Clofarabine Does Not Negatively Impact the Outcomes of Patients With Acute Myeloid Leukemia Undergoing Allogeneic Stem Cell Transplantation

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Abstract

We evaluated whether clofarabine-containing chemotherapy predisposed patients to hepatic toxicity (particularly venoocclusive disease [VOD]) after allogeneic stem cell transplantation (allo-SCT). In the group who received clofarabine and subsequent transplantation, there were no cases of VOD, and liver toxicity was comparable to a control group who received standard acute myeloid leukemia (AML) chemotherapy. Other transplant-specific outcomes, including overall survival (OS), were also similar when compared with the control group.

Background: Clofarabine is actively being investigated as a component of frontline chemotherapy for acute myeloid leukemia (AML). Hepatotoxicity is 1 of the primary adverse events associated with clofarabine and can occasionally can include severe venoocclusive disease (VOD). **Patients and Methods:** Many patients with AML undergo allogeneic stem cell transplantation (allo-SCT), a procedure that is also associated with hepatotoxicity. We identified AML patients undergoing allo-SCT and stratified them according to whether they received clofarabine-containing (clofarabine, idarubicin, and cytarabine [CIA]) or non–clofarabine-containing cytarabine-based induction/consolidation chemotherapy (idarubicin and cytarabine [ara-C] [IA]). We compared both groups for differences in posttransplantation hepatotoxicity, VOD, and other transplantation outcomes. Forty-two patients were identified (20 receiving CIA and 22 receiving IA). Patient and transplant characteristics were similar. All patients receiving clofarabine-based treatment received CIA within 2.5 months of their allo-SCT. **Results:** There was no difference in the incidence of VOD in the 30 days after transplantation (0 CIA, 1 IA; $P = 1.0$). Rates of grade 3/4 hepatotoxicity also did not differ between groups. Acute graft-versus-host disease (GVHD), early relapse, and survival were also not significantly different. **Conclusions:** We conclude that clofarabine-containing chemotherapy does not adversely impact the outcome of allo-SCT. Specifically, it does not predispose patients to an increased risk of hepatotoxicity, VOD, GVHD, or relapse.

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Introduction

The outcome of patients with acute myeloid leukemia (AML) is generally poor, with 5-year overall survival (OS) rates of approximately 40% for those younger than 60 years of age treated with intensive chemotherapy. Similar figures have also been reported for those undergoing allogeneic stem cell transplantation (allo-SCT) as a component of consolidation therapy.[1,2] However outcomes are highly variable when patients are stratified according to prognostic factors such as age, cytogenetic features, and gene mutations.[3] The combination of cytarabine and an anthracycline remains the standard of care for most patients diagnosed with AML.[4-6] Because there is a need to improve the outcome for the majority of patients with AML, novel agents are being developed.

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Clofarabine is a purine analogue that was rationally designed to optimize the pharmacologic shortcomings of 2 of its predecessors—fludarabine and cladribine.[7] The drug works through several mechanisms, including inhibition of DNA polymerases, inhibition of ribonucleotide reductase, and induction of apoptosis through DNA strand breaks and disruption of mitochondrial integrity.[7] When administered 3 to 6 hours before cytarabine in vitro, both drugs induce a synergistic effect against AML cells, possibly because of the ability of clofarabine to efficaciously block ribonucleotide reductase.[8] These data have formed the basis for several clinical studies that we and others have conducted in an attempt to exploit this relationship and hence improve AML outcomes. Clofarabine is currently approved for pediatric patients with relapsed and refractory acute lymphoid leukemia after failure of 2 previous regimens.[9] The most common adverse events experienced by patients treated with clofarabine include myelosuppression, transient hepatotoxicity, and rash. One of the notable toxicities associated with clofarabine therapy is hepatotoxicity, which occasionally has included rare cases of grade 4 hyperbilirubinemia or venoocclusive disease (VOD).[9,10]

Treatment guidelines indicate that patients with AML and poor prognostic features (eg, adverse cytogenetic characteristics, *FLT3* mutations) who achieve complete remission (CR) should be considered for allo-SCT.[3,4] This procedure is also associated with an increased risk of liver toxicity and/or VOD. Therefore we investigated whether pretransplantation exposure to clofarabine-containing chemotherapy regimens adversely impacted the outcomes of younger patients with AML who underwent allo-SCT compared with those treated with non–clofarabine-containing (but otherwise similar) chemotherapeutic regimens, particularly regarding liver toxicity.

Patients and Methods

Patient Cohorts and Inclusion Criteria

We identified patients newly diagnosed with AML who underwent allo-SCT between November 2007 and July 2011 after receiving frontline chemotherapy with either the IA regimen (a combination of idarubicin and cytarabine) or the CIA regimen (a combination of clofarabine, idarubicin, and cytarabine). All patients received therapy in clinical trials conducted at our institution after signing an institutional review board–approved consent form to participate in such studies. Of note, at the time of data collection and analysis, both protocols continued to enroll and follow patients. Patients had to have normal renal, cardiac, and hepatic function at baseline to be included.

Treatment Regimens

All patients in this analysis received chemotherapy for newly diagnosed AML. IA consisted of idarubicin 12 mg/m^2 intravenously (I.V.) on days 1 to 3, and cytarabine 1.5 g/m^2 I.V. by continuous infusion on days 1 to 4. CIA consisted of clofarabine 20 mg/m^2 (22.5 mg/m^2 before a protocol amendment) I.V. on days 1 to 5, idarubicin 10 mg/m^2 (6 mg/m^2 before a protocol amendment) I.V. on days 1 to 3, and cytarabine 1 g/m^2 (0.75 g/m^2 before a protocol amendment) I.V. on days 1 to 5. Both regimens allowed for up to 6 cycles of consolidation chemotherapy after induction, which included the same agents given according to an attenuated dosing schedule. Because clofarabine is known to be hepatotoxic, triazole antifungal agents were customarily held until 24 hours after the final dose was administered. In these cases, patients could receive an echinocandin as antifungal prophylaxis if they were neutropenic during chemotherapy. Neither protocol included patients with acute promyelocytic leukemia or those with core binding factor rearrangements [inv,(16)t(16;16) or t(8;21)]. All patients receiving at least 1 course of therapy according to protocol and who subsequently underwent allo-SCT were eligible for our study. Patients were excluded if they were not receiving their postchemotherapy follow-up (i.e., between cycles) at our center.

Evaluation of Response and Endpoint Definitions

CR was defined as a normalization of the neutrophil count (absolute neutrophil count $>1.0 \times 10^9$/L), platelet count ($>100 \times 10^9$/L), and <5% blasts in a normocellular bone marrow sample. Documentation of a diagnosis of VOD or graft-versus-host disease (GVHD) was made based on a review of clinical, laboratory, radiographic, and pathologic data. VOD was defined clinically according to the Baltimore criteria,[11] which include a serum bilirubin level ≥ 2 mg/dL and at least 2 of the following clinical findings: ascites, weight gain ≥5% higher than baseline, and new hepatomegaly. To determine whether clofarabine-containing chemotherapy predisposed transplant patients to non-VOD acute hepatotoxicity after SCT, we documented the peak in alanine aminotransferase (ALT) levels and total bilirubin levels during the first 30 days after transplantation. Transaminase elevations were graded according to version 4.0 of the Common Terminology Criteria for Adverse Events. We collected data on 30-day mortality and 100-day relapse for both groups. We also calculated the OS of all patients, which was defined as of the day of allo-SCT until death.

Statistical Considerations

We used the electronic medical record to extract the following variables: age, sex, karyotype of the leukemia cells, number of chemotherapy cycles, CR rate, whether allo-SCT was performed with the patient in CR, stem cell source, conditioning regimen, GVHD prophylaxis, engraftment day, incidence of VOD, incidence of acute hepatotoxicity after SCT, incidence of GVHD, early death, and early relapse. The primary endpoint was incidence of VOD in the 30 days after allo-SCT. Secondary endpoints included elevations in ALT and bilirubin levels in the 30 days after transplantation, incidence of GVHD, incidence of early relapse, and survival. Nominal data were compared using the χ^2 or Fisher exact test. Continuous variables were compared using the Student t test. Survival curves were constructed using the Kaplan-Meier method, and the curves were compared using the log-rank test.

Results

We identified 42 patients with newly diagnosed AML who had consecutively undergone allo-SCT after having received induction therapy, including 20 patients who received therapy with the CIA regimen and 22 who received therapy with the IA regimen. The baseline characteristics of both cohorts of patients are shown in Table 1. Patients were well matched in regard to median age (48 years in the CIA group vs. 48.5 years in the IA group, $P = .65$) and median number of chemotherapy cycles before allo-SCT (2 in the CIA group