Treatment of AIDS related non-Hodgkin’s lymphoma with combination mitoguazone dihydrochloride and low dose chop chemotherapy: Results of a Phase II study

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Summary

Purpose: To evaluate the response and side effects of combination therapy with low dose CHOP chemotherapy and mitoguazone dihydrochloride in patients with non-Hodgkin’s lymphoma associated with the acquired immunodeficiency syndrome (AIDS-NHL). Methods: Eighteen patients newly diagnosed with intermediate or high-grade AIDS-NHL were treated with low dose CHOP as follows: day 1, cyclophosphamide 350 mg/m², intravenously (IV); doxorubicin 25 mg/m² IV; vincristine 2 mg IV; and prednisone 100 mg given orally on days 1 through 5. In addition, mitoguazone dihydrochloride was given at a dose of 600 mg/m² IV on days 1 and 15 of each 28-day treatment cycle. Results: Seventeen males and one female patient were accrued. Twelve patients had high-grade pathologies while the remainder had an intermediate grade pathology (diffuse large cell). The median CD4+ lymphocyte count was 98/dl (range 1–924). Three patients (17%) reported an AIDS-defining illness prior to lymphoma diagnosis. Of 14 evaluable patients, 6 (43%) achieved a complete remission and 5 (35%) a partial remission. The median failure free and overall survival times were 6.5 and 8.4 months, respectively. Major toxicity was hematologic with grade 3 or 4 neutropenia in 72%; two patients died of neutropenic sepsis. Conclusions: Mitoguazone in combination with low dose CHOP is a safe regimen, associated with a response rate of 79% (CR 43%, PR 36%, 95% CI = 49–95%). These preliminary results suggest no major improvement in terms of response over use of CHOP without mitoguazone.

Introduction

The incidence of lymphoma in patients infected with the human immunodeficiency virus (HIV) (AIDS-NHL) is approximately 60–100 times greater than expected in the general population, and appears to increase over time during the course of HIV infection [1–3]. Clinically, AIDS-NHL is characterized by widespread dissemination of lymphomatous disease at initial diagnosis, a propensity for extra-nodal involvement, and short survival, despite treatment [4].

The optimal therapy for patients with AIDS-related non-Hodgkin’s lymphoma remains undefined. A review of nine published trials [5] describing at least 11 different chemotherapy regimens used in the treatment of patients with AIDS-NHL has revealed complete remission rates ranging from 8% to 72%, with a median survival time of approximately 6 months (range 2.6–15). Use of a low-dose modification of the mBACOD regimen [6] resulted in a complete remission rate of 46% with acceptable toxicity. A subsequent randomized study consisting of 198 patients was conducted by the AIDS Clinical Trials Groups (ACTG-142) in which patients were stratified by prognostic factors and randomized to receive either low-dose mBACOD or standard dose mBACOD with GM-CSF [7]. No significant differences were observed in response rates, disease-free or
overall survival, but standard dose mBACOD was associated with significantly increased toxicity.

Since dose intensity has not yet been associated with superior outcome, alternative treatment strategies are clearly needed. One such approach employs administration of standard cytotoxic agents by continuous intravenous infusion. Thus a 4-day infusional regimen of cyclophosphamide, doxorubicin, and etoposide (CDE) has been associated with a CR rate of 58% and median survival of approximately 18 months [8].

Another potential approach in patients with newly diagnosed AIDS-NHL would be combining low-dose chemotherapy with additional non-myelotoxic agent(s) with novel mechanism(s) of action. One such agent which has shown activity in both “de novo” and AIDS-NHL is mitoguazone dihydrochloride. The precise mechanism of mitoguazone as an antitumor agent remains unknown, although the drug is an effective inhibitor of polyamine biosynthesis, through competitive inhibition of S-adenosylmethionine decarboxylase [9]. Polyamines are important in the stabilization of DNA, and the major cytotoxic activity of Mitoguazone may result from this effect.

Mitoguazone was used initially in the early 1980s in patients with multiply relapsed “de novo” NHL, resulting in response rates of 29–49%, little myelotoxicity and a dose-limiting toxicity of mucositis [9]. Due to its very long half-life, the dosing schedule of mitoguazone was subsequently revised. Employing a dose of 600 mg/m² given IV on day 1, 8 and then every 2 weeks, mitoguazone was studied in heavily pretreated patients with relapsed or refractory AIDS-NHL [10]. Toxicity from this regimen was minimal, and an objective response rate of 22% was achieved in this group of patients with poor prognosis AIDS-NHL.

In an attempt to ascertain if the addition of mitoguazone to the low-dose CHOP regimen would result in acceptable toxicity with improved response rates, and/or longer overall survival, we conducted the current Phase II trial. Since pharmacokinetic studies have shown that mitoguazone crosses the blood–brain barrier [11], we also wished to determine the impact of early treatment with mitoguazone on central nervous system (CNS) relapse.

**Patients and methods**

**Patient selection**

Patients with a pathologically verified diagnosis of intermediate or high grade non-Hodgkin’s lymphoma of the following pathologic types were accrued: diffuse large cell lymphoma, immunoblastic, and/or small non-cleaved. Patients were required to be HIV seropositive by enzyme linked immunosorbent assay (ELISA) with Western blot confirmation. Patients were required to be 18 years of age or older with a Karnofsky performance status of 50% or greater.

Pretreatment laboratory requirements included adequate renal (serum creatinine <2.0 mg/dl) and hepatic function (bilirubin <2.0 gm/dl, aspartate transaminases less than five times the upper limit of normal) unless abnormalities were due to lymphomatous involvement. Adequate hematologic function (absolute neutrophil count more than 1000/mm³; platelet count more than 75,000/mm³) was required, unless secondary to lymphomatous infiltration of the bone marrow.

Patients were excluded from the study for the following reasons: primary CNS lymphoma, acute intercurrent infection, pregnant or nursing mothers, and/or presence of a second active tumor other than non-melanomatous skin cancer, carcinoma *in situ* of the cervix or Kaposi’s sarcoma not requiring systemic therapy. Patients who had received any prior therapy for AIDS-NHL were excluded.

This study was reviewed and approved by the Institutional Review Board of the University of Southern California School of Medicine. All patients gave signed informed consent prior to the first dose of therapy.

**Treatment evaluations**

Within 4 weeks of study entry, all patients were evaluated by a medical history and physical examination, complete blood counts with differential, serum chemistry, T and B- cell analysis, electrocardiogram, computerized tomographic (CT) scans of the chest, abdomen and pelvis, CT or magnetic resonance imaging (MRI) of the head, bone marrow aspiration and biopsy, lumbar puncture, and any other studies as clinically indicated for the assessment of lymphoma.

Complete blood counts with differential, serum chemistries, and toxicity evaluations were performed prior to each dose of mitoguazone. Patients were restaged after two, four, and six cycles of chemotherapy by repeating all studies which were abnormal at baseline evaluation.

**Treatment regimen**

The treatment regimen is summarized in Table 1. Low dose CHOP chemotherapy (cyclophosphamid,