Infusional CDE with Rituximab for the Treatment of Human Immunodeficiency Virus-Associated Non-Hodgkin’s Lymphoma: Preliminary Results of a Phase I/II Study

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Abstract

Infusional CDE (cyclophosphamide, doxorubicin, etoposide; iCDE) is one of the most effective chemotherapeutic regimen for human immunodeficiency virus (HIV)-associated non-Hodgkin’s lymphoma (NHL), with a complete remission rate of 46% and a median overall survival of 8.2 months (Sparano JA, Blood 1993; 81:2810). Since the majority of HIV-associated NHL are CD20-positive we reasoned that the addition of rituximab to iCDE (R-iCDE) could also improve the poor outcome of these patients. As a first step we investigated the safety of R-iCDE in a phase I/II study. Thirty patients with aggressive HIV-associated NHL were enrolled between June 1998 and October 2000. Characteristics of 29 evaluable patients were: median age: 38 years (range 29–65 years); male sex 24/29; histology: DLCL 16 (55%), Burkitt 10 (35%), ALCL 2 (7%), unclassified 1 (3%); stage: I (35%), II (10%), III (10%), IV (45%); International Prognostic Index: 0, 1 (59%), 2 (24%), 3 (17%), 4, 5 (0); CD4 count: median 132/mm³ (range 3–470/mm³). Patients received rituximab (375 mg/m²) in conjunction with iCDE (five or six cycles). All patients were treated with G-CSF and highly active antiretroviral therapy (HAART). Twenty-six of 29 patients received treatment as planned, while chemotherapy had to be discontinued in three patients (2 persistent thrombocytopenias, 1 cerebral hemorrhage). Grade 3 or 4 toxicity was observed as follows: neutropenia 79%, anemia 45%, thrombocytopenia 34%, bacterial infection 34%, opportunistic infection 7%, mucositis 17%. A dose reduction was necessary in 22%. Complete remission was achieved in 86% of the patients, partial remission in 4%.
Ten percent had progressive disease. After a median follow-up of 9 months the median overall survival is not reached. The actuarial survival at 2 years is 80% and the actuarial progression-free survival is 79%. Four of 29 patients (14%) have died, three from NHL and one from cryptosporidiosis. These findings suggest that the combination of rituximab with iCDE in patients with HIV-associated NHL is safe and feasible and that the addition of the anti-CD20 antibody does not increase the risk for infections. The high complete remission rate also indicates a potential therapeutic benefit and warrants further randomized trials.

**Introduction**

Despite massive efforts to improve treatment of human immunodeficiency virus (HIV)-associated non-Hodgkin’s lymphoma (NHL) the prognosis of these patients has not changed significantly over the years [1]. The major risk factors still include CD4 counts and the factors included in the international prognostic index (IPI) [2]. The median overall survival reported in various studies was between 3.5 and 11 months depending on CD4 counts and chemotherapeutic regimen [3]. Standard chemotherapy for aggressive NHL (CHOP, mBA-COD, CDE) results in a high number of infections and is therefore not superior to low-dose chemotherapy [4].

Instead of increasing the dose intensity of chemotherapy the results may therefore be improved rather by applying different scheduling, new antilymphoma agents, better supportive care, and intensified antiretroviral therapy. A trend for longer overall survival with the use of highly active antiretroviral therapy (HAART) in patients with HIV-associated NHL has recently been suggested [1]. Moreover, HAART can be administered with combination chemotherapy without excessive toxicity [5]. Continuous infusion of cyclophosphamide, doxorubicin, and etoposide (infusional CDE, iCDE) has been one of the most active regimens in HIV-associated NHL [6]. CDE resulted in complete remission rates of 46–58% with a median overall survival of 8.2–18.4 months [6, 7]. In the phase II trial CDE was successfully combined with didanosine, PCP and Candida prophylaxis, as well as with G-CSF. Immunotherapy with the CD20-antibody rituximab is a new antilymphoma therapy exploiting additional principles of cell kill specifically directed against CD20-positive mature B-cells. Since the antibody does not recognize stem cells or plasma cells its side effects on the immune system, and in particular on immunoglobulin produc-