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Mobilization of Leukemic Cells Using Plerixafor as Part of a Myeloablative Preparative Regimen for Patients with Acute Myelogenous Leukemia Undergoing Allografting: Assessment of Safety and Tolerability

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Allogeneic hematopoietic cell transplantation (HCT) is potentially curative for acute myelogenous leukemia (AML); however, a major cause of treatment failure is disease relapse. The purpose of this single-center Phase I study was to determine the safety and tolerability of administration of the CXCR4 inhibitor plerixafor (Mozobil; Sanofi Genzyme) along with myeloablative conditioning in patients with AML undergoing allogeneic HCT. The rationale was that plerixafor may mobilize leukemic stem cells, making them more susceptible to the conditioning chemotherapy (registered at ClinicalTrials.gov; identifier NCT01141543). Three patients were enrolled into each of 4 sequential cohorts (12 patients total). Patients in the first cohort received 1 dose of plerixafor (240 μg/kg s.c.) before the first dose of fludarabine and busulfan, and subsequent cohorts received injections before 2, 3, and 4 days of conditioning chemotherapy. The median age at HCT was 49 years (range, 38 to 58 years). All patients engrafted following HCT, with an absolute neutrophil count $\geq .5 \times 10^9$/L observed at a median of 14 days (range, 11 to 18 days). Adverse events possibly related to plerixafor were transient and not severe. Main adverse events following the injection were nausea and dizziness in 4 patients (33%) and fatigue in 4 patients (33%). Among the 12 patients, 2 patients (17%) relapsed post-HCT and 6 (50%) were alive at the last follow-up. The median follow-up of survivors was 67 months (range, 53 to 82 months). In conclusion, plerixafor administration is safe and well tolerated when included in a myeloablative conditioning regimen for allogeneic HCT for AML. Further study in a larger cohort is warranted for the investigation of the impact of plerixafor on post-allogeneic HCT outcomes.

INTRODUCTION

Acute myelogenous leukemia (AML) is a heterogeneous hematologic malignancy for which allogeneic hematopoietic cell transplantation (HCT) is a treatment option, particularly for intermediate and unfavorable cytogenetic risk categories [1,2]. However, allogeneic HCT recipients may experience complications associated with increased morbidity and mortality. A major post-HCT complication is disease relapse, which is reported with variable rates of occurrence, depending on the disease risk and conditioning intensity [3]. Treatment of AML relapse following allogeneic HCT is a major challenge, given the 1-year postrelapse survival of <20% and median survival after post-HCT relapse of approximately 3 months [4]. Therefore, prevention of relapse remains a significant objective in improving post-HCT survival.

The mechanism behind AML relapse post-HCT remains poorly understood. Relapse can occur early if the conditioning regimen was of insufficient intensity to decrease the tumor burden sufficiently to allow for an optimal graft-versus-leukemia (GVL) effect. In addition, the GVL might not occur if immune tolerance develops, allowing for immune escape of mutated immune-resistant progenitor cells [3]. The GVL effect also may be influenced by the addition of immunosuppression for the treatment of graft-versus-host disease (GVHD) [5], whereas early immune reconstitution post-HCT has been directly correlated with a reduced risk of relapse [6,7]. Moreover, sanctuary sites that can harbor extramedullary relapse are frequently responsible, because antileukemic T cells are not present [8].

The C-X-C chemokine receptor type 4 (CXCR4) and its ligand, stromal-derived factor 1 (SDF-1/CXCL12), play

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significant roles in the interaction between leukemia cells and the bone marrow (BM) microenvironment that facilitates the survival and proliferation of malignant cells [9]. Interaction between BM stromal cells and leukemia cells via increased expression of CXCR4 has been associated with increased relapse rates in patients with AML [10,11]. Plerixafor (Mozobil; Sanofi Genzyme) is a small-molecule inhibitor of CXCR4 that is routinely used as a stem cell mobilizing agent for patients with multiple myeloma or non-Hodgkin lymphoma undergoing autologous HCT. By disrupting the CXCR4/CXCL12 interaction using CXCR4 inhibitors such as plerixafor, leukemic cells can be mobilized and sensitized to the toxic effect of chemotherapy [12,13]. In a previous Phase I/II study, plerixafor administration to AML patients before chemotherapy was shown to be safe and effective for mobilizing leukemic blasts into the peripheral circulation [14].

The previously reported findings warrant the investigation of mobilization and sensitization of leukemic cells using CXCR4 inhibitors such as plerixafor in the allogeneic HCT setting. The purpose of this phase 1 study was to determine the safety and applicability of administration of plerixafor along with a myeloablative conditioning regimen in patients with AML undergoing allogeneic HCT.

METHODS

Study Population and Eligibility Criteria

Our study cohort included patients undergoing myeloablative allogeneic HCT, using related or unrelated donors, for the treatment of AML in remission (defined as <5% blasts detected on BM biopsy). Study patients underwent transplantation between October 2010 and June 2013. Other criteria for participation included age 18 to 60 years and eligibility for myeloablative transplantation in accordance with institutional protocol. Exclusion criteria included age 61 years or older; ineligibility to receive the institutional myeloablative conditioning regimen due to comorbidities; pregnancy or lactation; serum creatinine, bilirubin, aspartate aminotransferase, and alanine aminotransferase levels >2 times the upper normal limit; and left ventricular ejection fraction <50% (as seen on multigated acquisition scan). The present trial is registered at ClinicalTrials.gov (identifier NCT01141543.

Transplantation Procedures

The institutional myeloablative conditioning (MAC) regimen used included fludarabine 50 mg/m^2/day for 4 days, busulfan 3.2 mg/kg/day for 4 days, and total body irradiation 400 cGy in 2 fractions. GVHD prophylaxis consisted of cyclosporin A in combination with mycophenolate mofetil (n = 7), alemtuzumab (Campath; n = 4), or both agents (n = 1).

Study Design

The present prospective single-center observational phase 1 study was designed to evaluate the safety of administering plerixafor as part of a MAC regimen for patients with AML undergoing allogeneic HCT for the purpose of mobilizing residual leukemic stem cells in that setting. Three patients were enrolled into each of 4 sequential cohorts (12 patients in total). For all patients, adverse events (as defined below) were documented within the first 30 days post-HCT and reassessed again at 1 year post-HCT (with graft failure considered an adverse event possibly related to plerixafor). All doses of plerixafor (240 μg/kg s.c.) were given 6 hours before the administration of fludarabine, followed by busulfan. Patients in cohort 1 received 1 dose of plerixafor before administration of the first dose of chemotherapy. After demonstrating tolerability in cohort 1, in the absence of grade 4 adverse events by day +30, plerixafor doses were escalated in the subsequent cohorts (in the absence of grade 4 adverse events by day +30) to 2, 3, and 4 injections in total on consecutive days, to be administered before the respective second, third, and fourth doses of chemotherapy.

Enumeration of Circulating CD34$^+$ Cells

Flow cytometry for quantification of CD34$^+$ cells was performed on peripheral blood (PB) samples before the first dose of plerixafor, as well as 6 hours after plerixafor administration (on consecutive days -5 and up to and including day -2, depending on the cohort) and before the administration of fludarabine and busulfan. A 10-color surface immunophenotypic panel was developed including antibodies to CD38 and stem cell markers CD34 and CD117, as well as early differentiation markers (CD19), and the CXCR4 antigen CD184 (Figure 1). Data were acquired using a flow cytometer equipped with violet, blue, and red lasers and 10 photomultiplier tubes (Gallios; Beckman Coulter, Miami, FL), with a minimum of 2×10^5 events collected per sample. Data analysis was done using FCS Express 3.0 (De Novo Software, Glendale, CA).

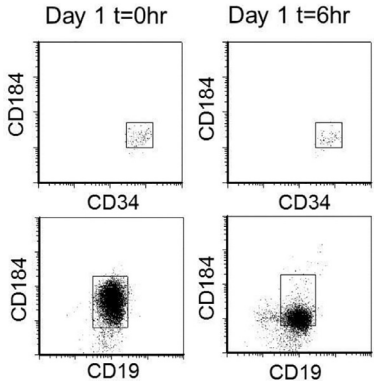

Figure 1. Immunophenotypic analysis of expression of CD34, CD184, and CD19 on PB samples at baseline and 6 hours after the first administration of plerixafor. Treatment with plerixaflor demonstrated decreased staining for the CXCR4 antigen CD184 on CD34$^+$ cells and CD19$^+$ B lymphocytes.

Data

Data collected included patient age at the time of HCT, type of donor (related versus unrelated), subtype of AML (de novo versus secondary), first complete remission (CR1) versus second complete remission (CR2), cytogenetics at diagnosis, prognostic molecular testing when available, and Hematopoietic Cell Transplant Comorbidity Index (HCT-CI) [15]. Post-HCT events documented include time from HCT to death or last follow-up, time to relapse when applicable, and cause of death where applicable. Complete blood counts and flow cytometry data were collected before and after plerixafor injections as described above. Cytogenetic risk at diagnosis was determined using the Medical Research Council criteria [16].

Engraftment data were recorded based on the Center for International Blood and Marrow Transplant Research criteria (http://www.cibmtr.org/DataManagement/TrainingReference/Manuals/DataManagement/Documents/posted-instruction.pdf). Absolute neutrophil count (ANC) was documented as the first of 3 consecutive days of an ANC $\geq .5 \times 10^9$/L. Platelet (PLT) recovery was documented as the first of 3 values with PLT $\geq 20 \times 10^9$/L on 3 consecutive measurements on different days, at least 7 days after the last PLT transfusion.

Study Endpoints and Statistical Analysis

Primary endpoint of the study was to establish the safety and tolerability (as measured by the occurrence of adverse events) of the administration of plerixafor in conjunction with the MAC regimen, determined over the course of 1 year. Adverse events were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4. Secondary endpoints included the quantification of CD34$^+$ progenitor cells after administration of plerixafor using a marker panel by flow cytometry, engraftment, overall survival post-HCT (defined as the time from transplantation to death or the last time reported alive), time to occurrence of AML relapse, and survival postrelapse. Patient, disease, and transplantation characteristics were reported using descriptive statistics (counts and percentages). Data were updated as of March 2018.

RESULTS

Baseline Patient Characteristics

Characteristics of the 12 study participants summarized in Table 1. The median age of participants at HCT was 49 years (range, 38 to 58 years). Seven of the patients were female. All patients received PB stem cell grafts. De novo AML was diagnosed in 10 patients, and 2 patients had secondary AML (previous endometrial adenocarcinoma in 1 patient and previous Crohn's disease in 1 patient). HCT was performed in CR1 for 10 patients and in CR2 in 2 patients. Primary induction failure necessitating reinduction chemotherapy occurred in 3 patients. Nine patients had intermediate cytogenetic risk, 1 patient had adverse risk, and 2 patients had no metaphases observed. Among the 10 patients who underwent molecular testing, 8 patients were NPM1$^-$/FLT3$^-$ and 2 were NPM1$^+$/FLT3$^+$.

Table 1
Patient Characteristics and Significant Events Post-HCT

Patient	Cohort (Days of Plerixafor)	Patient Age, yr	AML Characteristics	Donor Type	HCT-CI	GVHD Prophylaxis	Adverse Events in First 30 Days	GVHD Details	Outcome
1	1	47	sAML, int risk, CR2	Matched related	4	CyA, MF	Mucositis grade 2	Grade III aGVHD gut, limited cGVHD	Deceased at 7 mo
2	1	38	De novo, adv risk, CR1	Unrelated 9/10	1	Campath, CyA	Mucositis grade 2	Grade II aGVHD skin	Relapse at 14 mo, deceased at 16 mo
3	1	58	sAML, int risk, CR2	Matched related	5	CyA, MF	Mucositis grade 2, febrile neutropenia, aGVHD	Grade II aGVHD skin, gut, extensive cGVHD	Alive at 82 mo
4	2	51	De novo, int risk, CR1	Matched related	0	CyA, MF	Mucositis grade 2	Extensive cGVHD	Alive at 69 mo
5	2	48	De novo, int risk, CR1	Matched related	1	CyA, MF	Mucositis grade 2, HSV, CMV	Extensive cGVHD	Alive at 70 mo
6	2	48	De novo, failed cytogenetics, PIF, CR1	Matched related	1	CyA,MF	Nausea	Extensive cGVHD	Deceased at 65 mo
7	3	41	De novo, int risk, CR1	Matched related	0	CyA, MF	Mucositis grade 2, febrile neutropenia, aGVHD	Grade I aGCHD skin, extensive cGVHD	Alive at 64 mo
8	3	46	De novo, int risk, PIF, CR1	Unrelated 9/10	1	Campath, CyA, MF	Mucositis grade 2, febrile neutropenia, aGVHD	Grade III aGVHD gut	Deceased at 11 mo
9	3	51	De novo, int risk, CR1	Unrelated 9/10	0	CyA, MF	Mucositis grade 2, *C. difficile* colitis	Limited cGVHD	Alive at 53 mo
10	4	49	De novo, int risk, CR1	Unrelated 9/10	0	Campath, CyA	Mucositis grade 2, nausea, gum hypertrophy (CyA)	Grade III aGVHD gut	Deceased at 3 mo
11	4	54	De novo, int risk, PIF, CR1	Unrelated 10/10	0	Campath, CyA	Mucositis grade 2, HSV, febrile neutropenia, aGVHD	Grade II aGVHD skin	Relapse at 6 mo, deceased at 8 mo
12	4	52	De novo, failed cytogenetics, CR1	Unrelated 10/10	0	Campath, CyA	Mucositis grade 2, HSV, CMV, febrile neutropenia	Grade II aGVHD skin, gut	Alive at 54 mo

adv risk indicates adverse risk cytogenetics; CMV, cytomegalovirus; CyA, cyclosporine A; Gr, grade; HCT-CI, hematopoietic cell transplantation comorbidity index; HSV, herpes simplex virus; int risk, intermediate-risk cytogenetics; MF, mycophenolate mofetil; PIF, primary induction failure; sAML, secondary acute myelogenous leukemia.

Donors were HLA-matched related for 6 patients, fully matched 10/10 unrelated for 2 patients, and 9/10 mismatched for 4 patients. HCT-CI was calculated before transplantation as 0 in 6 patients, 1 in 4 patients, 4 in 1 patient, and 5 in 1 patient.

Transient Adverse Events Possibly Related to Plerixafor Administration

The transient adverse events that were possibly related to plerixafor administration are documented in Table 2 (along with grade). No severe adverse events related to plerixafor administration were observed. In the first cohort (plerixafor on day -5 of the conditioning regimen), 2 patients complained of nausea and dizziness, 2 patients experienced fatigue, and 1 patient had chest wall discomfort. In the second cohort (plerixafor on days -5 and -4), only 1 patient experienced hot flashes following the injection. In the third cohort (plerixafor on days -5 to -3), 2 patients had nausea and dizziness, 2 patients had fatigue, 1 patient had injection site erythema, and 1 patient had transient back pain. In the fourth cohort (plerixafor on days -5 to -2), no adverse events related to the plerixafor injection were documented.

No toxicity related to the chemotherapy regimen (eg, liver dysfunction, chemotherapy-related diarrhea, kidney dysfunction, erythema) was observed.

Engraftment Data

All 12 patients engrafted following HCT. ANC $\geq .5 \times 10^9$/L was observed at a median of 14 days (range, 11 to 18 days), and ANC $\geq 1.0 \times 10^9$/L was also seen at a median of 14 days (range, 11 to 23 days). PLT engraftment $\geq 20 \times 10^9$/L was seen at a median of 10 days (range, 7 to 11 days), PLT at $\geq 50 \times 10^9$/L occurred at a median of 12 days (range, 9 to 62 days), and PLT $\geq 100 \times 10^9$/L occurred at a median of 12 days (range, 10 to 81 days).

At day +30 post-HCT, the median WBC was 5.3×10^9/L (range, 1.8 to 15.5×10^9/L), median ANC was 4.0×10^9/L (range, 1.2 to 13.5×10^9/L), median absolute lymphocyte count was $.25 \times 10^9$/L (range, 0 to $.8 \times 10^9$/L) and median PLT was 109×10^9/L (range, 26 to 228×10^9/L). At day +180 post-HCT, median WBC was 5.0×10^9/L (range, 0 to 18.3×10^9/L), median ANC was 3.8×10^9/L (range, 0 to 13.9×10^9/L), median absolute lymphocyte count was $.7 \times 10^9$/L (range, 0 to 4.2×10^9/L), and median PLT was 157×10^9/L (range, 0 to 439×10^9/L).

Flow Cytometry for CD34$^+$ Blasts in PB

CD34$^+$ cells in the blast cell region, defined by CD45 and orthogonal light scatter, were detected in all patient samples at frequencies ranging from .01% to .4%, although in the majority they formed $\leq$.1% than the total of nucleated cells. Treatment with plerixaflor resulted in decreased staining for the CXCR4 antigen CD184 on CD34$^+$ blast cells and CD19$^+$ B lymphocytes (Figure 1). The monoclonal antibody used, 12G5, recognizes an epitope in the extracellular domain of CXCR4 that competes for plerixaflor binding [14]. It has been shown that the loss of 12G5 antibody staining is correlated with disruption of the SDF-1/CXCR4 axis during ex vivo treatment with plerixaflor [17], so that the decreased staining seen in the patient samples is indicative of drug target engagement. We did not observe consistent increases in CD34$^+$ cells in blood samples obtained 6 hours after plerixaflor treatment to suggest mobilization from the BM; however, there was a decrease in PB CD34$^+$ cells in most cases following conditioning with fludarabine plus busulfan.

Events Up to Day +30 Post-HCT

Significant events documented during the first 30 days post-HCT are summarized in Table 1. Bearman grade 2 mucositis was seen in 11 of the 12 patients (91%). Febrile neutropenia occurred in 5 patients (42%), grade II-IV acute GVHD (aGVHD) in 4 (33%), herpes simplex virus reactivation in 3 (25%), cytomegalovirus reactivation in 2 (17%), *Clostridium difficile* colitis in 1 (8%), and cyclosporine A-induced gum hypertrophy in 1 (8%).

Outcome Data

Of the 12 patients enrolled in the study, 2 (17%) relapsed post-HCT. The first relapse occurred at 14 months post-HCT in a patient with complex cytogenetics at diagnosis. The second relapse occurred at 6 months post-HCT in a patient with normal cytogenetics at diagnosis, NPM1$^-$/FLT3$^-$. Both patients had received alemtuzumab with GVHD prophylaxis. The first patient survived for 2 months, and the second patient survived for 3 months following relapse.

Grade I aGVHD of the skin developed in 1 patient and grade II-IV aGVHD developed in 7 patients (3 patients with gut, 2 with skin and 2 with skin and gut). Grade III-IV aGVHD developed in 3 patients (25%) (Glucksberg criteria). Chronic GVHD (cGVHD) developed in 7 patients (58%), including 2 with limited cGVHD and 5 with extensive cGVHD (Seattle criteria).

Of the 12 patients enrolled in the pilot cohort, 6 were alive at the last follow-up (50%, last follow-up in March 2018). To date, the median follow-up of the entire cohort is 53 months (range 3 to 82 months), and the median follow-up of survivors is 67 months (range 53 to 82 months).

Of the 6 patients who died, cause of death was bacterial sepsis in 2 patients, AML relapse in 2 patients, *Pneumocystis jirovecii* pneumonia in 1 patient, and cGVHD of the lungs in 1 patient.

Long-Term Outcomes

One patient developed a secondary malignancy in the form of squamous cell carcinoma of the skin, with the first occurrence at 45 months post-HCT, which was completely resected, and the second occurrence at 53 months post-HCT with invasive features, which was treated surgically.

Table 2
Transient Adverse Events Possibly Related to Plerixafor

Patient cohort	Cohort 1 (Plerixafor on Day -5)	Cohort 2 (Plerixafor on Days -5 and -4)	Cohort 3 (Plerixafor on Days -5 to -3)	Cohort 4 (Plerixafor on Days -5 to -2)
Nausea, dizziness	2 patients (grade 2)	None	2 patients (grade 2)	None
Fatigue	2 patients (grade 2)	None	2 patients (grade 2)	None
Chest wall discomfort	1 patient (grade 2)	None	None	None
Hot flashes	None	1 patient (grade 1)	None	None
Injection site erythema	None	None	1 patient (grade 1)	None
Back pain	None	None	1 patient (grade 2)	None

Among the 6 survivors at last follow-up, 4 patients had a Karnofsky Performance Status (KPS) score of 100 and no significant post-transplantation problems. Two patients, 1 with a KPS score of 80 and the other with a KPS score of 60, continued to have extensive cGVHD, which was under control on tapering immunosuppression at the last follow-up. Survivors were receiving an average of 5 medications related to transplantation-related complications or new comorbidities at the last follow-up.

DISCUSSION

In the present Phase I study, plerixafor was added to an MAC regimen before allogeneic HCT in patients with AML in CR1. The rationale behind this intervention was that the disruption of the CXCR4/CXCL12 interaction with plerixafor may potentially mobilize leukemic stem cells out of the bone marrow microenvironment and make them more susceptible to the effect of the administered conditioning chemotherapy. We demonstrated that the addition of plerixafor in this cohort was safe and well tolerated and did not impede engraftment, with all patients engrafting within a reasonable time frame. The injections were tolerated without significant adverse reactions directly related to plerixafor. Post-transplantation events, such as AML relapse and GVHD, were observed, as expected. Statistical analysis of these outcomes was not feasible due to the small number of patients in the cohort; however, only 2 patients (17%) experienced relapse post-transplantation. After more than 5 years of follow-up, 50% of patients remain alive. Using immunophenotype analysis, we also demonstrated that plerixafor interacted with $CD34^+$ cells circulating in the PB, although we did not detect a significant increase in the number of circulating $CD34^+$ cells that would imply an increase in mobilization from the bone marrow. The reason why we did not detect significant mobilization of $CD34^+$ cells on flow cytometry may be because the patients were in complete morphological remission at the time of transplantation, and also because the conditioning chemotherapy cleared the minute proportion of $CD34^+$ cells circulating in the PB to some degree.

Plerixafor, in combination with filgrastim [granulocyte colony-stimulating factor (G-CSF)], is currently used in clinical practice to mobilize $CD34^+$ hematopoietic stem cells into PB for collection via leukapheresis and subsequent autologous transplantation in patients with non-Hodgkin lymphoma or multiple myeloma [18,19]. The standard dosage for this indication is 240 μg/kg/day for 4 consecutive days before stem cell collection. Plerixafor may be used in this setting for remobilization following failed mobilization with G-CSF alone, or it may be used preemptively in select patients in whom mobilization with G-CSF alone is expected to fail [20]. Plerixafor remains the sole CXCR4 antagonist approved by the Food and Drug Administration for this indication. Recent studies have also provided evidence that plerixafor may be an effective alternative to G-CSF mobilization of PB stem cells for healthy allogeneic donors, associated with rapid engraftment and potentially lower rates of cGVHD [21].

In previous studies, plerixafor has demonstrated mild to moderate and manageable side effects. Danylesko et al [22] reported that 40% of patients in a small cohort demonstrated transient side effects, predominantly gastrointestinal. Mild and transient adverse effects were found in another Phase I study involving 26 healthy human volunteers [23]. Adverse effects observed were erythema or stinging at the injection site (69%), headache (27%), perioral paresthesias (31%), nausea (38%), and abdominal distention without diarrhea (19%), all of which resolved within 24 hours. Moreover, no significant abnormalities in blood biochemistry were noted. These observations seem to correlate with those in the present study, for nausea in particular; however, this adverse reaction did not seem to correlate with our study cohort and the number of plerixafor doses administered; the cohort with the most plerixafor injections (4 total) did not experience any adverse reactions to the drug.

The concept of combining plerixafor with chemotherapy to enhance antileukemic action is supported by the observed enhanced cytotoxic activity of immune cells in a mouse model of AML and subsequent increased susceptibility of leukemic cells to chemotherapy, suggesting that plerixafor also exerts biological effects on the microenvironment through immune cell activation [24]. Previous studies have shown that plerixafor is capable of mobilizing both normal and leukemic cells in the PB, at doses similar to those used in the present study [14]. A recent Phase I study combining decitabine and plerixafor in older non-allogeneic HCT recipients demonstrated mobilization of leukemia stem and progenitor cells using escalating plerixafor doses up to 810 μg/kg/day without promoting clinically significant hyperleukocytosis. However, they did not demonstrate a definite clinical benefit associated with the addition of the drug, bearing in mind that these patients had newly diagnosed AML with a significant disease burden [25].

Konopleva et al [26] previously demonstrated that plerixafor can be safely administered in patients undergoing allogeneic HCT. Their Phase I/II study of 45 patients included both AML and other myeloid malignancies. The study differed from the present study also regarding the dosage of plerixafor, with 4 consecutive days of the drug at different doses (ranging from 0 to 240 μg/kg) for different subgroups, along with concomitant G-CSF administration (which was not administered in the present study). Moreover, more than one-half of the patients in that study had primary refractory disease or relapsed disease, as opposed to our study, in which all patients underwent transplantation for AML in CR1. This is also reflected in the high post-HCT relapse rate of $>$50% in the study by Konopleva et al [26], in contrast to the 17% relapse rate in the present study. That study, similar to ours but with a significantly different population in terms of disease stage, demonstrated that plerixafor can be administered with the conditioning regimen for allogeneic HCT without significant acute toxicity, although regarding long-term outcomes, our study had a significantly longer survivor follow-up, exceeding 5 years.

In our cohort, grade II-IV aGVHD occurred in 58% of patients and grade III-IV aGVHD occurred in 25%, percentages comparable with those previously reported at our center during the same period [27]. We compare these findings with those of Konopleva et al [26], which actually demonstrated decreased incidences of aGVHD and cGVHD compared with historical controls. Research involving rhesus macaques has indicated that plerixafor promotes the mobilization of both effector and regulatory T cell populations in the PB of these animals [28]. These findings, coupled with the clinical data reported herein, suggest that the addition of plerixafor to allogeneic HCT regimens actually may have the potential to enhance immunologic mechanisms known to be associated with decreases in the incidence and severity of GVHD.

Based on our present data, we conclude that plerixafor administration is safe and well tolerated when included in an MAC regimen for allogeneic HCT for patients with AML in CR1. Our results indicate that further study in a larger cohort is warranted to investigate the impact of plerixafor on post-allogeneic HCT relapse rates and survival.

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