Lack of influence of human immunodeficiency virus infection status in the response to therapy and survival of adult patients with mature B-cell lymphoma or leukemia. Results of the PETHEMA-LAL3/97 study

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Background and Objectives. Short, intensive multiagent chemotherapy has resulted in significant progress in Burkitt's lymphoma and leukemia. A protocol was designed to treat all adult patients with mature B-cell lymphoma or leukemia with the aims of comparing the response to therapy and survival with regards to their HIV infection status.

Design and Methods. Fifty-three adult patients with advanced stage Burkitt's lymphoma or Burkitt's leukemia were treated. Response to therapy, survival and toxicity were evaluated according to their HIV infection status.

Results. The median age of the patients was 53 years (range 15-74). There were no differences in CR rates between HIV-negative (77%) and HIV-positive patients (71%). Only age > 60 years was associated with a lower CR rate (OR 0.18, 95%CI 0.04-0.81, p=0.026). The 2-year overall survival (OS) probability was 51% (95%CI, 38%-64%) for the 53 patients. The OS of HIV-negative and HIV-positive patients did not significantly differ. Only age > 60 years was associated with a shorter OS (OR 5.1, 95%CI 2.0-12.7, p=0.001). The 2-year disease free survival (DFS) for the 40 patients achieving CR was 60% (95%CI, 45%-75%). Age > 60 years was the only identified factor associated with a shorter DFS (OR 5.2, 95%CI 1.4-20, p=0.015).

Interpretation and conclusions. This study confirms the effectiveness of intensive strategies in adult patients with advanced stage Burkitt's lymphoma or leukemia. It also shows the feasibility of these strategies in individuals with HIV infection with comparable results. Advanced age proved to be the main adverse prognostic factor for response to therapy and survival.

Key words: Burkitt's lymphoma/leukemia, HIV infection, intensive chemotherapy.

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Mature B-cell lymphoblastic leukemia or FAB (French-American-British) L3 acute lymphoblastic leukemia (L3ALL) and Burkitt's lymphoma (BL) are regarded as different manifestations of the same neoplasia.[1] Short, intensive multiagent chemotherapy including high-dose methotrexate, cytarabine and anthracycline has resulted in significant progress in the treatment of Burkitt's lymphoma/leukemia in children.[2-6] These same protocols have also been associated with high complete remission (CR) and long-term event-free survival rates in adults.[7-11]

Burkitt's or Burkitt-like lymphomas represent 20% to 40% of human immunodeficiency virus (HIV)-associated lymphomas.[12] The risk of patients with acquired immunodeficiency syndrome (AIDS) developing these lymphomas is 200 to 1,000 times higher than that of the general population.[13] In contrast to other HIV-associated lymphomas, BL may develop earlier during the natural course of HIV infection, when $CD4^+$ lymphocyte counts are relatively preserved.[14,15] Nevertheless, the prognosis of patients with HIV-associated BL is considered to be poor.

The use of highly active antiretroviral therapy (HAART) has changed the long-term outcome of patients with HIV infection, improving CD4 lymphocyte counts, decreasing the incidence of AIDS-associated opportunistic infections, and resulting in prolonged survival.[16] HAART has also led to a decrease in the incidence of Kaposi's sarcoma[17] and primary central nervous system (CNS) lymphoma.[18] HAART has been associated with a higher probability of long-term disease-free survival and overall survival in primary CNS lymphoma,[19] systemic non-Hodgkin's lymphoma[20,21] and Hodgkin's disease[22,23] in patients with HIV infection.

The PETHEMA group designed a prospective, non-controlled, multicenter study (PETHEMA-LAL3/97) to treat all consecutive adult patients with mature B-cell lymphoma/leukemia regardless of their HIV status. The aims of this study were to report the overall results of the protocol and to compare the response to therapy and survival with regards to HIV infection status.

Design and Methods

Eligibility and diagnostic criteria

From June 1997 to May 2001, 58 adult (> 15 years) patients with newly diagnosed BL or L3ALL were prospectively included in the PETHEMA (*Programa para el Estudio y Tratamiento de las Hemopatias Malignas*,

Spanish Society of Hematology) LAL3-97 trial. Patients were eligible for the study if they were over 15 years of age and had been newly diagnosed as having advanced stage BL (stages III and IV or stage II with a bulky mass) or L3ALL, including those who had history of immunodeficiency or a previous malignant disease. There was no restriction by performance status, older age, or organ dysfunction if it was due to BL or L3ALL. HIV infected patients were eligible regardless of the $CD4^+$ lymphocyte count, use of antiretroviral therapy, or history of other AIDS-defining conditions.

The diagnosis of BL or L3ALL was established according to REAL/WHO[1] and FAB criteria,[24] respectively. L3ALL was considered if atypical bone marrow cells were higher than 20%. A mature B-cell immunophenotype was defined as reactivity to B-cell antigens (CD10, CD19, CD20, CD22, CD24 in cell suspensions or frozen tissue, or CD20 and CD79a in fixed tissue) and monoclonality of surface immunoglobulins. Cytogenetic study of bone marrow, peripheral blood or lymph node or tumor mass was performed in institutional laboratories using direct methods and unstimulated short-term (24 and 48 hours) cultures with G-banding, following the *International System for Human Cytogenetics*[25] guidelines. Central nervous system disease was defined as the presence of blasts in the cerebrospinal fluid (CSF), cranial nerve palsy not related to a facial tumor, clinical signs of spinal cord compression or an intracranial mass.

Parameters evaluated

At the time of referral, the history of the patients was determined and a physical examination was performed. Complete blood cell count, coagulation and biochemical profiles, bone marrow aspiration or biopsy, lumbar puncture for cytological CSF analysis, chest radiography and chest, abdomen and pelvis computerized tomography (CT) scans were carried out. Assessment of left ventricular cardiac function was recommended before the onset of therapy. Immunophenotypic and cytogenetic studies were performed in both cytological samples and/or fixed tissue whenever possible.

Sequential evaluations included complete blood counts, liver and renal function studies and coagulation profiles. CD4 lymphocyte counts (by flow cytometry) and HIV viral load counts (Nuclisens HIV-1QT, Organon Teknica, Doxtel, The Netherlands) were obtained from HIV positive patients.

After completion of therapy, assessments were performed every three months for the first year, every six months during the second year and annually thereafter.

Chemotherapy regimen

The chemotherapy schedule was derived from the German Adult Lymphoblastic Leukemia (GMALL) B-ALL 05/93 protocol with slight modifications and is summarized in Table 1. Briefly, a pre-phase treatment with cyclophosphamide 200 mg/m^2 intravenously (iv) over 1 hour and prednisone 60 mg/m^2 iv every 24 hours for five doses on days 1-5 was given to prevent the tumor lysis syndrome. Afterwards, eight courses of alternating intensive chemotherapy were given at three-week intervals. A-cycles (induction and consolidations, 2, 4, and 6) included vincristine, methotrexate, iphosphamide, dexamethasone, VM26 and cytarabine. B-cycles (consolidations 1, 3, 5, and 7) consisted of the same doses of vincristine, methotrexate and dexamethasone, cyclophosphamide and doxorubicin. Central nervous system prophylaxis included intrathecal administration of methotrexate, cytarabine and hydrocortisone on days 1 and 5 of each cycle. During induction the first dose of intrathecal treatment was administered on day 1 of the pre-phase treatment. Patients with documented CNS involvement received intrathecal chemotherapy twice weekly during induction until the CSF cell count normalized and the cytological examination was negative and then followed the prophylactic scheme described above. Patients provided informed consent according to institutional guidelines before entering the study.

Supportive care and complementary treatment

During the first course, allopurinol was given together with intravenous hydration and alkalinization to reduce the complications of tumor lysis. At the time this protocol was started, rasburicase was not authorized in Spain and, thus, was not used. Afterwards, only hydration (3,000 mL/m^2 day) and alkalinization (40 mmol of sodium bicarbonate per liter of hydration) were mandatory. Calcium leucovorin was given at a dose of 75 mg/m^2 iv 12 hours after the completion of methotrexate; a second dose of 30 mg/ m^2 iv was given 3 hours later and continued at a dose of 10 mg/m^2 iv every 6 hours until methotrexate blood levels were less than 0.2 μ/L. Afterwards, two additional doses of oral calcium leucovorin were given. Standard doses of methotrexate were reduced to 0.5 g/m^2 for patients aged >50 years, or those with serum creatinine >2 mg/dL or serum total bilirubin > 2 mg/dL, being raised according to tolerance in subsequent cycles. G-CSF (5 μg/kg/day subcutaneously) was administered in each cycle if severe neutropenia was present in the previous cycle in order to maintain the intervals between cycles. No maintenance therapy was administered after completion of the eight cycles. Hospitalization, prophylaxis and management of infections and transfusion policy were not prescribed by the protocol and were implemented according to the specific protocols of each participating hospital. Triple drug HAART (at least one or

two protease inhibitors and two nucleoside reverse transcriptase inhibitors)[26] was recommended to all HIV infected patients upon diagnosis of Burkitt's lymphoma/leukemia. Patients who were already receiving antiretroviral therapy prior to the diagnosis of Burkitt's lymphoma/leukemia continued their therapy; otherwise, HAART therapy was started during the first chemotherapy course and was continued after the end of therapy.

Response criteria and toxicity evaluation

Complete remission (CR) was defined as 5% blasts in a normocellular marrow associated with peripheral blood recovery and complete resolution of extramedullary disease as assessed by clinical examination, imaging studies and CSF cytology. An induction death was defined as death within four weeks of the initiation of therapy. Resistant disease was diagnosed when a patient survived the induction treatment but did not achieve CR, and relapse was defined as disease recurrence at any site after at least two months of documented CR. CR was assessed after induction treatment in L3ALL patients and at the end of consolidation in patients with BL. Overall survival (OS) was calculated from the first day of chemotherapy to death due to any cause or to the date of the last follow-up contact for patients who were alive (July 2002).

Disease-free survival (DFS) was calculated for patients having achieved CR from the day of documented CR to death due to any cause, relapse or to the date of the last follow-up contact for patients who did not experience any event. As there was no provision in the protocol for stem cell transplantation (SCT), patients submitted to this procedure were censored from analysis of OS and DFS at the time of SCT. In HIV-infected patients, a virological response to HAART was defined as having total HIV RNA loads below the limit of detection in serum (<80 copies/mL). Toxicity was evaluated according to the WHO criteria.

Statistical methods

Patients were stratified according to their HIV status and the diagnosis (BL or L3ALL). Parameters tested for association with CR and survival included age, sex, performance status, bulky disease, leukemic disease, stage, central nervous system involvement, LDH, albumin and HIV status. The associations between the initial characteristics and comparisons among strata were explored by means of the χ^2 test, Fisher's exact test or Student's t test. Prognostic factors associated with CR were calculated using the χ^2 test and odds ratios and 95% confidence intervals (95%CI) were calculated by logistic regression analysis. OS and DFS were plotted according to the Kaplan-Meier method.[27] The log-rank test[28] was used for univariate analyses and the Cox model for multivariate analyses of OS and DFS.

Table 1. PETHEMA LAL3/97 protocol treatment.

Pre-phase		
Cyclophosphamide	200 mg/m^2 iv over 1 hour	Days 1-5
Prednisone	60 mg/m^2 iv bolus	Days 1-5
Treatment A. Odd-numbered cycles (induction and consolidations courses 2, 4 and 6).		
Vincristine	2 mg iv	Day 1
Methotrexate	3 g/m^2 iv over 24 hours	Day 1
Ifosfamide	800 mg/m^2 iv over 1 hour	Days 1-5
Dexamethasone	10 mg/m^2 daily either orally or iv	Days 1-5
VM26	100 mg/m^2 iv over 1 hour	Days 4-5
Cytarabine	150 mg/m^2 iv over 1 hour every 12 hours	Days 4-5
Treatment B. Even-numbered cycles (consolidation courses 1, 3, 5, and 7).		
Vincristine	2 mg iv	Day 1
Methotrexate	3 g/m^2 iv over 24 hours	Day 1
Cyclophosphamide	200 mg/m^2 iv over 1 hour	Days 1-5
Dexamethasone	10 mg/m^2 daily either orally or iv	Days 1-5
Doxorubicin	25 mg/m^2 iv over 15 minutes	Days 4-5
Central nervous system prophylaxis		
Methotrexate	12 mg it	Days 1 and 5 of each cycle*
Cytarabine	30 mg it	Days 1 and 5 of each cycle*
Hydrocortisone	20 mg it	Days 1 and 5 of each cycle*

*iv: intravenous; it: intrathecal; *administered on day 1 of pre-phase in induction cycle.*

Results

Patients

A total of 58 patients were enrolled between June 1997 and May 2001. Five patients were excluded from the analysis: two due to inadequate data at diagnosis, 2 because of lack of adequate follow-up and one because the cytogenetic analysis revealed the t(9;21) as the only alteration. Fifty-three patients were treated; their clinical characteristics are presented in Table 2. Thirty-seven patients were males (70%), with a median age of 53 years (range, 15-74). Thirty-one patients (58%) were classified as having L3ALL. Among patients with BL, 5 had Ann Arbor stage II bulky disease and 17 patients had stage III or IV. Five patients with L3ALL and one

Table 2. Characteristics of 53 adult patients with Burkitt's leukemia/lymphoma.

Characteristic		*All patients*	*HIV-infected patients*
		N=39	N=14
Age (years)	Median (range)	35 (15-74)	45 (23-65)
Over 60 years N (%)		8(1)	1(7)
Male/Female N (%)		25 (64)/14 (36)	12 (86)/2 (14)
Performance status N (%) 23 (59)/16 (43)7 (50)/7 (50)Zubrod 0-1 / Zubrod>1			
Stage		N (%)	N (%)
II bulky / III-IV		5 (13)/9 (23)	0/8 (57)
L3ALL (>20% BM blasts)		25 (64)	6 (43)
Bulky disease	N (%)	17 (44)	10 (71)
CSF involvement	N (%)	3 (8)	3 (21)
LDH (U/L)	Median (range)	1990 (160-33840)	757 (100-84667)
Albumin (g/L)	Median (range)	35 (23-49)	36 (26-46)
HIV-infected	N (%)		14 (28)
No HAART treatment			7 (50)
HAART prior to diagnosis		2 (14)	
HAART from diagnosis			5 (36)

HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus; CSF: cerebrospinal fluid.

Table 3. Toxicity of induction and consolidation courses.

	Induction Pre-phase+ A cycle	*Consolidation B cycles*	*Consolidation A cycles*
Evaluable cycles	53	100	61
Toxic death	11(21%)	1(1%)	-
Tumor lysis syndrome	6 (11%)	-	-
Withdrawal	-	3 (3%)	-
Dose modification	2 (4%)	20(20%)	16 (26%)
Infection *	11 (21%)	7 (7%)	-
Mucositis *	5 (9%)	14 (14%)	2 (3%)
Hepatotoxicity *	2 (4%)	6 (6%)	1 (2%)
Nephrotoxicity *	1 (2%)	2 (2%)	1 (2%)
Neurotoxicity *	2 (4%)	2 (2%)	-
Neutropenia°	10 (0-28)	2 (0-13)	5 (0-13)
Thrombocytopenia#	7 (0-28)	0 (0-40)	2 (0-16)

**Grade III-IV episodes; median days (range) to recovery of neutrophils >0.5¥10⁹/L° and platelets > 20¥10⁹/L.# See Table 1 for description of A and B cycles.*

with BL had CNS involvement at diagnosis (11%), abdominal masses were present in 25 (47%) and bulky disease in 17 (32%). Seven L3ALL patients had active infection at the time of diagnosis and 3 presented with renal insufficiency. Twenty-seven patients (51%) had an evaluable cytogenetic analysis: a typical Burkitt's karyotype, t(8;14)(q24;q32) or t(8;22)(q24;q11), was the only abnormality present in 13 and 1 patients, respectively, 4 had complex additional chromosomal abnormalities and 9 had normal diploid karyotypes. Nine patients were diagnosed with HIV infection at the time of diagnosis of Burkitt's lymphoma/leukemia and 5 patients had been diagnosed with HIV infection 1 to 13 years before diagnosis. Three of them had had prior AIDS-defining conditions (oral candidemia, esophageal candidemia and tuberculosis infection). The median CD4 count at diagnosis among the 9 patients with available information was 420/μL (range 49-884/μL) with 3 patients having values < 200/μL. The median HIV viral load, measured in 8 patients at the time of diagnosis, was 400,000 copies/mL (range <80 - 1,097,000 copies/mL). Seven patients (50%) did not receive HAART, 2 patients had started HAART before the diagnosis of Burkitt's lymphoma/leukemia and were in complete virological response at the beginning of chemotherapy, 5 patients started HAART at diagnosis or during the first courses of chemotherapy. Virological response to HAART was documented after chemotherapy in the 5 patients under HAART treatment who achieved a complete response.

Six patients were considered non-immunocompetent despite being HIV negative: four were taking immunosuppressive drugs because they had undergone cardiac, hepatic or renal (2 cases) transplant, one developed L3ALL 12 months after autologous SCT for peripheral T-cell lymphoma and the remaining patient had suffered from Hodgkin's disease 4 years before. These patients were included in the description of HIV-negative patients but were excluded from tests comparing HIV-positive and HIV-negative patients.

Table 4. Prognostic factors on multivariate analyses.

	b	OR	95%CI for OR	p(Wald)
*Risk of failure to achieve CR**				
Age > 60 years	1.7	5.6	1.2-25.6	0.026
L3ALL	0.9	2.4	0.5-11.6	0.26
HIV infection	0.8	2.3	0.5-10.8	0.31
Disease-free survival°				
Age > 60 years	1.7	5.2	1.4-19.7	0.015
L3ALL	0.4	1.5	0.4-5.0	0.53
HIV infection	0.2	1.2	0.3-4.4	0.82
Overall survival°				
Age > 60 years	1.6	5.1	2.0-12.7	0.001
L3ALL	0.9	2.6	1.0-6.9	0.06
HIV infection	0.8	2.3	0.9-5.9	0.11

OR: odds ratio; 95%CI: confidence interval;
CR: complete remission; L3ALL: Burkitt's leukemia;
**Logistic regression analysis; °Cox regression analysis.*

Response to induction treatment

Among the 39 HIV-negative patients treated, 30 achieved CR (77%), 7 died during induction treatment and 2 had resistant disease and subsequently died. Ten of the 14 HIV-positive patients (71%) achieved CR and 4 died during induction. Major infection (7 cases), tumor lysis syndrome (3) and hemorrhage (1) were the main causes of death in the 11 patients (4 HIV-positive) who died during induction. The overall CR rate of the series was 75%. There were no differences in induction-related mortality or in CR rates between HIV-negative and HIV-positive patients. Among HIV-negative patients, those with L3ALL tended to have a lower CR rate than those with BL (BL 13/14, L3ALL 17/25, p=0.077). Thirty-six of the 44 patients up to 60 years old achieved CR (82%) and 4 out of 9 older patients (44%) did so (p=0.031). Only age > 60 years was significantly associated with a lower CR rate on both univariate and multivariate analyses (Table 4). The probability of achieving CR was approximately 5-fold lower among patients over 60 years old (OR 0.18, 95%CI 0.04-0.81, p=0.026).

Consolidation treatment

Six patients (4 HIV-positive) did not complete the planned eight cycles of therapy because of excessive toxicity. In 5 of these 6 cases excessive toxicity appeared after even-numbered cycles (2 cases after the first consolidation cycle and 3 cases after the third, including one death). Additionally, five patients (2 HIV-positive) relapsed while on therapy. Twenty-nine patients (55%) completed the eight scheduled cycles. The proportion of individuals who completed the treatment plan was significantly lower among HIV-positive patients (28% in HIV^+ cases and 64% in HIV^- cases, p=0.022).

Treatment-related toxicity and morbidity

Table 3 summarizes the main adverse events of 214 cycles in which toxicity was evaluated. Myelosuppression was the main complication during induction treatment, especially in L3ALL patients. For induction therapy the median time after induction to recovery of neutrophils to 0.5×10^9/L was 10 days (range, 0-28 days) and platelets to 20×10^9/L was 7 days (range, 0-28 days). Myelosuppression was shorter in subsequent cycles. Mucositis and infectious episodes requiring hospitalization were more frequent after even-numbered cycles. Most dose modifications involved methotrexate (20/38). Neurotoxicity related to either vincristine or to intrathecal treatment was frequent, although severe toxicity was unusual. Grade 3 or 4 neurotoxicity was present in two patients, 65 and 70 years old, respectively. Toxicity caused discontinuation of the treatment in 2/30 HIV-negative patients and in 4/10 HIV-infected patients (p=0.02).

Survival

Six patients (all HIV-negative) relapsed after completing treatment one to eight months after achievement of CR. One HIV-positive patient who had abandoned chemotherapy and HAART after three consolidation cycles died in CR due to an opportunistic infection. Six patients were submitted to high dose chemotherapy followed by autologous (5 cases) or allogeneic (1 case) SCT, with no patient relapsing after the procedure. These patients were censored from follow-up at the time of SCT. Twenty-two of the 29 patients who completed all scheduled cycles remained in first CR at the time of the last contact, after a median follow-up of 25 months (range 12 to 60 months). Six patients (4 HIV-positive) who abandoned treatment before completing the scheduled consolidations were in first remission at last contact.

The 2-year OS probability was 51% (95%CI, 38%-64%) for the overall series with a median follow-up of 24 months. The OS of HIV-negative patients (55% at 2 years; 95%CI, 40%-70%) and HIV-positive patients (43% at 2 years; 95%CI, 18%-68%) did not differ significantly. In contrast, OS was significantly shorter (p=0.014) in patients with L3ALL (37% at 2 years; 95%CI, 21%-53%) than in those with BL (71% at 2 years; 95%CI, 51%-90%) (Figure 1). This difference was also significant when the analysis was restricted to the subset of immunocompetent patients (84%, 95%CI 65-100 vs. 39%, 95%CI 21-57; p=0.008). The median OS was not achieved in any BL subgroup while it was

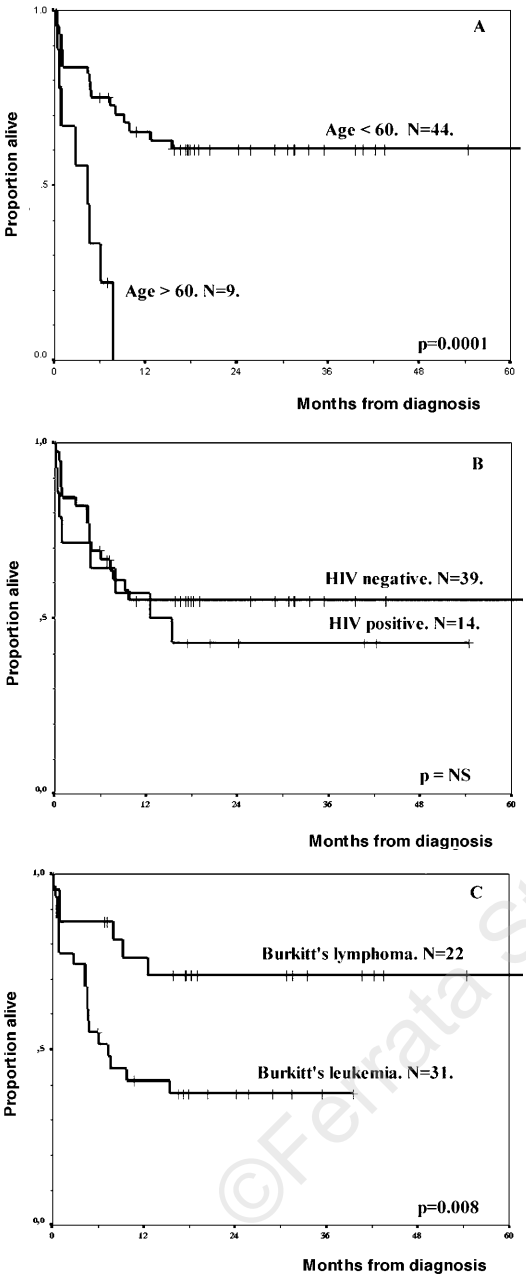

Figure 1. Overall survival of the 53 patients according to age (A), HIV status (B) and leukemic disease (C).

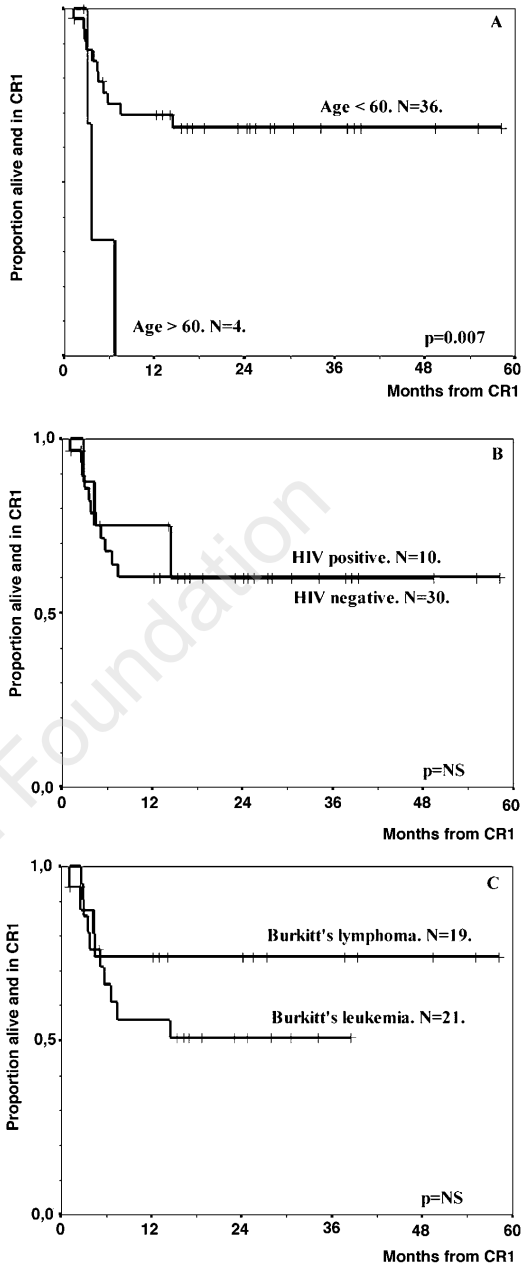

Figure 2. Disease-free survival of the 40 patients achieving a complete remission according to age (A), HIV status (B) and leukemic disease (C).

7 months (95%CI 3-12) and 5 months (95%CI 0-22) for HIV-negative and positive patients with L3ALL, respectively. With respect to age, only 1 out of 9 patients >60 years remained alive at one year while the OS for younger patients was 60% at 2 years (95%CI 48-75, p=0.0001). These differences remained when only HIV-negative patients were considered (67% at 2 years for patients under 60 years, 95%CI 51-83, p=0.0005). The 2-year OS for HIV-negative patients up to 60 years old with L3ALL and BL were 54% (95%CI 30-78) and 84% (95%CI 65-100), respectively. Age > 60 years was the only prognostic factor associated with OS that remained significant on multivariate analysis (OR 5.1, 95%CI 2.0-12.7, p=0.001) while L3ALL had borderline significance (OR 2.6, 95%CI 1.0-6.9, p=0.06) (Table 4).

The 2-year DFS for the 40 patients achieving CR was 60% (95%CI, 45-75%). DFS did not differ between HIV-negative patients (60% at 2 years; 95%CI, 43-77%) and HIV-positive cases (60% at 2 years; 95%CI, 24-96%). Differences in DFS between patients with L3ALL (51% at 2 years; 95% CI, 30-73%) and BL (74% at 2 years; 95% CI, 52-96%) did not reach statistical significance (Figure 2). DFS at 2 years for patients up to 60 years of age was 66% (95%CI 51-82). Of the 4 patients over 60 years achieving CR only one remains alive and in first CR at one year, while one relapsed, one died due to consolidation toxicity and one died of infection after consolidation therapy. Thus, age > 60 years was the only factor associated with a shorter DFS identified on both univariate (p=0.0071) and multivariate analyses (OR 5.2, 95%CI 1.4-20, p=0.015) (Table 4). The differences remained significant when HIV-positive patients were excluded from analysis (2-year DFS for younger patients 67%, 95%CI 50-85, p=0.0115).

Among the seven HIV-positive patients who received HAART throughout the chemotherapy and thereafter, five remained alive and in CR at the time of the last control, while six of the seven patients who did not receive HAART had died (p=0.051).

Discussion

Short, intensive multiagent chemotherapy with high-dose methotrexate, cytarabine and anthracycline has become the standard treatment for mature B-cell (i.e. Burkitt's) lymphoma/leukemia. This report presents the results of a prospective, multicenter study in a series of 53 patients with BL or L3ALL treated with the PETHEMA-LAL3/97 protocol, a slight modification of the GMALL protocol for mature B-cell ALL. The OS in this series was about 50% in unselected adult patients with advanced stage disease, including BL or L3ALL secondary to immunosuppression due to either HIV infection or to immunosuppressive therapy. These results are slightly poorer than those of other published series of adult patients with more stringent inclusion criteria.[9-11] When considering only patients up to 60 years old, DFS and OS rise to 66% and 60%, respectively, advanced age being the main adverse prognostic factor for achievement of CR, DFS and OS. Increasing age has proven to be an adverse prognostic factor in several reports.[9,11] Toxicity accounts for most of the deaths observed in the subset of older patients. Nevertheless, most older patients in our series had additional adverse features such as leukemic involvement (in 8 cases) or an immunocompromised status (one was a recipient of a liver transplantation after hepatitis C virus-related hepatocarcinoma and received immunosuppressive agents, 1 had been submitted to intensive chemotherapy and auto-SCT one year previously because of a T-cell lymphoma and 1 had untreated HIV infection).

The best therapeutic approach for elderly patients is unclear; intensification is unfeasible for most. As occurs in other leukemic diseases, tailoring therapy may be the best choice for elderly patients, although if lower-dose therapy is used, a decrease in toxicity may be paralled by a reduction in efficacy. In our protocol, the reduction of the dose of methotrexate for patients over 50 years did not appear to reduce toxicity for elderly patients. After adjustment for age, leukemic disease had border-line significance on multivariate analysis, although this might be due to insufficient statistical power. Patients with leukemic disease fared worse than patients with BL irrespective of their immunological status.

A significant proportion of overall mortality can be attributed to a high rate of induction mortality (21%). However, induction deaths occurred among elderly patients (3 cases) or high-risk patients, not usually included in prospective trials (4 in HIV-infected patients, 2 in recipients of a renal transplantation undergoing immunosuppressive therapy and one in a patient previously treated for Hodgkin's disease). Despite the pre-phase treatment and the preventive measures, tumor lysis syndrome remains a matter of concern, since it was clinically severe in 6 cases and contributed to early death in 3 patients. The uricolytic agent rasburicase[29] was not available at the time of the approval and development of this protocol but will be included in future studies.

As reported in other series, most events occurred early during the follow-up of the patients. In our series no relapses were detected beyond 12 months after CR achievement. Given this relapse pattern, the role of intensification with high-dose therapy and SCT remains unclear and should be analyzed prospectively, especially among higher risk subgroups such as those with L3ALL. However, most other reported prognostic factors (bulky disease, CNS infiltration, LDH levels) did not show statistical significance in our series. One of the main objectives of this protocol was to evaluate the results and the toxicity of such an intensive approach in HIV-infected patients with BL or leukemia. The risk of HIV-infected individuals developing NHL is 150- to 250-fold higher than that in the general population.[12,13] While the use of HAART has reduced the incidence of Kaposi's sarcoma and primary central nervous system NHL, data on the incidence of systemic NHL in HIV-infected patients receiving HAART are inconclusive.[30] The treatment of patients with AIDS-associated BL has been challenging as the response rate using conventional therapy has been low and there has been little enthusiasm for treating these patients with more intensive regimens.

However, several reports have shown a clear trend to better results of therapy in patients receiving

HAART in addition to chemotherapy (usually CHOP or CHOP-like regimens) in patients with HIV-related lymphomas,[20, 21,31] with the better prognosis in HAART responders.[21,32] Although the sample size of this uncontrolled study is small, in our experience, such a specific intensive regimen is feasible in patients with AIDS-related BL and L3ALL; the 2-year survival of 43% is comparable to the results obtained in immunocompetent patients. To our knowledge there are no similar published studies, although a recent report of 13 HIV positive patients with BL or L3ALL treated with hyper-CVAD regimen[33] seems to confirm this fact. Other authors have employed intensive multiagent chemotherapy (i.e. CODOX-M/IVAC) for HIV- positive[34] and negative patients[35] with similar promising results. Five out of six HIV-infected patients in continuous CR received HAART throughout their chemotherapy and afterwards. Although no specific studies aimed to analyze the pharmacologic interactions of antiretroviral and chemotherapeutic agents were performed in our series, the administration of HAART was not associated with any increase in toxicity compared with that seen in those patients not receiving HAART or in HIV-negative patients. Thus, in agreement with the observations made in diffuse large B-cell lymphomas,[20,21,31] the widespread use of HAART may increase the possibility of a prolonged DFS for HIV-infected patients with Burkitt's leukemia or lymphoma. The study confirms the effectiveness of intensive strategies in adult patients with advanced stage Burkitt's lymphoma or leukemia, except for in elderly patients, in whom the optimal treatment remains to be defined. Furthermore, it shows the feasibility of these strategies in individuals with HIV infection, in whom a significant proportion of durable responses are obtained. In these patients, the use of HAART in combination with chemotherapy is strongly recommended and probably contributes to an improved outcome.

Appendix

The following institutions and investigators participated in the PETHEMA LAL3-97 trial: Clínic, Barcelona (J Esteve); Santa Creu i Sant Pau, Barcelona (S Brunet, J Sierra); La Fe, Valencia (MA Sanz, G Martin); Germans Trias i Pujol, Badalona (A Oriol, JM Ribera, M Batlle, B Xicoy); General, Castelló (R Garcia-Boyero); General, Alicante (P Fernández-Abellán); Mútua, Terrassa (JM Martí, C Estany); Mar, Barcelona (E Abella); Universitario, Valladolid (D Borrego, J Fernández-Calvo); Virgen de la Victoria, Málaga (MJ Moreno, G Ramírez); Son Dureta, Palma de Mallorca (A Novo, J Besalduch); Rio Hortega, Valladolid (MJ Peñarrubia); General Universitario, Valencia (M Sánchez-Delgado); Carlos Haya, Málaga (C Bethencourt); Juan Canalejo, A Coruña (G Deben), Puerta del Mar, Cádiz (V Martín-Reina), Txagorritxu, Gasteiz (JM Guinea).

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Pre-Publication Report & Outcomes of Peer Review

Contributions

JMR and JJO were primarily responsible for the design of the PETHEMA LAL3-97 protocol. AO and JMR wrote the paper. The remaining authors qualified for authorship according to the WAME criteria and take specific responsibility for the following parts of the content: AO and JMR for data handling, and statistical analyses. JE, MAS, SB, RGB, PFA. JMM, EB, MSD, MJP, JB, MJM, DB and EF performed the studies at diagnosis and followed the patients clinically.

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In the following paragraphs, the Editor-in-Chief summarizes the peer-review process and its outcomes.

What is already known on this topic

Burkitt's or Burkitt-like lymphomas represent 20% to 40% of human immunodeficiency virus (HIV)-associated lymphomas. The risk of developing these lymphomas is much higher among patients with acquired immunodeficiency syndrome than among the general population. These malignancies develop early during the natural course of HIV infection, and their prognosis is considered to be poor.

What this study adds

This study confirms the effectiveness of intensive strategies in adult patients with advanced stage Burkitt's lymphoma or leukemia, and shows the feasibility of these strategies in individuals with HIV infection.