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Original

Comparison of CHOP treatment with specific short-intensive chemotherapy in AIDS-related Burkitt's lymphoma or leukemia

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ABSTRACT

Background and objective: AIDS-related Burkitt's lymphoma or leukemia (BLL) is increasingly treated with specific and intensive multiagent schedules. This retrospective study aimed to compare the results of CHOP with those from two protocols (PETHEMA-LAL3/97 and BURKIMAB) of specific therapy in Spain.
Patients and methods: Patients from Group A (n = 31) received 6 standard CHOP cycles every 3 weeks. Patients from group B (n = 44) received six multiagent cycles including high-dose methotrexate and high-dose cytarabine. The response to therapy, disease-free survival and overall survival (OS) were compared in the two groups.
Results: Both groups were comparable for the main clinical and biological parameters at diagnosis except for risk activity, previous HAART, bone marrow involvement, bulky disease and extranodal involved sites. Complete remission (CR) was achieved in 10 out of 31 (32%) patients in group A and 28 out of 44 (67%) patients in group B ($P = .005$). After a median (range) follow-up of 70 (26-139) and 17 (1-134) months, the 5-year (95% CI) DFS probability was 87% (64%-100%) for group A and 70% (51%-89%) for group B ($P = .374$), and the 5-year (95% CI) OS was 27% (10%-43%) for Group A and 57% (40%-74%) for group B ($P = .028$). Multivariate analyses showed that specific therapy was associated with an improved CR and OS.
Conclusions: In AIDS-related BLL short intensive specific chemotherapy is feasible, with higher remission rate and improved survival than that obtained with CHOP-based regimens.

Comparación de los resultados del tratamiento con CHOP con los de la quimioterapia intensiva específica en pacientes con linfoma o leucemia de Burkitt e infección por el virus de la inmunodeficiencia humana

Palabras clave:
Sida
Infección por VIH
Leucemia de Burkitt
Linfoma de Burkitt
Quimioterapia específica

RESUMEN

Fundamento y objetivo: En pacientes con infección por el VIH el tratamiento de la leucemia/linfoma de Burkitt con esquemas intensivos y específicos es cada vez más frecuente. Este estudio retrospectivo comparó los resultados del tratamiento con CHOP con el de dos protocolos de quimioterapia específica (PETHEMA-LAL3/97 and BURKIMAB) en España.
Pacientes y método: Los pacientes del grupo A (n = 31) recibieron 6 ciclos de CHOP estándar cada tres semanas. Los pacientes del grupo B (n = 44) 6 ciclos de poliquimioterapia que incluía metotrexato y citarabina a altas dosis. Se comparó la respuesta al tratamiento, la supervivencia libre de enfermedad y la supervivencia global (SG) en ambos grupos.
Resultados: Ambos grupos fueron comparables en las principales características clínicas al diagnóstico excepto en la actividad de riesgo, tratamiento previo con TARGA, afección de médula ósea, enfermedad

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◇ A list of investigators from the PETHEMA and GESIDA groups who participated in the study is presented at the end of the article in Appendix A.

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voluminosa y afección extranodal. Se obtuvo la remisión completa (RC) en 10 de 31 (32%) pacientes en el grupo A y 28 de 44 (67%) pacientes en el grupo B (p = 0,005). Tras una mediana (extremos) de seguimiento de 70 (26-139) y 17 (1-134) meses, la probabilidad de SG a los 5 años (IC 95%) fue del 87% (64%-100%) en el grupo A y 70% (51%-89%) en el grupo B (p = 0,374), y la SG a los 5 años (IC 95%) fue del 27% (10%-43%) en el grupo A y 57% (40%-74%) en el grupo B (p = 0,028). El análisis multivariable demostró que el empleo de tratamientos específicos se asoció a una mayor probabilidad de RC y SG. *Conclusiones:* En la leucemia/linfoma de Burkitt asociada a la infección por el VIH el tratamiento intensivo específico es factible, con unas mejores tasas de RC y SG que la obtenida con los regímenes tipo CHOP.

Introduction

Burkitt's lymphoma or leukemia (BLL) is the second most frequent lymphoid neoplasia observed in patients infected by the human immunodeficiency virus (HIV). These patients have been traditionally treated with non-specific and non-intensive chemotherapy schedules (i.e CHOP, m-BACOD), mainly due to their impaired immune function, the risk of opportunistic infections (OI) and early deaths under treatment, thereby explaining their poor outcome.[1]

In the highly active antiretroviral therapy (HAART) era, the same specific short-duration and intensive multiagent chemotherapy schedules for BLL employed in non-immunocompromised patients have been used in HIV-related BLL. Several reasons have supported this approach. First, CD4 lymphocyte counts are often moderately decreased in HIV-related BLL; second, the use of HAART has improved the immunological status of the patients, reducing the risk of OI, and third, the advances in anti-infectious prophylaxis and supportive care allow more dose intensive regimens to be safely administered. In some studies, the results of therapy and the outcome of HIV-infected patients with BLL are similar to those obtained in non-immunocompromised patients, especially if response to HAART is observed. However, there are scarce studies comparing the results of CHOP-derived regimens with those from specific short-intensive schedules in HIV-related BLL.

The main objective of this retrospective study from the Spanish GESIDA (*Grupo Español de Estudio del SIDA*) and PETHEMA (*Programa Español para el Tratamiento en Hematología*) groups was to compare the results of therapy and outcome in 31 patients with HIV-related BLL treated with CHOP with those observed in 44 patients treated with two consecutive short-intensive and specific multiagent protocols (PETHEMA-LAL3/97 and BURKIMAB) for BLL.

Material and methods

Two groups of patients were studied: group A: Patients diagnosed with HIV-related BLL treated with CHOP (cyclophosphamide 750 mg/m^2 i.v. on day 1, doxorubicin 50 mg/m^2 i.v. on day 1, vincristine 1,4 mg/m^2 i.v. on day 1 and prednisone 60 mg/m^2 i.v. or p.o. on days 1 to 5) given every 3 weeks for 6 courses, with or without the addition of rituximab (375 mg/m^2 i.v. on the first day of each CHOP cycle) in 15 Spanish hospitals from 1996 to 2004, and group B: patients with HIV-related BLL treated with two consecutive protocols for BLL (PETHEMA LAL3/97 and BURKIMAB), the later adapted from the protocol B-ALL/NHL2002 of the German Multicenter Adult Lymphoblastic Leukemia (GMALL) Group,[2] conducted in 14 Spanish hospitals between 1997 to 2003 and between 2004 and 2006, respectively. Although the last protocol is still active, we only included patients diagnosed up to 2006 to ensure sufficient follow-up. Both protocols included a pre-phase with cyclophosphamide and prednisone followed by six cycles of chemotherapy including high-dose methotrexate and high-dose cytarabine in combination with other cytotoxic drugs (Tables 1 and 2). In the BURKIMAB protocol rituximab was administered in each cycle of chemotherapy plus two additional courses at the end of chemotherapy.

HIV serology was assessed by enzyme-linked immunoabsorbent assay and confirmed by Western blot in all patients. The revised Centers for Disease Control (CDC) classification system for HIV infection was used for AIDS diagnosis.[3] Viral load of HIV was measured in each participating center. Diagnosis of BLL was performed according to the Revised European-American Classification of Lymphoid Neoplasms (REAL/WHO) and FAB criteria, respectively.[4] L3ALL was considered if there were more than 20% atypical mature B-cells cells in the bone marrow. Immunophenotypic study was performed in cell suspensions or tumor tissue in each institution and BLL was defined if CD10, CD19, CD20, CD22, CD24 were positive together with the presence of monoclonality of surface immunoglobulins. Cytogenetic studies of bone marrow, peripheral blood or tumor mass were performed in each center using direct methods and unstimulated short-term (24-48 hours) cultures with G-banding, following the International System for Human Cytogenetics Guidelines.[5] Diagnosis of BLL was considered when t(8;14), t(8;11) or t(2;8) or *C-MYC* rearrangements were identified. Central nervous system (CNS) involvement was defined as the presence of blasts in the cerebrospinal fluid (CSF), cranial nerve palsy or paresthesia not related to facial tumor, clinical signs of spinal cord compression or an intracranial mass.

From 1996, HAART was recommended at diagnosis of BLL if patients were not receiving it. HAART consisted of one or two protease inhibitors and two nucleoside reverse transcriptase inhibitors. Patients received trimetroprim-sulfametoxazol thrice weekly or aerosolized pentamidine as prophylaxis against *Pneumocystis jiroveci* infection, according to institutional practices. Use of G-CSF, hospitalization, prophylaxis and management of infections, transfusion support and prophylaxis against tumor lysis syndrome (i.e.: intravenous hydration plus allopurinol or rasburicase) were performed according to the institutional practices of each center.

The following parameters related to lymphoma were recorded in each patient: age, sex, lymphoma subtype, leukemic disease, Eastern Cooperative Oncology Group (ECOG) score, B symptoms, bulky disease, bone marrow or other extranodal involvement, serum lactate dehydrogenase (LDH) and stage of BL according to the Ann Arbor staging system; The parameters related to HIV infection were: risk activity, HAART given before or started at diagnosis, CD4 lymphocyte count, HIV viral load at diagnosis and opportunistic infections (OI) during treatment. This study was conducted according to the rules of good clinical practice of the PETHEMA and GESIDA groups.

For cases of Burkitt's leukemia, complete remission (CR) was considered as less than 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 cerebrospinal fluid cytology; for cases with Burkitt's lymphoma, complete response (CR) was considered as the