Original Article

Dose-Intensive Chemotherapy Including Rituximab in Burkitt's Leukemia or Lymphoma Regardless of Human Immunodeficiency Virus Infection Status

Final Results of a Phase 2 Study (Burkimab)

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BACKGROUND: The use of rituximab together with intensive chemotherapy in Burkitt's lymphoma or leukemia (BL) has been scarcely explored. This study prospectively evaluated and compared the outcome and toxicity of human immunodeficiency virus (HIV)-positive and HIV-negative patients with BL who were treated in an intensive immunochemotherapy-based and age-adapted trial. **METHODS:** A total of 118 adult patients (80 HIV-negative and 38 HIV-positive) aged 15 to 83 years were treated with 4 (nonbulky stages I-II) or 6 (stages II bulky, III-IV) cycles of intensive chemotherapy combined with rituximab. Reduction in chemotherapy doses and modification of the cycle schedules was performed in patients older than 55 years. **RESULTS:** The clinical characteristics of HIV-positive patients were comparable with those who were HIV-negative. Complete remission rates were 82% and 87%, respectively, and 9 patients died in induction, 9 died in remission, and 7 relapsed. After a median follow-up of 2.5 years, nonsignificant differences were observed in the 4-year disease-free survival and overall survival (OS) probabilities (77% and 63% for HIV-positive and 80% and 78% for HIV-negative patients, respectively). Young HIV-infected patients presented higher incidences of grade 3 or 4 mucositis and severe infectious episodes. Poor general status and bone marrow involvement, but not advanced age, were associated with a shorter OS, allowing the definition of 3 prognostic groups, with the OS ranging from 50% to 92%. **CONCLUSIONS:** Age-adapted intensive immunochemotherapy is highly effective in both HIV-negative and HIV-positive patients, with a higher toxicity in the latter group. Poor general status and bone marrow involvement had a negative impact on survival. ***Cancer*** **2013;119:1660–8.** © *2013 American Cancer Society.*

KEYWORDS: immunochemotherapy, human immunodeficiency virus, Burkitt's lymphoma or leukemia, prognostic factors.

INTRODUCTION

Burkitt's lymphoma or leukemia (BL) is a highly aggressive mature B-cell non-Hodgkin's lymphoma, with high incidence in immunosuppressed patients in Western countries, especially when associated with human immunodeficiency virus (HIV) infection.[1] The standard treatment consists of specific regimens incorporating intensive courses of chemotherapy with fractionated alkylating agents and phase-specific agents capable of crossing the blood–brain barrier. Intensive chemotherapy regimens have improved the outcome in both children and adults.[2] Some uncontrolled studies suggest that the addition of rituximab is efficacious and may be particularly valuable in adult patients.[3]

In HIV-associated lymphomas, the use of highly active antiretroviral therapy (HAART) has led to an improved tolerance to full-dose chemotherapy. However, the outcomes for HIV-infected patients have only been occasionally compared

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with those from HIV-negative patients receiving the same chemotherapeutic protocols.[4] The addition of rituximab has proven to be effective in aggressive lymphomas arising in HIV-infected patients.[5]

In the Spanish PETHEMA (Programa Español de Tratamiento en Hematología) cooperative group, patients with BL have been routinely treated with specific regimens irrespective of HIV status.[6] In July 2003, a trial adding rituximab to a specific regimen for BL (the BURKIMAB trial) was activated. A report of the first 36 patients (17 HIV-negative and 19 HIV-infected) in advanced stages showed the feasibility of the inclusion of HIV-infected patients, with similar outcome.[7] We report the final analysis of this trial, including a study of prognostic factors.

MATERIALS AND METHODS

Eligibility and Diagnostic Criteria

The PETHEMA Group adapted the study B-ALL/NHL2002 (ClinicalTrials.gov identifier NCT00199082) from the GMALL (German Multicenter Study Group for the Treatment of Adult Acute Lymphoblastic Leukemia) for the treatment of BL. The main modification in the Spanish study (BURKIMAB, ClinicalTrials.gov identifier NCT00388193) was the inclusion of patients with HIV-related BL. Accrual began in July 2003 for HIV-negative patients and in September 2004 for HIV-positive individuals, and the study was closed for inclusion in July 2011 and for follow-up in December 2011.

Inclusion criteria were age higher than 15 years and BL confirmed by morphology, immunological markers (including CD20 positivity), and cytogenetics. HIV-infected patients had to be under or had to begin HAART. The study was approved by the institutional research boards of the PETHEMA Group and of each center. Informed consent was obtained from all patients.

Diagnosis of BLL was performed according to the Revised European-American Classification of Lymphoid Neoplasms (REAL/WHO) criteria,[8] and cases were reclassified according to the World Health Organization Classification[9] after review of pathologic reports. Bone marrow (BM) involvement was assessed by aspiration or biopsy (in case of absence of infiltration by BM aspiration). Cytogenetic studies were performed in each center using direct methods and unstimulated short-term (24 and 48 hours) cultures with G-banding,[10] and the reports were centrally reviewed. Burkitt's leukemia was defined as $>20\%$ Burkitt's cells in BM. Central nervous system (CNS) disease was defined as cerebrospinal fluid (CSF) involvement by Burkitt's cells, cranial nerve palsy not related to a facial tumor, clinical signs of spinal cord compression, or an intracranial mass.

Parameters Evaluated

The following data were analyzed at baseline: general status (Eastern Cooperative Oncology Group score); the main hematologic and biochemical tests; computed tomography (CT) scan of the chest, abdomen, and pelvis; BM study; CSF study; and age-adjusted International Prognostic Index (aaIPI).[11] Bulky disease was defined as a tumor mass >10 cm in diameter. In HIV-infected patients, HIV viral load and CD4 lymphocyte counts were also recorded.

After therapy, the following evaluations were performed: physical examination, hematologic and biochemical parameters, BM study (if positive at diagnosis), and CT scans of the involved areas at baseline, in addition to CD4 count and viral load of HIV for HIV-infected patients. Response was evaluated after 2 therapy cycles and at the end of the fourth or sixth cycles for patients in localized or advanced stages, respectively. Patients in complete response (CR) were evaluated every 3 months during the first year, every 6 months during the second year, and annually thereafter.

Chemotherapy Regimen

Table 1 shows the therapy of the patients. Patients in advanced stage (bulky stages II or stages III-IV) and younger than 55 years received 2 courses of cycles A, B, and C, whereas older patients received 3 courses of alternating cycles A and B, for a total of 6 cycles. Patients with localized stage (nonbulky stages I-II) received 4 cycles of treatment. Reduction of 50% in methotrexate and cytarabine doses was performed in patients older than 55 years. A single dose of rituximab was administered before each cycle. After completion of chemotherapy, those patients in advanced stages who experienced CR received 2 additional doses of rituximab. CNS prophylaxis consisted of 8 doses of triple intrathecal therapy (TIT). CNS-directed therapy included TIT chemotherapy twice weekly until normalization of the cytologic study of CSF. Once they achieved a negative CSF status, patients followed the prophylactic scheme described above.

Supportive Care and Complementary Treatment

Intravenous hydration, rasburicase use, and general supportive measures were not prescribed by the protocol. The dose of methotrexate was reduced to 0.5 g/m^2 in patients with levels of creatinine >2 mg/dL or bilirubin >2 mg/dL, and 25% to 50% of dose reduction of methotrexate, cytarabine, and vincristine were recommended if severe

TABLE 1. Protocol Treatment[a]

Cycle/Day	Drug	Dose (mg/m^2)	Route
Prephase			
1-5	Cyclophosphamide	200	IV (1h)
1-5	Prednisone	60	IV bolus
Cycle A			
7	Rituximab	375	IV (4h)
8	Vincristine	2 mg (absolute)	IV bolus
8	Methotrexate	1500	IV (24h)[b,c]
8-12	Iphosphamide	800	IV (1h)
8-12	Dexamethasone	10	IV bolus
11-12	Teniposide (VM26)	100	IV (1h)
11-12	Cytarabine	150	IV (1h)/12h
Cycle B			
28	Rituximab	375	IV (4h)
29	Vincristine	2 mg (absolute)	IV bolus
29	Methotrexate	1500	IV (24h)
29-33	Cyclophosphamide	200	IV (1h)
29-33	Dexamethasone	10	IV bolus
32-33	Doxorubicin	25	IV (15min)
Cycle C			
49	Rituximab	375	IV (4h)
50	Vindesine	3 (maximum 5 mg)	IV bolus
50	Methotrexate	1500	IV (24h)[b]
50-54	Dexamethasone	10	IV bolus
53-54	Etoposide (VP16)	250	IV (1h)
54	Cytarabine	2000	IV (3h)/12h
Central nervous system prophylaxis			
1-8-12-29-33	Methotrexate	15 mg	intrathecal
	Cytarabine	40 mg	
	Dexamethasone	20 mg	

[a] Cycles A to C are repeated from days 77 to 124 to complete 6 treatment cycles after the prephase. After completion of the treatment, 2 additional doses of rituximab were given (weeks 21 and 24) for a total of 8 doses of rituximab.
[b] Folinic acid rescue from 12 hours after the end of infusion.
[c] One-half to one-third in patients over 55 years of age.
Abbreviation: IV, intravenous.

mucositis, liver toxicity, or severe neurotoxicity occurred in previous cycles.

HAART was not uniform in all patients, but should include 1 protease inhibitor or a non-nucleoside reverse transcriptase inhibitor plus 2 nucleoside reverse transcriptase inhibitors, and was started at BLL diagnosis in HIV-infected patients who did not previously receive it. *Pneumocystis jiroveci* prophylaxis was scheduled for HIV-infected patients who had a CD4 cell count below 200/μL at baseline. Granulocyte colony-stimulating factor was allowed for use from neutrophils $< 0.5 \times 10^9$/L until recovery for each cycle.

Response Criteria, Outcome Measures, and Evaluation of Toxicity

Complete response was defined as disappearance of extramedullary disease, as determined by physical examination and imaging studies after 2 cycles. In cases of Burkitt's leukemia, a normocellular marrow with $< 5\%$ blasts and recovery of peripheral blood counts was required. Partial remission (PR) was defined as $> 50\%$ reduction of all measurable lesions. Progressive disease (PD) was considered when $> 25\%$ increase in the size of lesions was documented. Both PR and PD were considered as treatment failures.

Early death (ED) was defined as death within 8 weeks of therapy onset (before first response evaluation). Treatment failure was defined when a patient did not reach PR after the first 2 cycles or CR after 4. Relapse was defined as disease recurrence at any site after at least 2 months of documented CR. Overall survival (OS) was calculated from the date of diagnosis to death or to the last follow-up. Disease-free survival (DFS) was defined as the time interval between CR and relapse, death due to any cause, or to the date of the last follow-up.

Toxicity was evaluated according to National Cancer Institute (NCI) Common Toxicity Criteria, version 3.0.

Statistical Methods

Toxicity, response to therapy, and prognostic factors for ED, CR, OS, and DFS were the main variables under study. Chi-square test, Fisher's exact test, Student *t* test, or Kruskal-Wallis test were used for comparisons of baseline characteristics and for comparisons among study groups. Prognostic factors associated with early death and CR were calculated using the Student *t* test or chi-square test when appropriate. In the multivariate analysis, odds ratios and the 95% confidence intervals (95% CIs) were calculated by logistic regression analysis. Survival curves were plotted according to the Kaplan-Meier method[12] and were compared by the log-rank test.[13] The Cox proportional hazard ratio model was used for univariate and multivariate survival analyses.[14]

RESULTS

Patients

A total of 140 patients were registered at 23 Spanish centers, of whom 118 were valid for this study. Twenty-two patients (16%) were excluded because they fulfilled the WHO criteria for B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt's lymphoma[9] after review of the pathologic reports. Table 2 shows the characteristics of the 118 valid patients (80 HIV-negative and 38 HIV-positive). The cohorts of HIV-positive and HIV-negative patients were comparable for the main clinical and biological parameters at diagnosis. There was a trend to a lower frequency of Burkitt's leukemia in HIV-infected patients. In HIV-positive patients, the CD4 lymphocyte count was lower than 200/μL in 21 of 37 cases (57%)

TABLE 2. Baseline Characteristics of the 118 Patients According to Human Immunodeficiency Virus Infection Status

Characteristic		HIV-Infected (n = 38)	Non-HIV-Infected (n = 80)	All (n = 118)	*P*
Sex, male n (%)		31 (82%)	54 (68%)	85 (72%)	.129
Age, median (minimum; maximum)		42 (20; 58)	47 (15; 83)	44 (5; 83)	.111
Diagnosis, n (%)	**Burkitt lymphoma**	34 (90%)	59 (74%)	93 (79%)	.057
	Burkitt leukemia	4 (10%)	21 (26%)	25 (21%)	
Stage, n (%)	**Non-bulky I-II**	5 (13%)	21 (26%)	26 (22%)	.154
	II(bulky), III-IV	33 (87%)	59 (74%)	92 (78%)	
ECOG ≥2, n (%)		21 (55%)	34/79 (43%)	55 (47%)	.240
Extranodal involvement (≥2 sites), n (%)		17 (45%)	38 (48%)	55 (47%)	.845
CNS involvement, n(%)		3 (8%)	11 (14%)	14 (12%)	.544
Bulky disease, n(%)		14 (37%)	17 (21%)	31 (26%)	.079
LDH level above normal, n(%)		37 (97%)	69/78 (89%)	106/116 (91%)	.162
Age-adjusted IPI, n (%)	**Low**	1 (3%)	5/78 (6%)	6/116 (5%)	.203
	Low-intermediate	3 (8%)	14/78 (18%)	17/116 (15%)	
	Intermediate-high	14 (37%)	32/78 (41%)	46/116 (40%)	
	High	20 (52%)	27/78 (35%)	47/116 (40%)	

Abbreviations: CNS, central nervous system; ECOG:Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

(median = 194/μL; range = 20-1180/μL), HIV viral load was detectable in 28 of 37 patients (76%), and BLL led to the diagnosis of HIV infection in 4 patients (11%).

Response to Treatment and Survival

Table 3 shows the main outcomes of the whole series and of the HIV-positive and HIV-negative patients. Although no statistically significant differences in any response parameter were observed between HIV-positive and HIV-negative patients, it is notable that ED was more frequent in HIV-infected patients. Infection was the cause of all early deaths.

Among patients achieving CR (n = 101), toxicity led to permanent interruption of treatment in 5 cases and 9 additional patients died in CR, during the treatment (6 in C1, 1 in A2, 1 in B2, and 1 in C2), with the main cause of death being infection (Table 3). After a median follow-up of 2.5 years (range = 0.5-6.8 years), 7 relapses (4 in bone marrow, 2 in CNS, and 1 in small bowel) have been documented, with the 4-year DFS probability of 80% (95% confidence interval [CI] = 69%-91%) (Fig. 1A) showing no differences between the 2 cohorts of patients. Thirty patients have died (9 in induction, 1 after withdrawal from therapy, 6 after failure, 9 in remission, and 5 after relapse). Two patients are alive in second CR after rescue chemotherapy. Autologous hematopoietic stem cell transplantation was performed in 1 patient and the remaining patient was waiting for transplantation at the time of this report. The 4-year OS probability of the series was 73% (95% CI = 65%-81%) (Fig. 1B), with only a trend for a lower survival in HIV-infected patients (78% [range = 68%-88%] versus 63% [range = 48%-78%] for HIV-uninfected and HIV-infected patients, respectively, *P* = .07). Interestingly, no differences were observed in response attainment and in relapse rate in elderly patients, in comparison with those from young patients: 93% CR in young patients versus 100% in older patients, and 5 relapses of 77 young patients who had CR (7%) versus 2 of 24 older patients with CR (8%). The 5-year OS probability of the 91 patients younger than 55 years was 72% ± 10%, versus 76% ± 17% for those aged ≥ 55 years (n = 27).

TABLE 3. Treatment Outcome for the Overall Group and According to Human Immunodeficiency Virus Infection Status

Variable	HIV-Infected	Non-HIV-Infected	All
Evaluable patients	38	80	118
Early withdrawal	–	2 (3%)	2 (2%)
Death in induction	5 (13%)	4 (5%)	9 (8%)[a]
Failure	2 (5%)	4 (5%)	6 (5%)
Complete response	31 (82%)	70 (87%)	101 (85%)
Relapse	2 (6%)	5 (7%)	7 (7%)
Death in remission	5 (16%)[a]	4 (6%)[a]	9 (9%)[b,c]

[a] Systemic fungal infection (n = 3, *Scedosporium prolificans*, *Geotrichum capitatum*, and *Candida glabrata*), septic shock (n = 4), and bilateral pneumonia (n = 2).
[b] *Aspergillus* spp. (n = 2), *Candida albicans* (n = 1), gram-negative sepsis (n = 4, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* [n = 2]), central nervous system hemorrhage (n = 1), pneumonia (n = 1).
[c] A total of 6 patients died in C1, 1 patient in A2, 1 patient in B2, and 1 patient in C2.Abbreviation: HIV, human immunodeficiency virus.

Prognostic Factors and Risk Groups Assessment

Because no significant differences were found between HIV-positive and HIV-negative patients in any outcome

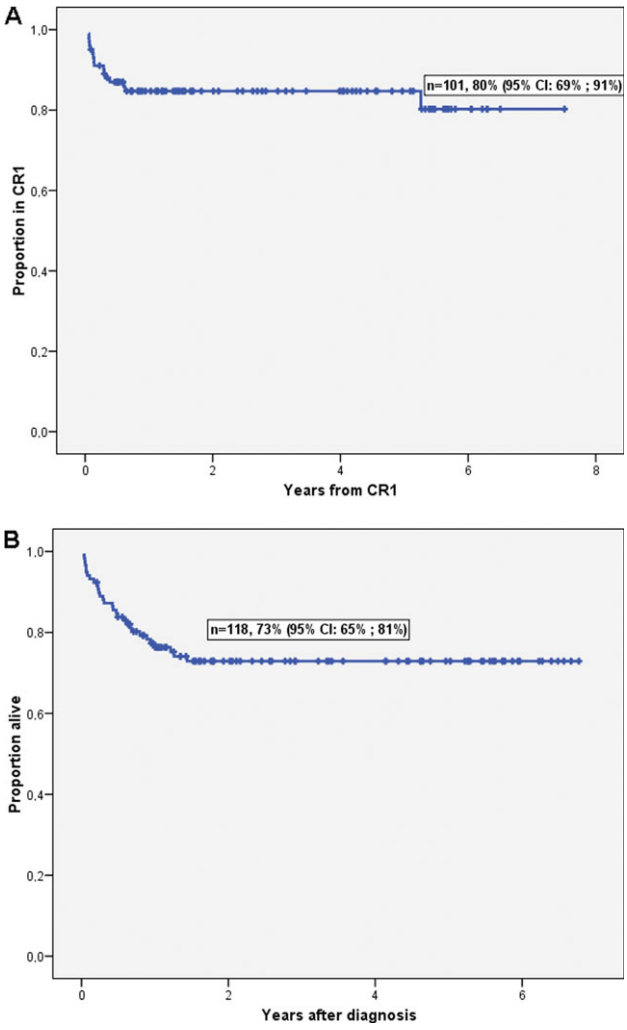

Figure 1. (A) Disease-free survival and (B) overall survival are shown of the patients from the series.

TABLE 4. Results of Multivariate Analysis of Prognostic Factors in the Patients of the Series

Outcome	Variable	Unfavorable Category	OR/ HR	95% CI	*P*
Death in induction	ECOG	≥2	1.2	1.1–1.3	.001
CR	CNS involvement	Yes	9.1	1.6–50	.023
DFS	BM involvement	Yes	4.9	1.5–16.2	.008
OS	ECOG	≥2	2.3	1.1–5	.045
	BM involvement	Yes	2.7	1.2–6.1	.014

Abbreviations: BM, bone marrow; CI, confidence interval; CNS, central nervous system; CR, complete response; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OR, odds ratio; OS, overall survival.

measure, a joint analysis of prognostic factors was performed. Table 4 shows the results of the multivariate analyses for each of these outcomes. Poor general status influenced the probability of ED, whereas CNS involvement at baseline was associated with a lower probability of CR (Table 5), BM involvement was associated with a shorter DFS, and poor general status and BM involvement were associated with a shorter OS (Table 6). There was no relationship between the CD4 lymphocyte count at the end of the treatment (median = 200 [range = 1-659]/μL) and the DFS and OS. According to the presence of 0, 1, or 2 prognostic factors for survival, 3 groups with different survival were identified with 4-year survival probabilities ranging from 50% to 92% (Fig. 2).

Treatment-Related Toxicity

Tables 7 and 8 show the toxicity according to the age groups, the cycle of chemotherapy, and HIV infection status. In HIV-infected patients younger than 55 years, hematologic toxicity, mucositis, and infections were significantly more frequent than in HIV-negative patients, whereas no differences in toxicity were observed in patients ≥ 55 years according to HIV infection status. Interestingly, no significant differences were observed in the overall frequency of grade 3 or 4 infections on comparison of the age groups (161 infections in 438 chemotherapy cycles [37%] in young patients versus 37 of 125 [30%] in older patients). Granulocyte colony-stimulating factor was effectively used in the 91% of the cycles, without differences in both age groups.

DISCUSSION

This final analysis shows that this age-adapted immunochemotherapeutic schedule is feasible and effective for adult patients with BL, regardless of their HIV infection status, although more hematologic, mucosal, and infectious toxicities were observed in young HIV-infected patients. General status and the presence of CNS and BM involvement, but not age, were the main prognostic factors.

The development of specific chemotherapies by pediatric groups has been the main hallmark in the therapy of BL, with curability indexes of approximately 80% to 90% of cases.[15,16] The adaptation of these schedules to adults has led to an increase in the response rate and survival, ranging from 60% to 70% of cases in some series.[17] The addition of rituximab to these specific therapies may represent a step forward in the therapy of BL. Although no randomized trials on the use of rituximab have been published to date, and most of the studies are retrospective and include a limited number of patients, the tolerability and efficacy of specific immunochemotherapy seems to be

TABLE 5. Death in Induction and Complete Response (Univariate Analysis)

Variable	Category	n	Dead, n (%)	*P*	n	CR, n (%)	*P*
Sex	Male	85	9 (11%)	.06	75	71 (95%)	.99
	Female	33	0		32	30 (94%)	
LDH (U/L)	Normal	10	0	.616	10	10 (100%)	.99
	Elevated	106	8 (8%)		96	91 (95%)	
Extranodal involvement		63	3 (5%)	.301	60	59 (98%)	.085
	=2 sites	55	6 (11%)		47	42 (89%)	
CNS involvement	No	104	9 (9%)	.380	94	91 (97%)	.023
	Yes	14	0		13	10 (77%)	
Bulky disease	No	87	6 (7%)	.696	79	75 (95%)	.651
	Yes	31	3 (10%)		28	26 (93%)	
Age (y)		91	7 (8%)	.99	83	71 (95%)	.334
	=55	27	2 (7%)		24	24 (100%)	
ECOG score		62	0	.001	61	59 (97%)	.648
	=2	55	9 (16%)		45	42 (93%)	
Age-adjusted IPI	Low/low-intermediate	23	0	.209	23	23 (100%)	.583
	Intermediate-high/high	93	8 (9%)		83	78 (94%)	
BM involvement	No	72	4 (6%)	.479	67	63 (94%)	.99
	Yes	46	5 (11%)		40	38 (95%)	
Burkitt leukemia	No	93	7 (8%)	.99	85	79 (93%)	.342
	Yes	25	2 (8%)		22	22 (100%)	
Ann Arbor stage	Nonbulky I–II	26	0	.204	26	26 (100%)	.332
	II (bulky), III–IV	92	9 (10%)		81	75 (93%)	
HIV infection	No	80	4 (5%)	.145	74	70 (95%)	.99
	Yes	38	5 (13%)		33	31 (94%)	

Abbreviations: BM, bone marrow; CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

TABLE 6. Disease-Free Survival and Overall Survival (Univariate Analysis)

Variable	Category	n	5-y DFS (±95% CI)	*P*	n	5-y OS (±95% CI)	*P*
Sex	Male	71	82% ± 13%	.411	85	74% ± 10%	.815
	Female	30	79% ± 15%		33	70% ± 17%	
LDH (U/L)	Normal	10	No events (100%)	.176	10	No events (100%)	.091
	Elevated	75	78% ± 12%		106	72% ± 9%	
Extranodal involvement		59	88% ± 9%	.171	63	81% ± 10%	.028
	=2 sites	42	65% ± 30%		55	64% ± 13%	
CNS involvement	No	91	86% ± 7%	.027	104	76% ± 9%	.036
	Yes	10	0%		14	50% ± 26%	
Bulky disease	No	75	79% ± 13%	.974	87	73% ± 10%	.877
	Yes	26	85% ± 14%		31	73% ± 16%	
Age (y)		77	79% ± 12%	.662	91	72% ± 10%	.697
	=55	24	87% ± 14%		27	76% ± 17%	
ECOG score		59	88% ± 9%	.231	62	82% ± 10%	.014
	=2	42	72% ± 20%		55	64% ± 13%	
Age-adjusted IPI	Low/low-Intermediate	23	No events (100%)	.025	23	No events (100%)	.005
	Intermediate-high/high	78	75% ± 14%		93	68% ± 10%	
BM involvement	No	63	94% ± 6%	.001	72	84% ± 9%	.001
	Yes	38	56% ± 27%		46	56% ± 15%	
Burkitt leukemia	No	79	83% ± 13%	.098	93	77% ± 9%	.179
	Yes	22	71% ± 20%		25	59% ± 21%	
Ann Arbor stage	Nonbulky I-II	26	No events (100%)	.015	26	No events (100%)	.002
	II (bulky), III-IV	75	74% ± 14%		92	66% ± 10%	
HIV infection	No	70	80% ± 17%	.264	80	78% ± 10%	.062
	Yes	31	77% ± 15%		38	63% ± 15%	

Abbreviations: BM, bone marrow; CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; IPI, International Prognostic Index; LDH, lactate dehydrogenase; OS, overall survival.

good, with response rates between 70% and 90% and survival ranging from 70% to 80%.[17-21]

The high frequency of virologic and immunologic response to HAART and the improvement in supportive therapy have encouraged some groups to treat patients who have HIV-related BL with the same aggressive schedules as those used in patients without immune suppression, with promising results and acceptable tolerability.[22-26] Several studies have added rituximab to these schedules,

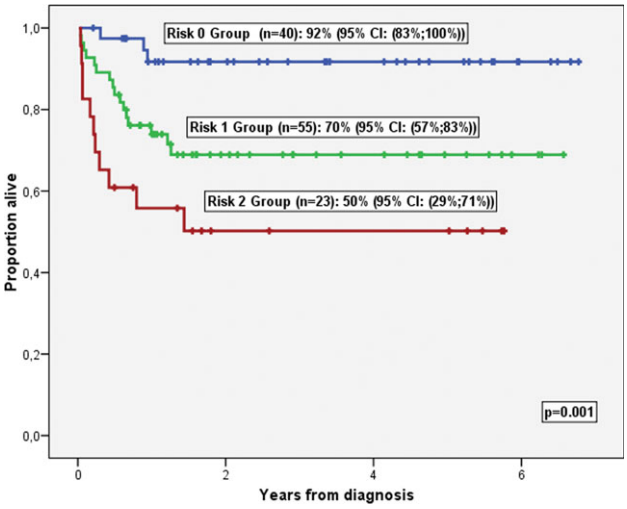

Figure 2. Risk categories are shown for overall survival according to the prognostic factors.

with results comparable to those obtained in HIV-negative patients.[27,28] However, to our knowledge, no prospective comparison between HIV-positive and HIV-negative patients with BL has been performed.

The BURKIMAB study prospectively evaluated the efficacy and tolerability of the specific immunochemotherapy B-ALL/NHL2002 protocol from the GMALL group,[17] with the main modification being the inclusion of patients with HIV-related BLL. This was consistent with our previous studies showing the applicability and equivalent results of specific chemotherapeutic schedules in HIV-positive and HIV-negative BL patients.[7,29] A report of the first 36 patients (17 HIV-negative and 19 HIV-infected) in advanced stages showed the applicability of this schedule in both groups of patients, with similar outcomes.[7] In this final analysis, both cohorts of patients had similar baseline characteristics. The CR was similar in both groups, and the frequency of relapses or resistant disease was very low. A matter of concern was the high frequency (9%) of deaths (mainly due to infection), occurring in patients in remission during chemotherapy, being slightly higher in HIV-infected than in HIV-negative patients. Although the relapse rate, DFS, and OS were not significantly different in HIV-positive and HIV-negative patients, grade 3 or 4 myelosuppression and mucositis were more common in young HIV-infected patients, with major infection in half of the cycles.

TABLE 7. Grade 3–4 Adverse Events in Patients <55 Years Old According to HIV Infection and Cycle of Chemotherapy

	HIV-Infected (n = 35)			Non-HIV-Infected (n = 56)		
	Cycles A	Cycles B	Cycles C	Cycles A	Cycles B	Cycles C
Number of cycles	59	50	47	104	94	90
Neutropenia[a]	57/58	38/45	39/41	89/104	42/91	63/90
Days (median [range])	8 [1; 24]	5 [1; 19]	6 [1; 17]	6 [1; 25]	5 [1; 15]	4 [1; 19]
Thrombocytopenia[b]	47/58	24/44	31/41	74/104	22/91	46/89
Days (median [range])	6 [1; 20]	6 [1; 22]	6 [1; 31]	4 [1; 25]	4 [1; 22]	3 [1; 38]
Hepatic[c]	8/55	1/43	0	4/102	2/90	1/83
Renal	2/55	0	0	3/102	1/90	0
Neurologic	2/55	2/43	0	0	0	2/83
Gastrointestinal	1/55	0	0	0	1/90	0
Mucositis[d]	22/55	23/46	11/42	11/99	11/90	5/82
Tumor lysis syndrome	2/32	–	–	3/55	–	–
Infection[e]	35/59	27/49	23/45	37/104	24/94	15/87
Death by infection[f]	6/59	1/49	3/45	1/104	0	2/87
Other	7/55	3/44	2/42	1/102	0	2/83

[a] Significant differences between HIV and non-HIV groups in cycles A, B, and C ($P = .007$, $P < .001$, and $P = .001$).
[b] Significant differences between HIV and non-HIV groups in cycles B and C ($P = .001$ and $P = .012$).
[c] Significant differences between HIV and non-HIV groups in cycles A ($P = .026$).
[d] Significant differences between HIV and non-HIV groups in cycles A, B, and C ($P < .001$, $P < .001$ and $P = .003$).
[e] Significant differences between HIV and non-HIV groups in cycles A, B, and C ($P = .005$, $P = .001$ and $P < .001$).
[f] Significant differences between HIV and non-HIV groups in cycles A ($P < .003$).
Abbreviation: HIV, human immunodeficiency virus.

TABLE 8. Grade 3-4 Adverse Events in Patients ≥55 Years Old According to HIV Infection and Cycle of Chemotherapy

	HIV-Infected (n = 3)		Non-HIV-Infected (n = 24)		*P*	
	Cycles A	Cycles B	Cycles A	Cycles B	Cycles A	Cycles B
Number of cycles	9	8	58	56		
Neutropenia	9/9	8/8	38/54	31/51	.097	.042
Days (median [range])	4 [1; 12]	4 [1; 7]	6 [1; 28]	4 [1; 12]		
Thrombocytopenia	5/9	3/8	26/54	15/51	.732	.690
Days (median [range])	2 [2; 3]	2 [2; 5]	6 [1; 25]	4 [1; 19]		
Hepatic	0	0	2/56	1/53		
Renal	0	0	2/56	0		
Neurologic	2/9	0	0	0		
Mucositis	2/9	2/8	7/55	10/51		
Tumor lysis syndrome	0	–	3/23	–		
Infection	3/9	0	20/57	14/51		
Death by infection	1/9	0	3/57	0		
Other	0	0	1/56	1/53		

Abbreviation: HIV, human immunodeficiency virus.

Although CD4 counts were assessed at the end of therapy, the lack of monitoring of HIV viral load and CD4 lymphocyte counts during and sequentially after the treatment could not allow us to determine if there were differences in toxicity and outcomes based on these features. In both HIV-positive and HIV-negative patients aged 55 years or older, the frequency of cytopenias was similar but the duration was lower, with fewer infections and mucositis, probably due to reduced intensity of chemotherapy given to these patients.

The prognostic factors identified in this study (CNS and BM involvement and poor general status) are consistent with those identified in other trials[15-28] or in population-based studies[30] with the exception of advanced age. We have attributed the lack of poor prognosis in older patients to 2 features. First, the strategy of dose reduction and schedule modification for older patients did not translate into a lower remission rate or increased relapse rate in this population. Second, there was not an excess of toxicity causing treatment-related deaths in older patients in this study. Other trials such as Hyper-CVAD and rituximab showed improvement in disease-related outcomes of de novo BL, particularly for older patients. Future trials should therefore examine whether less-intensive treatment protocols including rituximab can reduce toxicity while maintaining high efficacy. In addition, improved therapeutic strategies are needed for the poorest prognostic group of patients, who have only a 50% probability of survival.

In spite of similar baseline characteristics and results of treatment in HIV-positive and HIV-negative patients, a selection bias cannot be ruled out in this study, especially for the HIV-infected patients, in whom the frequency of BL was lower. However, the high survival rate observed in HIV-related BL also supports the use of intensive protocols with age-adapted immunochemotherapy in these patients. These regimens are feasible, with high CR and very low relapse rates. However, the toxicity is relevant especially with regard to infections and mucositis. The occurrence of deaths during chemotherapy in patients in CR calls for future trials examining protocols with decreased dose-intensity in postremission therapy. The use of risk-adapted therapy, the incorporation of targeted therapies, and the study of minimal residual disease will be useful in the definition of future therapeutic strategies.

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