Original Study

High Response Rate for Treatment With Gemtuzumab Ozogamicin and Cytarabine in Elderly Patients With Acute Myeloid Leukemia and Favorable and Intermediate-I Cytogenetic Risk

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Abstract

Recent studies have reevaluated whether gemtuzumab ozogamicin (GO) improves the outcome of acute myeloid leukemia (AML) in elderly patients. Over 5 years, we treated 16 elderly patients with AML with GO and cytarabine. A high response rate, prolonged survival, and low toxicity were observed in the favorable and intermediate-I genetic groups of AML. Our study raises the issue about the optimal protocol for these patients.

Background: The benefit of gemtuzumab ozogamicin (GO) in combination with chemotherapy as frontline therapy in patients with acute myeloid leukemia (AML) is still debated. **Patients and Methods:** We evaluated the safety and efficacy of low-dose GO with cytarabine in elderly patients with newly diagnosed AML. Over the past 5 years, we have treated 16 elderly patients with AML (64-82 years) with GO (3 mg/m^2) followed by continuous infusion of cytarabine (100 mg/m^2) for 7 days. **Results:** Complete remission (CR) was achieved in 68.8% of patients; however, this was true only in patients in the favorable or intermediate-I cytogenetic risk groups. Of the 12 patients with AML in the favorable and intermediate-I genetic groups, 11 (91.7%) achieved CR. By comparison, of all 4 patients in the intermediate-II or adverse genetic groups, none of the patients achieved CR ($P = .003$). The median disease-free survival and overall survival (OS) was 10.9 and 18.8 months, respectively, for patients who achieved CR. The estimated median survival was 15 months in the favorable and intermediate-I cytogenetic groups and only 4.4 months in the intermediate-II and unfavorable risk groups ($P = .008$).

The toxicity profile was also manageable in patients with AML who were mainly older than 70 years with good performance status (PS). The 8-week mortality rate was 6.25%, which is relatively low in this high-risk group of patients. These data are in line with results from 2 randomized trials suggesting that the addition of low-dose GO should be further investigated to reevaluate its role in selected elderly patients with AML and raises the issue of the optimal protocol.

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Introduction

The incidence of acute myeloid leukemia (AML) is increasing substantially for individuals 65 years of age or older. However, older adults with AML have the worst prognosis because of a higher incidence of comorbid diseases, secondary leukemia, unfavorable cytogenetic abnormalities, and drug resistance. Treatment options consist of supportive care, low- to high-dose chemotherapy, or investigational agents. In elderly patients treated with intensive induction chemotherapy, the risk of early death is much higher than it is in younger patients. With different regimens, some improvement in complete remission (CR) rates was observed (40%-60%), although the median survival was 7 months, urging the development of additional therapies. Moreover, since most AML trials exclude older patients, it is uncertain whether patients with AML > 70 years

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of age would benefit from intensive chemotherapy because of the high risks of induction mortality and morbidity.[1-3]

Gemtuzumab ozogamicin (GO) is a humanized anti-CD33 monoclonal antibody conjugated with the antitumor antibiotic calicheamicin. The target antigen is expressed in normal progenitor and mature myeloid cells as well as in leukemic blasts from more than 80% of patients with AML but is absent on pluripotent hematopoietic stem cells and nonhematopoietic cells. Binding of GO to the CD33 antigen leads to the internalization of the drug-antigen complex and the hydrolytic release of the toxic calicheamicin component, which subsequently causes DNA damage and cell death.

The CD33 receptor site saturation data and the dose escalation studies suggested 9 mg/m^2 to be the maximum tolerated dose.[4] Unrandomized phase II studies in patients with AML in first relapse showed a CR of 13% and CR with incomplete platelet recovery of 13%, using 9 mg/m^2 GO given as 2 single doses 14 days apart.[4,5] Of note, there were no significant differences in the overall remission rates between patients younger than 60 years and patients aged 60 years or older. Also, in older patients with newly diagnosed AML, the clinical benefit of sequential GO monotherapy was modest and was not effective in patients $>$ 75 years of age because of excessive hematologic and liver toxicity.[6,7] Venoocclusive disease (VOD) occurred in 5% of patients treated with full doses of GO, and in patients undergoing subsequent myeloablative hematopoietic stem cell transplantation (HSCT), the risk of VOD developing was higher. In 2000, this agent was approved by the US Food and Drug Administration (FDA) for older adults in first relapse who were not suitable candidates for intensive chemotherapy.

Several randomized studies have addressed the issue of whether the administration of GO at a lower dose in combination with intensive chemotherapy would improve the outcome of patients with AML. In the Southwest Oncology Group (SWOG) 106 study, 627 patients with de novo AML aged 18 to 60 years were randomly assigned to receive induction therapy with daunorubicin (60 mg/m^2) and cytarabine or the addition of 6 mg/m^2 GO to a lower dose of daunorubicin (45 mg/m^2) and cytarabine. There was no difference in CR or overall survival (OS) between the 2 arms, with a significantly higher fatal toxicity rate in patients who received GO (5.8% vs. 0.8%).[8] Based on these data, the FDA recommended the removal of GO from the US market. However, in other studies, the addition of low-dose GO (3 mg/m^2) to chemotherapy was well tolerated and did not increase toxicity.[9-11] Moreover, 2 prospective randomized trials recently showed a significant improvement in OS with the addition of GO to induction therapy in elderly patients with AML, especially in the treated group of patients with favorable and intermediate-risk cytogenetic characteristics.[11,12] Still the most effective and well-tolerated combination therapy of chemotherapy and low-dose GO in elderly patients with newly diagnosed AML has not been determined. In the present study, we report our experience with the combination of low-dose GO and cytarabine in elderly patients with AML who we have treated during the past 5 years.

Patients and Methods

Patients

All patients were treated at the Sourasky Medical Center and the protocol was approved by the Helsinki Board of Sourasky Medical Center. The diagnosis of AML was based on routine morphologic evaluation and immunophenotyping using the French-American-British classification. Cytogenetic analysis and mutation status were examined in diagnostic material. The cytogenetic risk groups were defined using the new genetic risk classification of the European LeukemiaNet Recommendations.[13] In particular, patients with normal karyotype who had *NPM1*-mutated AML without *FLT3* internal tandem duplication mutations were classified as a favorable-risk group.

Eligibility criteria included de novo or secondary AML, previous treatment with hydroxyurea only, age $\geq$ 60 years, performance status (PS) $<$ 2, creatinine level $<$ 2.0 mg/dL, and aspartate transaminase and alanine transaminase levels $<$ 2.5 times the upper limit of normal. Of note, immunophenotypic analysis of the CD33 antigen was carried out for all patients at diagnosis, and CD33 expression was required in at least 80% of blast cells by flow cytometry. Patients with a diagnosis of acute promyelocytic leukemia or uncontrolled infection were excluded.

Treatment

The induction therapy included GO (3 mg/m^2/2 h on day 1) plus cytarabine (100 mg/m^2/24 h on days 2-8). A morphologically normal bone marrow aspirate containing $<$ 5% blast cells and at least 1.0×10^9/L granulocytes and 100×10^9/L platelets in the peripheral blood were considered to be criteria for the achievement of CR.

Consolidation therapy was not predefined. Among 11 patients who achieved CR, 8 patients received consolidation with cytarabine 100 mg/m^2 or with cytarabine 500 mg/m^2 every 12 hours on days 1 to 5, and 2 patients received repeated courses of low-dose GO (3 mg/m^2). Eight patients did not receive further therapy because of poor PS or because they did not respond to induction therapy. Two patients underwent allogeneic HSCT.

Statistical Analysis

Clinical and categorical variables are presented as percentages (N). Continuous variables are presented by their median and range. The Fisher exact test and χ^2 tests were used for comparison of categorical variables. OS was defined as the interval from registration until death, whatever the cause, or last date of follow-up (for censored observations). Disease-free survival (DFS) was defined as the time from CR until the first relapse or death, whatever the cause, or last date of follow-up (for censored observations). Actuarial curves were computed using the Kaplan-Meier method; comparisons between the times to event outcomes were performed using the log-rank test. Data were considered significant if the P value was $<$ .05. SPSS, version 16 (IMB Corp., Armonk, NY) was used for all data analysis.

Results

In this retrospective study, we included all elderly patients with newly diagnosed AML treated with GO and cytarabine at our institution between May 2006 and November 2011. A total of 16 patients (8 women, 8 men) were included in this study. The median age was 72 years (range, 64-82 years). Two patients had secondary AML preceding myelodysplastic syndrome and 1 patient had therapy-related AML. Five patients were in the favorable cytogenetic and molecular risk group, 7 patients were in the intermediate-I risk group, and 4 patients were in the intermediate-II and unfavorable risk