Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2013 April ; 13(2): 139–143. doi:10.1016/j.clml.2012.11.004.

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.

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Disclosure

The authors have stated that they have no conflicts of interest.

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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.

Keywords

Acute myeloid leukemia; Allogeneic stem cell transplantation; Clofarabine; Hepatotoxicity; Venooclusive disease

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.

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 venooclusive 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/m² intravenously (I.V.) on days 1 to 3, and cytarabine 1.5 g/m² I.V. by continuous infusion on days 1 to 4. CIA consisted of clofarabine 20 mg/m² (22.5 mg/m² before a protocol amendment) I.V. on days 1 to 5, idarubicin 10 mg/m² (6 mg/m² before a protocol amendment) I.V. on days 1 to 3, and cytarabine 1 g/m² (0.75 g/m² 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 $\geq 5\%$ 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 vs. 2 in the IA group; $P = .72$). However more patients in the CIA group were in CR at the time of allo-SCT (85% vs. 73%; $P = .0001$) (Table 1). According to the European LeukemiaNet classification, adverse risk AML (defined by the presence of inv, (3)t(3;3),t(6;9),-5,del(5q),-7, complex karyotype, *FLT3-ITD*, *MLL* rearrangement, and/or abnormalities at chromosome 17p) was present in 45% of the patients treated with CIA, compared with 55% of the patients treated with IA ($P = .76$). Detailed information on cytogenetic features for both patient cohorts is shown in Table 1.

Most patients in both groups received fully myeloablative conditioning regimens prior to transplant (70% in the CIA group, 77% in the IA group). Further, GVHD prophylaxis was similar between groups, with most patients receiving tacrolimus and methotrexate (5 mg/m² on days 1, 3, 6, and 11 post-transplant). The GVHD prophylaxis regimen was not modified for patients receiving pre-transplant clofarabine. No patient received sirolimus for GVHD prophylaxis.

Pretransplantation AML Therapy

The median number of chemotherapy courses for patients treated with CIA was 2 (range, 1-5) and it was 2 for those treated with IA (range, 1-6). Most patients underwent allo-SCT after having achieved a CR with either CIA (85%) or IA (73%). Most patients either received a matched related donor (MRD) transplant (40% among those treated with CIA and 41% among those treated with IA) or an matched unrelated donor (MUD) transplant (40% among those treated with CIA and 41% among those treated with IA), and the majority of patients received busulfan/fludarabine-based conditioning regimens. Importantly, 2 patients in each group received clofarabine as part of their conditioning regimen (Table 2).

Peritransplantation Liver Toxicity

We found no numerically or statistically significant differences in the incidence of VOD or acute hepatotoxicity after SCT. In fact, there was only 1 documented case of VOD in the entire cohort, and this occurred in a patient who had received IA chemotherapy. The highest documented total bilirubin level in the 30 days after SCT in the CIA group was 2.8 mg/dL. Therefore the most severe hyperbilirubinemia in the clofarabine-treated patients was grade 2. The rates of grade 3 or 4 transaminase elevation were very modest in both of the treatment groups. No patient experienced grade 4 transaminase elevations, but grade 3 transaminitis developed in 9% of patients in the IA group, compared with 10% patients in the CIA group. No differences were observed regarding the median peak of ALT and total bilirubin levels between the groups of patients treated with CIA and those treated with IA (Figure 1). Numerically, more cases of acute GVHD occurred among patients treated with IA (9 [20%] cases vs. 4 [41%] in the CIA group), although the difference did not reach statistical significance ($P = .19$). Acute liver GVHD was infrequent in both groups, with only 1 case in each group. We found only one documented case of grade III/IV GVHD in the CIA group (grade III skin), compared to none in the IA group. Other transplant-specific outcomes were similar between groups (Table 3).

Outcomes After Allo-SCT

Given that no significant differences regarding liver toxicity were observed in the peritransplantation period between the cohort of patients treated with IA and the cohort treated with CIA, we next analyzed potential differences in clinical outcomes. The mean engraftment day for patients treated with CIA was 13.9 days (range, 11-33 days), whereas it was 14.5 days (range, 10-29 days) for those previously treated with IA ($P = .7$). There were no deaths in the 30 days after allo-SCT in either group. At 100 days, there were no deaths in the CIA group compared to 2 (9%) in the IA group. The median OS in the CIA group was not reached compared with 16 months in the IA group ($P = .03$) (Figure 2). The rate of relapse within 100 days was low and comparable between the 2 groups, being 15% in the CIA group and 18% in the IA group. Therefore no apparent differences were observed in survival between either chemotherapeutic regimen.

Discussion

The development of VOD is a very serious complication for patients undergoing allo-SCT, with a reported mortality rate recently estimated to be approximately 84%.¹² Clinically, this complication is classically characterized by elevated bilirubin levels, ascites, weight gain, and right upper quadrant pain that occurs within 30 days after SCT.¹³ Therefore, the antecedent use of agents that are potentially hepatotoxic raises the question of whether they will increase the risk of liver complications in the post-allo-SCT setting. One such agent is clofarabine, which is approved by the US Food and Drug Administration for pediatric acute lymphoblastic leukemia and is currently being developed by our group (and others) as a component of chemotherapeutic regimens for AML. This is the first detailed report, to our knowledge, describing adult patients receiving frontline clofarabine-containing chemotherapy for AML before undergoing allo-SCT. This is relevant when considering the risk of hepatotoxicity after allo-SCT, which is also 1 of the primary adverse effects

associated with clofarabine administration. An important question to be answered therefore is whether adding clofarabine to frontline AML therapy will, in any way, impact negatively on the outcome of allo-SCT, particularly regarding an increase in hepatotoxicity in the peritransplantation period. Examples of other hepatotoxic drugs impacting the outcomes of patients with AML have been previously reported. For instance, this scenario was encountered with gemtuzumab ozogamicin (GO), a monoclonal antibody against CD33 attached to the cytotoxin calicheamicin. This agent was previously approved as a salvage option for elderly patients with AML. Contrary to the results of the present study, administration of GO for AML within 3.5 months before allo-SCT significantly increased the incidence of VOD, which often proved fatal.¹⁴ All patients in our study underwent allo-SCT within 3.5 months of their last clofarabine exposure, with no documented cases of VOD. Although an obvious limitation of the present study is the fact that data were collected retrospectively, we are confident that we have not missed any case of VOD because most patients remained in the hospital for the majority of the first 30 days after allo-SCT and in those discharged before day 30, liver function test results were monitored daily in our ambulatory treatment center. It should also be noted that the sample size of this study was small, and the results should be interpreted with this limitation in mind. Overall, these results are reassuring because any toxicity after SCT that was associated with clofarabine would potentially negate the purported enhanced antileukemic benefit.

Patients treated with pretransplantation clofarabine did not experience any additional acute hepatotoxicity after allo-SCT compared with patients who received standard anthracycline and cytarabine-based chemotherapy. There is typically a predictable rise in liver function laboratory parameters after the administration of clofarabine, although this is generally mild and transient. However it was unclear as to whether the cumulative effect in some way predisposed patients to future hepatotoxicity after undergoing very intensive procedures like allo-SCT. Serial evaluation of transaminase levels and total bilirubin levels indicated no increased risk for liver toxicity after transplantation when clofarabine is administered before transplant conditioning chemotherapy.

We also evaluated the potential impact of clofarabine on other important posttransplantation characteristics. Although not statistically significant, the incidence of acute GVHD in the group treated with clofarabine was lower than that in the group treated with IA. No differences were observed regarding day of engraftment or early mortality within 30 days of allo-SCT between the groups. Furthermore, the median OS for the clofarabine-containing chemotherapy group was not adversely impacted, although the median follow-up of this group is shorter than that of the nonclofarabine group.

Conclusion

In conclusion, the incidence of VOD or acute hepatotoxicity after allo-SCT is not increased by the use of clofarabine as part of the frontline management of AML. Other transplantation-related outcomes, such as day of engraftment, acute GVHD, and early mortality, are also not adversely impacted by the use of a clofarabine-containing chemotherapy regimen.

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Clinical Practice Points

- Clofarabine is a nucleoside analogue that exhibits synergistic anti-leukemic effects with cytarabine and is being incorporated into frontline therapy for AML.
- Clofarabine is hepatotoxic and has been associated rarely with VOD.
- Allo-SCT is also associated with VOD, which is often a fatal complication.
- It is unknown whether clofarabine exposure before transplantation increases a patient's risk for the development of VOD.
- We found no difference in acute liver toxicity or VOD after transplantation in patients who received clofarabine-containing vs. non-clofarabine-containing chemotherapy for AML.
- There was also no difference in other transplantation outcomes between the 2 groups.

Figure 1. Peak Alanine Aminotransferase (A) and Total Bilirubin (B) Levels for Patients Treated With Clofarabine, Idarubicin, and Cytarabine (CIA) vs. Idarubicin and Cytarabine (ara-C) (IA) During the First 30 Days After Allogeneic Stem Cell Transplantation

Figure 2. Overall Survival of Patients Receiving Clofarabine, Idarubicin, and Cytarabine (CIA) or Idarubicin and Cytarabine (ara-C) (IA) Chemotherapy Before Allogeneic Stem Cell Transplantation

Table 1

Patient Characteristics

Variable	CIA (n = 20)	IA (n = 22)	P Value
Demographic Information			
Median age	48	48.5	.65
% male	25	64	.0001
% CR	90	77	.02
Median No. of cycles (range)	2 (1-5)	2 (1-6)	.72
% SCT in CR	85	73	.46
Cytogenetic/Molecular Information			
Diploid (%)	3 (15)	6 (27)	.332
Adverse risk (%) ^a	9 (45)	12 (55)	.76
Other (%)	8 (40)	4 (18)	
FLT3 ITD (%)	3 (15)	4 (18)	.779

^a According to the EuropeanLeukemiaNet classification.

Table 2

Transplant Characteristics

Characteristic	CIA (n = 20)	IA (n = 22)	P Value
MRD ^a (%)	8 (40)	9 (41)	.9
MUD ^b (%)	8 (40)	9 (41)	.9
Other ^c (%)	4 (20)	4 (18)	.9
Umbilical Cord (%)	2 (10)	1 (5)	.497
Haploidentical (%)	1 (5)	2 (9)	.610
Mismatched (%)	1 (5)	0 (0)	.289
Umbilical Cord/MRD	0 (0)	1 (5)	.337
Reduced Intensity Conditioning (%)	6 (30)	5 (23)	.73
Clofarabine in Conditioning (%)	2 (10)	2 (9)	.9

Abbreviations: CIA = clofarabine, idarubicin, and cytarabine; IA = idarubicin and cytarabine (ara-C); MRD = matched related donor; MUD = matched unrelated donor.

^aMRD (8 in CIA group, 10 in IA group).

^bMUD (8 in CIA group, 9 in IA group).

^cOther = umbilical cord blood, haploidentical, mismatched, or other (4 in CIA group, 4 in IA group).

Table 3

Liver Toxicity in Peritransplantation Period for Groups of Patients Treated With CIA or IA

Toxicity	CIA (n = 20)	IA (n = 22)	P Value
VOD (total cases)	0	1	1.0
Acute GVHD (total cases)	4	9	.19
Acute Liver GVHD	1	1	1.0
Median 30-Day Peak Bilirubin (range)	0.9 (0.5-2.8)	0.8 (0.4-3.7)	.86
Median 30-Days Peak ALT (range)	81 (30-830)	72 (16-332)	.76

Abbreviations: ALT = alanine aminotransferase; CIA = clofarabine, idarubicin, and cytarabine; GVHD = graft versus host disease; IA = idarubicin and cytarabine (ara-C); VOD = venoocclusive disease.