaldi, MD, Ematologia, Dipartimento di Biotecnologie Cellulari ed Ematologia, University "La Sapienza" of Rome, via Benevento, 6 00161 Rome, Italy.
Phone: international +39.06.857951. Fax: international +39.06.44241984. E-mail: gastaldi@bce.med.uniroma1.it

Background and Objectives. Intensive chemotherapy (CHT) in AIDS-related non-Hodgkin's lymphoma (AIDS-NHL patients) is a vexing problem. Our purpose was to evaluate the feasibility of a high dose idarubicin (HD-IDA)-based regimen in diffuse large cell (DLC) AIDS-NHL patients.

Design and Methods. Fourteen stage I-IV untreated DLC AIDS-NHL patients with a performance status <3 and no prior AIDS-related diseases received CIOD: cyclophosphamide, HD-IDA (25 mg/m^2 in 8 patients, 20 mg/m^2 in 6 patients) vincristine and dexamethasone plus granulocyte colony-stimulating factor (G-CSF) and prophylaxis against infections. The outcomes measured were: rate of response, disease-free survival (DFS), overall survival (OS) and the impact of chemotherapy on immunologic and virological parameters.

Results. Complete response was achieved in 13/14 cases (response rate: 93%). The median time of response and survival was 33 (range 5-79) and 35.5 (range 6-84) months, respectively. At 60 months the DFS and OS were 71% and 44%, respectively. CIOD with idarubicin 20 mg/m^2 was better tolerated than that with 25 mg/m^2 and was administered with a higher mean average-relative-dose-intensity (95.38±7% vs 83.35±15.59%, p=0.0001). Opportunistic infections were more frequent in patients with a baseline CD4 <100 than those with >100 cells/µL (4/5 vs 1/9: p=0.0229). After 3 CIOD courses the mean CD4 cells/µL was significantly lower (p=0.001) and the mean HIV.1 RNA load was significantly higher (p=0.045) than at baseline.

Interpretation and Conclusions. The proposed chemotherapeutic regimen for AIDS-related non-Hodgkin's lymphoma is feasible in an outpatient setting in selected patients with relatively well-preserved immune function.

Key words: AIDS-NHL, idarubicin, response, toxicity, survival.

Non-Hodgkin's lymphoma (NHL) is one of the most frequent cancers in human immunodeficiency virus (HIV) infected subjects and has recently been estimated to account for about 5% of the world acquired immunodeficiency syndrome (AIDS)-defining illnesses.[1] AIDS-NHL displays several therapeutic problems related to its unusual clinical and biological features such as a primarily disseminated and extranodal manifestation, aggressive growth and highly malignant B-cell histology; moreover, the presence of impaired immune function is the main obstacle to an adequate therapeutic approach.[2-6] The tolerance to chemotherapy is usually poor and in spite of the good response rates obtained with doxorubicin-based regimens similar to those used in HIV-negative NHL, patients generally have a short complete response (CR) and a short survival (<1 year).[2-5,7-9] An AIDS-related disease prior to or at the time of the diagnosis of NHL, an absolute CD4 <100 cells/µL and a poor *performance status* (World Health Organization: *P.S.* >2) are strongly prognostic of poor survival. Moreover, age less than 35 years, a high level of lactate dehydrogenase (LDH) and advanced tumor stage have been recently related to a poor prognosis in AIDS-NHL.[2-5,7-11] Nevertheless, prophylaxis against opportunistic infections and the use of hematopoietic growth-factors have

a beneficial impact on the clinical course of these patients.[12]

The good results obtained with doxorubicin-based regimens in HIV-negative NHL,[13,14] have favored experimental and preclinical studies to find doxorubicin analogs with a higher therapeutic index. Among the studied analogs, idarubicin (4-demethoxydaunorubicin) compared favorably with doxorubicin, particularly regarding cardiotoxicity.[15] Furthermore, preliminary results indicated that high dose idarubicin (20-25 mg/m^2) in combination with dexamethasone and conventional doses of cyclophosphamide and vincristine (CIOD), associated with G-CSF is well tolerated in DLC-HIV-negative NHL.[16]

The present pilot study, shows the results obtained with the CIOD regimen including a high dose of idarubicin in AIDS-NHL patients. Primary endpoints of this work were: 1) the feasibility of the CIOD regimen; 2) the rate and duration of responses and overall survival (OS). A secondary endpoint was to determine the effect of the CIOD regimen on the HIV infection.

Design and Methods

Between January 1994 and January 1997, 26 consecutive previously untreated AIDS-NHL patients were evaluated in our hematology department (Dipartimento di Biotecnologie Cellulari ed Ematologia, Università degli Studi di Roma *La Sapienza*, Italy) for enrollment in this pilot study. The inclusion criteria were: age between 15 and 65 years, a histologic picture of aggressive DLC-NHL (categories G and H of the Working Formulation Classification), Ann Arbor stage I-IV of disease including patients with leptomeningeal involvement, a World Health Organization (WHO) performance score <3, absence of an AIDS-defining illness (opportunistic infection or other AIDS related-neoplasms) of category C according to the revised Center for Disease Criteria (CDC) for HIV infection. Patients with an absolute CD4 <200 cells/μL (immunologic AIDS) subgroup 3 of asymptomatic and symptomatic but not AIDS patients (category A and B of CDC, respectively) were also included.[17-20] All patients had liver and renal functional parameters less than double the normal value and normal heart function with a left ventricular ejection fraction (L-VEF) >50%.

The exclusion criteria were: liver and renal functional parameters more than 2.5 times the normal value, compromised heart function with a L-VEF <50% and an AIDS-defining illness prior to or at the time of the diagnosis of NHL (category C of CDC). At the end patients with primary cerebral NHL and other associated neoplasms were excluded.

Out of 26 AIDS-NHL patients, 12 were excluded from the study because five had small non-cleaved cell Burkitt's type NHL, five were already category C of the CDC at the onset of NHL and two had active hepatitis C virus infection. Therefore a total of 14 patients who met the inclusion criteria were enrolled in the pilot study. Written informed consent was obtained from each patient.

Staging procedures included accurate physical examination, routine blood analyses including LDH, bone marrow aspiration and bilateral bone biopsies, chest radiogram, brain-chest-abdomen computerized tomography and spinal tap with cerebral fluid examination.

All patients were evaluated according to the age-adjusted international prognostic index (IPI) for aggressive NHL of the general population (tumor stage, performance status and serum LDH level).[21]

Immunologic and virological parameters

Peripheral blood lymphocyte immunophenotyping was performed by flow cytometry using two color immunofluorescence: fluorescein-conjugated (FITC) CD3, phycoerythrin (PE) CD4; CD3-FITC/ CD8-PE antibodies. Stained samples were analyzed gating the lymphoid population, using a FAC-Scan flow cytometer (Becton Dickinson).

The quantitative measurement of HIV viral RNA was performed on the plasma by the Nuclisens system (Organon Teknika). The limit of detection of the assay was 400 copies per mL.

Patients' characteristics

The pre-treatment clinical and laboratory characteristics of the AIDS-NHL patients are listed in Table 1. Out of the 14 patients, 9 (64%) were symptomatic for HIV infection (category B of CDC) at diagnosis of NHL and 5 (36%) of them had already received antiretroviral therapy (zidovudine and/or didanosine) for a median time of 8 months (range: 2-39). The mean CD4 count was 270 cells/μL (range 24-900, median 272). Of the 14 patients 5 (36%) had an absolute CD4 count <100 cells/μL. The mean HIV.1 RNA viral load of 10 tested patients was 810,819±1,080,485 copies/mL (range 94,000-3,800,000).

According to the age-adjusted IPI, out of 14 patients 2 were at low risk, 8 at low-intermediate and 3 at high-intermediate risk. Furthermore 10 patients had systemic B symptoms: fever was

Table 1. Characteristics of patients.

Parameters	Patients	
	No.	%
Number of patients	14	
Gender:		
Male	10	71
Female	4	29
Mean age (range), years	37 (29-50)	
Risk group for HIV infection		
Intravenous drug user	4	29
Homosexual	4	29
Heterosexual	6	42
HIV disease categories*		
A	5	36
B	9	64
Working Formulation histology		
G	6	43
H	8	57
Extranodal sites°	8	57
Performance Status		
0	6	43
1	8	57
Systemic B symptoms	10	71
Ann Arbor clinical stage		
I+II	3	21
III+IV	11	79
Lactate dehydrogenase: ≥ 1 n.l.	4	28
Risk factor (IPI)#		
Low	2	14
Low intermediate	8	57
High intermediate	4	28
High	–	
CD4 cell/μL <100	5	36
CD4 cells/μL, mean (range)	270 (24-900)	
CD4 cells/μL, median (range)	272 (24-900)	
HIV-1 RNA,° mean copies/mL (range)*	810,819+1,080,485 (94,000-3,8000,000)	

**Revised Center of Disease Control Criteria of HIV infection, 1993; °Extranodal sites: oral cavity = 3, bone marrow = 2, sinus+bone = 1, kidney = 1, lung = 1. #IPI= International Prognostic Index for aggressive non-Hodgkin's lymphoma. °The HIV-1 RNA was measured in 10 patients.*

present in 5 patients, weight loss in 2, and fever plus weight loss plus drenching night sweats in 3.

Treatment regimen

The treatment regimen, named CIOD, consisted of intravenous (iv.) injection of: cyclophosphamide 750 mg/m^2 on day 1; vincristine 1.4 mg/m^2 on day 1 (maximum dose of 2 mg), high dose idarubicin 25 mg/m^2 on day 1 and dexamethasone 10 mg/m^2 from days 1 to 5. The CIOD regimen was administered on an out-patient basis and repeated every 3 weeks (for a maximum of 6 courses) if the absolute neutrophil count (ANC) was >1.5×10^3/μL and/or platelet count >50×10^3/μL. The regimen was delayed by one week if ANC and/or platelet counts were lower than the above values. A 50% reduction of the baseline dose of idarubicin was made if ANC and/or platelet counts remained low for more than 28 days.

The first 8 patients enrolled were treated with CIOD including idarubicin at a dose of 25 mg/m^2; thereafter, the idarubicin dose-intensity, CIOD average relative-dose intensity and AIDS-related disease observed in these patients suggested treating the subsequent 6 patients with CIOD including idarubicin at a dose 20 mg/m^2.

Supportive treatment

Concomitantly to chemotherapy, 12 mg of methotrexate were administered intrathecally as central nervous system prophylaxis. The methotrexate was given on the first day of the CIOD regimen for 1 to 3 courses. G-CSF was given subcutaneously (s.c.) at the dose of 5 μg/kg body weight daily starting from day 3 of each CIOD course until ANC >1.5×10^3/μL.

Four doses of ondansetron 8 mg iv/orally were administered every 12 hours at the start of chemotherapy and repeated during each course as antiemetic medication.

All patients received continuous oral antimicrobial prophylaxis until the end of chemotherapy. This prophylaxis consisted of acyclovir 800 mg daily, fluconazole 100 mg daily and trimethoprim-sulphamethoxazole (TMP/SMZ) 160 mg/ 800 mg daily given three times a week (or inhaled pentamidine 300 mg every 30 days in allergic patients). Oral ciprofloxacin 500 mg twice a day was also given from day 7 until ANC >1.5×10^3/μL during each CIOD course. No patients received antiretroviral therapy during the CIOD regimen. Antiretroviral therapy was started after chemotherapy according to good clinical practice at the time: before 1996 antiretroviral therapy consisted of 2 associated nucleoside transcriptase inhibitors, after this date it consisted of 2 associated nucleoside transcriptase inhibitors plus a protease inhibitor (highly active antiretroviral therapy: HAART). Packed red blood cells (RBC), or platelet transfusions were administered when the hemoglobin level was <8 g/dL or the platelet count was <20×10^3/μL or greater if the patient was symptomatic.

Definition of response and follow-up

The response was evaluated 4 weeks after CHT was discontinued. Complete response (CR) was defined as the disappearance of all clinical signs

with normalization of all radiographic studies and bone marrow. A partial response (PR) was defined as a 50% or greater reduction in the sum of the products of the two largest perpendicular diameters in all measurable sites of tumor. All other patients were classified as having no response (NR).

Non-responders or those who developed uncontrolled opportunistic infections during chemotherapy discontinued the CIOD regimen but were still included in the analysis of data on an intention-to-treat basis. Actual dose intensity (ADI) for each drug was expressed as mg/m^2 per week and the relative dose intensity (RDI) as a percent of dose-intensity corresponding to protocol doses and schedule. These were calculated in each patient as follows: ADI= (total dose of drugs administered)/(body surface × weeks of treatment); RDI= (ADI × 100)/(protocol dose-intensity); the average RDI was calculated on a patient basis and indicated the mean RDI of the four drugs.

Toxicity was graded according to standard WHO criteria.[19]

Statistical analysis

The chi-squared test with Yates's correction and Fisher's exact test were used when appropriate for analysis of categorical data.[22] Continuous variables were expressed as mean±standard deviation and analyzed using the Student's t-test.[22] All *p* values were two-tailed and were considered statistically significant when they reached the probability level < 0.05. Miettinen test-based confidence limits for relative risk (RR) were calculated.[19] Survival time was calculated from the beginning of the CIOD regimen to date of death or date of last follow-up. Disease-free survival (DFS) was calculated from the time of response until relapse, death or date of last follow-up. Patients who died without evidence of lymphoma were considered censored. The Kaplan- Meier method was used to estimate lymphoma DFS and overall survival (OS), differences in the curves being estimated by the log-rank test.[22]

Results

Response to treatment

The CIOD regimen was administered on an outpatient basis and all patients received at least three CIOD courses (mean 4.7±0.9 courses, range 3-6). Of the 14 patients, 13 (93%) achieved CR with a median duration of 33 months (range: 5-79). One patient did not respond and died from NHL in progression 6 months after diagnosis. Relapse occurred in 3 patients at 11, 15 and 29 months from CR and all died of lymphoma at 18, 22 and 34 months from diagnosis, respectively.

Of the 10 patients in continuous CR (CCR), 4 died: three from opportunistic infections and one from secondary acute myeloid leukemia at 10, 13, 37 and 29 months from NHL diagnosis, respectively. The remaining 6 (43%) patients in CCR are still alive at 51, 51, 53, 64, 75 and 84 months from NHL diagnosis. The median survival of the 14 patients was 35.5

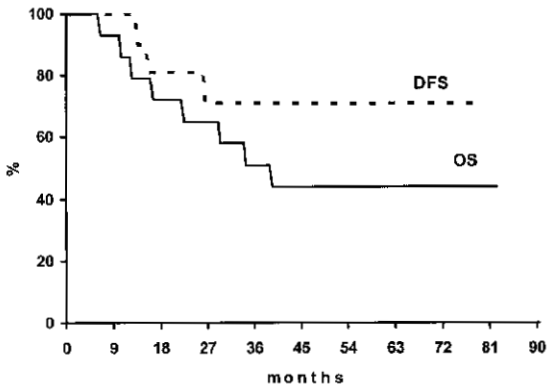

Figure 1. Disease-free survival (DFS) in patients achieving complete response (13 cases) and overall survival (OS) of 14 AIDS-related non-Hodgkin's lymphoma patients treated with the CIOD regimen.

Table 2. Who grading of hematologic toxicity.

Parameters	*Total (%)*	*IDA dose of CIOD Regimen* 25 mg/m^2 (%)	20 mg/m^2 (%)	*p value*
Number of courses	66	38	28	
Hemoglobin g/dL				
6.5-7.9=G3	20 (30)	13 (34)	7 (25)	n.s.
<6.5=G4				
ANC ×10^3/µL				
0.5-0.9=G3	6 (9)	4 (10)	2 (7)	n.s.
<500=G4	49 (74)	30 (70)	19 (69)	n.s.
Platelets ×10^3/µL				
25.0-49.9=G3	16 (24)	12 (31)	4 (14)	n.s.
<25.0=G4	9 (14)	7 (18)	2 (7)	n.s.

Abbreviations: IDA=idarubicin; ANC=absolute neutrophil count; n.s.= not significant. Note: the p value was calculated by two-tailed Fisher's exact test; p significant < 0.05.

Table 3. Toxicity of the CIOD regimen.

Parameters	CIOD regimen, mean±SD (range)			p
	Total	IDA 25 mg/m^2	IDA 20 mg/m^2	
Number of courses	66	38	28	
Hb g/dL, nadir	9.3±1.7 (6.5-13.7)	8.9±1.5 (6.5-12)	9.5±1.9 (7.2-13.7)	.207
ANC ×10^3/µL, nadir	0.66±1.0 (0.01-5,0)	0.44±0.8 (0.01-4,4)	0.62±0.08 (0.01-2,6)	.354
Plts ×10^3/µL, nadir	70±42 (7-166)	55±25 (7-145)	78±4.0 (10-166)	.016
G-CSF, days	11.7±5.2 (7-27)	12.5±3.7 (7-27)	10.8±2.0 (8-17)	.019
ANC <500/µL, days	3.1±2.6 (1-11)	4.1 ±2.8 (1-11)	2.4±1.4 (1-6)	.008
PLTs <50×10^3/µL, days	11.6±11 (2-50)	12.8±12.2 (2-50)	7.5±3.4 (2-12)	.102

SD: standard deviation; IDA: idarubicin; Hb: hemoglobin; ANC: absolute neutrophil count; PLTs: platelets; G-CSF: granulocyte-colony stimulating factor Note: The p value was calculated by the two-tailed Student's t-test; p significant < 0.05.

Table 4. Mean dose intensity (DI), relative dose Intensity (RDI) and average relative dose intensity (ARDI) of the CIOD regimen according to idarubicin dosage.

Parameters	CIOD regimen, mean±SD			
	Idarubicin 25 mg/m^2		Idarubicin 20 mg/m^2	
	DI mg/m^2/wk	(RDI%)	DI mg/m^2/wk	(RDI%)
Number of patients	8		6	
Number of courses	38		28	
Cyclophosphamide	212.4±36	(85)	240.43±15	(96)
Idarubicin	6.39 ±1.7	(76.5)	6.1±0.7	(94)
Vincristine	0.39±0.07	(85)	0.45±0.03	(96)
Dexamethasone	2.81±0.47	(85)	3.16±0.21	(96)
ARDI*	83.35±15.59%		95.38±7.02%	

**Two tailed Student's test: p = 0.0001.*

months (range 6-84). The DFS and OS rates were 71% and 44%, respectively at 60 months (range: 6-84) (Figure 1). The overall mortality rate was 57% (8/14 cases) but no deaths related to drug toxicity were observed. No significant differences regarding response and survival times were observed in patients with baseline CD4 <100 cells/µL and those with >100 cells/µL (DFS: 60% vs 89%, log-rank: p = 0.900 and OS: 60% vs 68%, log-rank: p = 0.1.00).

Out of the 14 AIDS-NHL patients, 11 received antiretroviral therapy after chemotherapy (4 patients were treated with 2 nucleoside transcriptase inhibitors, 7 received HAART) while the remaining 3 patients were not treated because of toxicity. At present alive patients have been on HAART for a median time of treatment of 46 months (range 8-56).

Toxicity

Hematologic toxicity of the CIOD regimen is reported in Table 2. In particular, grade 4 neutropenia was observed in 49/66 (74%) CIOD courses associated with concomitant severe thrombocytopenia in 9 courses. Nine of the 14 patients (64%) received packed RBC (53 total units on 23/66 courses) and 3 of them were also transfused with platelets (36 total units on 3/66 courses). Febrile neutropenic episodes were observed in 13/66 (31%) CIOD courses: 8 of these episodes were FUO, 3 were opportunistic infections and 2 *Staphylococcus spp.* septicemia. AIDS-related events occurred during chemotherapy in 5/14 (36%) patients: cytomegalovirus retinitis in 3 cases, cytomegalovirus retinitis plus cryptosporidiosis plus neurotoxoplasmosis in one case and disseminated mycobacteriosis plus Kaposi's sarcoma plus leishmaniosis in the last case. The rate of these opportunistic infections was statistically higher in patients with a baseline CD4 <100 cells/µL than in those with >100 cells/µL (4/5 vs 1/9; p = 0.0229; RR 7.20, 95% CI: 1.5-34.19). The four patients who developed cytomegalovirus retinitis during chemotherapy had an absolute CD4 count <100 cell/µL (median: 41 cell/µL, range: 24-99) at baseline. Extra-hematologic toxicity grade 3-4 was limited to transient alopecia grade 3 in 3 cases while a L-VEF of 45%, without any clinical symptoms, was observed in one case.

The toxicity of the CIOD regimen according to the idarubicin dose is reported in Table 3.

CIOD including idarubicin 20 mg/m^2 was associated with significantly shorter G-CSF administration, shorter duration of neutropenia and a higher platelet count nadir.

The mean dose intensity and RDI of each drug and the mean ARDI of the CIOD regimen are reported in Table 4. Compared to patients treated with idaru-

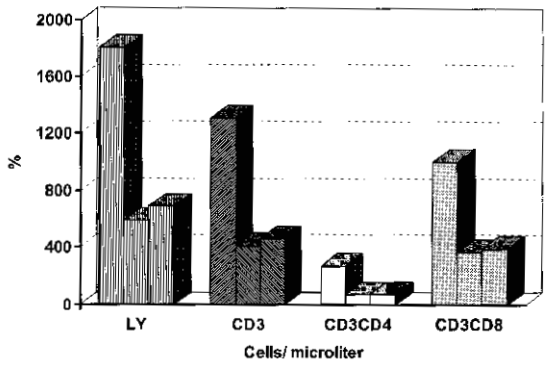

Figure 2. Lymphocyte subsets in 14 AIDS-related non-Hodgkin's lymphoma patients treated with the CIOD regimen. ***Abbreviations: Ly= lymphocytes. Note: The first column of each parameter corresponds to evaluation before CIOD therapy, the second after the 3rd course and the third one month after the end of CIOD.***

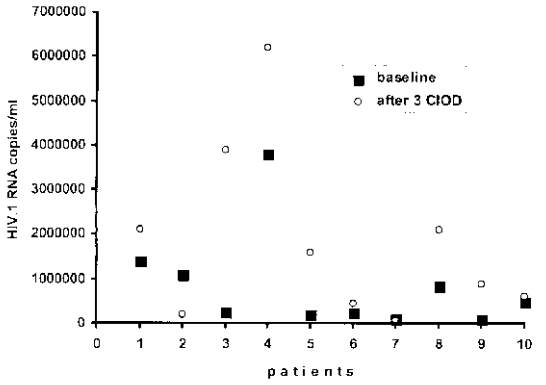

Figure 3. HIV.1 RNA viral blood in 10 AIDS diffuse large cell non-Hodgkin's lymphoma patients treated with the CIOD regimen.

Table 5.

Parameters	Cells/μL, mean ± SD			p value	
	Pre-CIOD A	After 3rd CIOD B	At the end of CIOD C	A vs. B	A vs. C
Lymphocytes	1,807±1,622	591±534	691±428	0.011	0.015
CD3	1,309±1,432	414±440	461±375	0.036	0.033
CD3CD4	270±244	71±80	71±92	0.001	0.002
CD3CD8	1,003±1,184	367±376	390±332	0.067	0.065

Abbreviations: SD: standard deviation. Note: the p value was calculated by the two tailed Student's t-test; p significant < 0.05.

bicin 25mg/m^2, those treated with 20 mg/m^2 received a significantly higher mean ARDI of chemotherapy (95.38±7 vs 83.35±15.59, *p* 0.0001) with a mean idarubicin RDI >90%. Of the 14 patients enrolled in the study, 11 completed the treatment while 3 discontinued chemotherapy after 3 CIOD courses because of cytomegalovirus retinitis (two patients were being treated with CIOD including idarubicin 25 mg/m^2 and one including idarubicin 20 mg/m^2).

Immunologic and virological parameters

The changes of the lymphocyte subsets during the CIOD regimen are reported in Figure 2 and Table 5. The mean value of the absolute peripheral blood lymphocytes, of CD3 and CD3CD4 cells were statistically lower after the third CIOD course with respect to the baseline level (p = 0.011, p = 0.036 and p = 0.001, respectively). All these parameters remained significantly reduced one month after the end of chemotherapy.

The changes of the HIV.1 RNA load during the CIOD regimen are reported in Figure 3.

A high level of plasma viral load was observed before chemotherapy in all 10 patients tested (mean 810,819 ±1,080,485 copies/mL, range 94,000-3,800,000) and the mean HIV.1 RNA load rose significantly after the third CIOD course (1,762,279± 1,840,434 copies/mL, p = 0.045, Student's t-test). In particular, a high viral load concomitant with CD4 <100 cells/μL was observed in 8/10 patient of whom 4 had adverse events: opportunistic infection in three cases and no response to chemotherapy in the other.

Discussion

The therapeutic approach to patients with aggressive AIDS-NHL remains one of the most controversial areas of medical oncology. The results obtained with the use of the standard CHOP regimen in unselected AIDS-NHL are disappointing with remission rates ranging from 36% to 56% and median survivals between 4 and 7 months.[9,11] Sparano *et al.*[23] reported a long median survival of about 18 months with the use of infused cyclophosphamide, doxorubicin and etoposide (CDE) plus G-CSF with or without didanosine antiretro-

viral treatment, although if a high rate of opportunistic infections (56%) was observed.[23] In contrast, Tosi *et al.*[24] reported an absence of AIDS-related infections using high dose zidovudine and methotrexate with or without G-CSF.

Intensive chemotherapy in selected AIDS-NHL patients with a relatively well-preserved immune function may be a useful alternative treatment.[9,11] On the other hand, in a trial of selected, risk-adjusted patients intensive chemotherapy showed no advantage over the conventional CHOP regimen in patients without HIV adverse prognostic factors.[25] In addition, no advantage was reported[26] when standard dose or low-dose methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine and dexamethasone (m-BACOD) was utilized in unselected AIDS-NHL patients.

Gisselbrecht *et al.*[9] used a high dose of doxorubicin (75 mg/m^2) as part of induction chemotherapy in AIDS-NHL.

The aim of this study, planned in 1994 in the light of results of intensive chemotherapy in AIDS-NHL patients[9] and preliminary data in patients with DLC-NHL without HIV infection treated with high dose idarubicin in a CHOP-like regimen,[16] was to evaluate the anthracycline analogs at an equivalent doxorubicin dose of at least 100 mg/m^2 in DLC AIDS-NHL. Therefore the idarubicin dosage utilized in our CIOD regimen is about 2-2.5 greater than the dose of doxorubicin in the standard CHOP protocol, corresponding to 100-125 mg/m^2 of doxorubicin.

The results of the present pilot study show that the regimen including high dose of idarubicin is feasible in an out-patient setting without any toxic death. The therapeutic efficacy of this regimen for AIDS-DLC NHL is suggested by the high rate of CR (93%) and high DFS (71%) and OS (44%) at 60 months; these data, to our knowledge, have not been reported before in AIDS-NHL patients. It is worth noting that 43% of the patients are still alive in first response and without AIDS-related diseases after a median time of 55.5 months. Our results are in agreement with those reported by Gisselbrecht *et al.*, who obtained a high CR (63%) rate and an OS of 50% at 24 months in patients with baseline HIV infection characteristics similar to those of our cases.[9] Furthermore, the rates of response observed in our study were similar to those reported for low-intermediate risk (the main category of risk in our patients) according to age-adjusted IPI for patients with aggressive NHL without HIV infection.[21]

The good results of this study could be related to positive criteria selection: however, five patients (36%) had a CD4 count <100 cell/μL and all had DCL morphology, which is characteristically related to symptomatic HIV infection.[27,28]

The main toxicity of the regimen used in this study was myelosuppression which occurred in 74% of the CIOD courses and was related to the dose of idarubicin.

As far as the effects of a high dose of idarubicin in a CIOD regimen on immunologic function are concerned, a significant decrease in CD3, CD3CD4 and in absolute lymphocyte count was observed after 3 CIOD courses and at the end of chemotherapy, similar to the results obtained in HIV-positive and negative NHL patients reported by others.[30,31]

We, like others,[7,23] observed an overall high frequency of opportunistic infections (37%) occurring during chemotherapy and 3 out of 8 patients died in CCR of infection. These opportunistic infections seem to be strongly related to a pre-treatment CD4 count <100 cell/μL. In contrast, the low rate of non-opportunistic infections and the absence of *Pneumocystis carinii* pneumonia could be linked to the antimicrobial prophylaxis used.

It is well known that the CD4 count reflects the degree of HIV-induced immunosuppression and is a powerful prognostic factor for progression to AIDS, independently of the presence or not of a lymphoma.[29] Moreover, the absolute CD4 cell count is a more important predictor of survival than chemotherapy dose intensity.[3-7]

According to results obtained, in spite of the high rate of opportunistic infections occurring during chemotherapy in patients with baseline CD4 <100 cell/μL, intensive chemotherapy could be administered to these patients, and no differences in DSF and OS rates were observed between patients with a CD4 cell count below or above 100 cell/μL.

On the other hand, in the setting of HIV itself, viral load is the most sensitive predictor of progression to AIDS and/or development of opportunistic infections, even within CD4 subsets, but its role as a prognostic factor during chemotherapy in AIDS-NHL patients is still unknown.[30,32,33,35,36]

In this work the high level of HIV.1 RNA load observed at diagnosis of NHL increased significantly after 3 CIOD courses whether or not the patients developed AIDS-related diseases.

Recently, preliminary results indicate that the use of a combination of antiretroviral therapy associated with chemotherapy can prevent complications and improves remission rate in HIV-related NHL.[34–38] In the present study all patients alive at the end of chemotherapy were treated with HAART and this therapy could play a role in survival of these patients.

The results of our small pilot study suggest that the CIOD regimen with a high dose of idarubicin is feasible in selected AIDS DLC-NHL patients. Patients with relatively well-preserved immune function can be successfully treated with reasonably aggressive treatment. Nevertheless any new regimen for treatment of NHL[39,40] require validation in large, prospective clinical trials, so that this therapeutic approach cannot be recommended at present in routine clinical practice.

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RG, PM and FM were responsible for the design of the study and for the clinical care of the patients. RG, GGe and AC interpreted the results and wrote the paper. VP collaborated in collecting the data. GGi, LP, MA and IC performed virological and immunologic studies and CT monitored cardiologic function. GA contributed to the critical revision of the manuscript. All the authors approved the final version of manuscript. The authors thank Carla Mazzone and Maurizio Martelli from the Dipartimento di Biotecnologie Cellulari ed Ematologia, for clinical care support and Keren Deirdre Hobgen, who revised the English of this paper.

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Potential implications for clinical practice

Selected patients with relatively well-preserved immune function may be treated with the proposed chemotherapeutic regimen within a clinical trial, but careful attention should be paid to AIDS-related complications.

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