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Haploidentical Donor Transplantation Using a Novel Clofarabine-Containing Conditioning Regimen for Very High-Risk Hematologic Malignant Neoplasms

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Abstract

Recurrent/refractory hematologic malignancies have a poor prognosis, and there is a need for novel treatment regimens that can be tolerated by this heavily pretreated patient group. Clofarabine has antileukemic activity with an acceptable toxicity profile. In a phase I clinical trial (NCT00824135), we substituted clofarabine for fludarabine in a well-established reduced-intensity conditioning regimen for a T cell-depleted, mismatched related (haploidentical) donor transplant backbone and explored the maximum tolerated dose of clofarabine in this combination in 15 patients undergoing hematopoietic cell transplantation for recurrent/refractory or secondary leukemia. Clofarabine was well tolerated at a dose of 50 mg/m²/day for 5 days in this regimen, with minimal treatment-related mortality in a heavily pretreated group of high-risk patients. All patients exhibited quick hematopoietic recovery, with median times to neutrophil and platelet engraftment being 11 and 16 days, respectively. Transient elevation of transaminases was the most common toxicity - observed in 13 patients (86.7%), with 6 (40%) grade III or above. Three patients (20%) developed hepatic veno-occlusive disease. Eleven patients (73.3%) died, with the most common cause of death being disease relapse (in 9 patients [60%]), followed by treatment-related mortality (in 2 patients [13.3%]). Four (26.6%) of the patients are long-term survivors.

Keywords

Clofarabine; reduced intensity conditioning; haploidentical donor; hematopoietic cell transplantation

INTRODUCTION

Primary refractory hematologic malignant neoplasms, secondary leukemias, and recurrent malignant disease after an allogeneic hematopoietic cell transplant (HCT) all have a dismal prognosis [1–9]. In patients with such disease, salvage attempts with additional chemotherapy are usually ineffective, and toxicity arising from prior exposure to multiple chemotherapeutic agents, along with a resistant leukemic burden, typically makes the patients poor candidates or, more commonly, ineligible for HCT [5,6,10–16]. Historically, in these heavily pretreated populations, both regimen-related mortality and disease recurrence have been major causes of treatment failure in patients who were eligible for HCT [5,10–16]. Hence, novel treatment regimens that demonstrate effective antileukemic activity, minimize regimen-related toxicity, and promote rapid immune recovery are needed.

Clofarabine (2-chloro-2'-fluoro-deoxy-9-β-D-arabinofuranosyladenine) is a second-generation nucleoside analog that elicits a substantial response in patients with relapsed/refractory leukemia [17–19] and shows an encouraging level of activity in older patients with newly diagnosed myeloid malignant neoplasms who are unable to tolerate intensive chemotherapy [20,21]. It is approved for treating pediatric patients with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens [22]. Clofarabine has been successfully combined with intermediate-dose cytarabine [18,19,21,23] and high-dose cyclophosphamide to treat acute leukemias and myelodysplastic syndromes [24–26]. Hepatic and skin toxicity are the typical dose-limiting toxicities (DLTs) with this drug [27]. In contrast to the severe and often irreversible or fatal neurotoxicity observed with cladribine and fludarabine at the doses effective against acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), clofarabine treatment has not been associated with neurotoxicity [17,27]. Additionally, the immunosuppressive properties of clofarabine are equal or superior to those of fludarabine [28,29]. The recommended dose for monotherapy with clofarabine in children is 52 mg/m² daily for 5 days; an acceptable dose for combination chemotherapy has not been established [30].

Prior to 2008, we predominantly used a fludarabine, thiotepe, and melphalan-based reduced-intensity conditioning regimen and T cell-depleted, mismatched related (haploidentical) donor grafts in institutional trials of treatments for patients with refractory hematologic malignant neoplasms. This approach resulted in consistent engraftment and had good tolerability, but disease recurrence was a primary cause of treatment failure. We developed the present phase I study (NCT00824135) in 2008 by substituting escalating doses of clofarabine for fludarabine in the well-established haploidentical HCT backbone, anticipating that clofarabine would provide additional cytotoxicity while reducing fludarabine-associated neurotoxicity. The goal of this trial was to determine the maximum

tolerated dose (MTD) of clofarabine and its dose-limiting toxicity (DLT) when used in combination with melphalan and thiotepea.

PATIENTS AND METHODS

Study group

Eligible patients included those aged 21 years or younger with a refractory hematologic malignant neoplasm (i.e., with chemoresistant relapse or primary induction failure), those who had experienced relapse after receiving a prior allogeneic HCT, and those who had developed a secondary (therapy-related) hematologic malignant neoplasm for which standard myeloablation was contra-indicated. Organ-specific criteria included having a cardiac shortening fraction of 25% or more; an estimated glomerular filtration rate of at least 90 mL/min/1.73 m²; a forced vital capacity of at least 40% of predicted; a performance score of at least 50; no active graft-versus-host disease (GvHD); no active bronchiolitis obliterans or bronchiolitis obliterans organizing pneumonia; and total bilirubin, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels not exceeding 1.5 times the upper limit of normal for the patient's age. Other eligibility criteria were not being pregnant or lactating and having a suitable HLA partially matched related donor available for progenitor cell donation.

Donors had to be partially (single haplotype) HLA-matched (haploidentical) and related; at least 18 years of age; HIV negative; and not pregnant or lactating. Donor eligibility was determined in accordance with 21CFR 1271 requirements. If more than one family member was available as a donor, the individual having the largest KIR repertoire mismatch with the recipient was selected as the donor. The study was approved by the Institutional Review Board and the FDA and was conducted in accordance with the basic principles of the Declaration of Helsinki.

Treatment plan

Patients began the conditioning regimen on day -9 before transplant with the administration of muromonab-CD3 (OKT3), which continued daily through day +17. Clofarabine administration was initiated on day -8, with daily dosing continuing for 5 days. Daily dosing was started at 40 mg/m²/day for dose level 1 recipients, increasing to 45 mg/m²/day for dose level 2 recipients and to 50 mg/m²/day for dose level 3 recipients. Thiotepea was administered at 5 mg/kg/dose in two doses given 12 h apart on day -3. Melphalan was administered at 60 mg/m²/dose on days -2 and -1. For GvHD prophylaxis, mycophenolate mofetil administration was started on day -2 at 600 mg/m²/dose given twice daily, with the goal of stopping administration by day +45. Rituximab was administered at 375 mg/m² on day -1 to deplete B cells as Epstein-Barr virus (EBV) prophylaxis. G-CSF administration was initiated at 5 µg/kg/day on day +6 and continued until neutrophil engraftment was confirmed.

Peripheral blood progenitor cells (PBPCs) were obtained from the donor by leukapheresis after combined granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) mobilization. The target dose for the total

product was at least 5×10^6 CD34⁺ cells/kg, which typically necessitated 2 days of collection. The PBPCs obtained were processed using standard operating procedures. T-cell depletion was accomplished with a CliniMACS cell-separation system and CD3 MicroBeads (Miltenyi Biotech) under an FDA issued Investigational Device Exemption. The target T-cell dose was 1×10^5 CD3⁺ cells/kg. After processing, the graft was infused fresh on day 0 and day +1.

Patients undergoing HCT were housed in a HEPA-filtered unit and received standard transplant supportive care, including antimicrobial prophylaxis and transfusion support, along with fosphenytoin administration for seizure prophylaxis concomitant with OKT3.

Response and toxicity criteria

Neutrophil engraftment was defined as having occurred on the first of 3 consecutive days on which the absolute neutrophil count exceeded 500/ μ L. Platelet engraftment was defined as having occurred when the platelet count exceeded 20,000/ μ L without transfusion support. Relapse was defined as having occurred when there was evidence of hematologic, cytogenetic, or molecular recurrence of the primary disease at any site in the host. Survival data was calculated based on patient status at the time of last follow-up.

The evaluation period for clofarabine DLT began upon the initial infusion of the drug and continued through day +30 post HCT. The MTD was defined as the highest dose of clofarabine that could be administered without causing unacceptable DLT. DLTs were defined as follows: 1) Non-engraftment/primary graft failure—ANC never reaching or exceeding 500/ μ L for 3 consecutive days and no evidence of donor chimerism at day 21 post transplant; 2) Any NCI grade III or IV allergic reaction to clofarabine at the time of administration; and 3) Any grade IV organ toxicity not due to the underlying malignant neoplasm or to GvHD within 30 days post transplant. Hepatic veno-occlusive disease (VOD) was assessed and diagnosed using the Jones/Baltimore criteria [31]. Adverse events (AEs) were scored according to the criteria specified by the NCI CTC, version 3.0. NCI grade I–V AEs were collected from the initiation of conditioning through day 30 post transplant. Thereafter, NCI grade III–V AEs and clinically significant grade I or II AEs were collected.

Statistical methods

The primary objective of this study was to determine the MTD and DLT of clofarabine when it was combined with thiotepe and melphalan in a conditioning regimen for patients undergoing a haploidentical HCT with an engineered graft depleted of CD3⁺ cells that was obtained by negative selection on a CliniMACS system. Dose escalation was performed using a traditional 3+3 phase I trial design [32].

Additional objectives were to evaluate the 1-year overall survival (OS), leukemia-free survival (LFS), and event-free survival (EFS) rates in the study participants, along with their hematopoietic recovery, donor-cell engraftment, cumulative incidence (CIN) of relapse, incidence of GvHD, and nonhematologic regimen-related toxicity and mortality. Nonhematologic regimen-related toxicity and mortality were descriptively summarized. The Kaplan-Meier method was used for survival estimates. Overall survival was defined as the time from transplant until death from any cause. Leukemia-free survival was defined as the

time from transplant until a relapse of the leukemia. All surviving participants were censored at the time of the last follow-up for OS and LFS. Patients who died of causes other than relapse were censored at the time of their event for LFS analysis. Event-free survival was defined as the time from transplant until relapse and/or death due to any cause, whichever occurred first. The CIN of ANC, platelet engraftments, and relapse was estimated by the method of Kalbfleisch and Prentice [33]. The CIN of neutrophil and platelet engraftment was defined as the time from transplant until engraftment. The CIN of relapse was defined as the time from transplant until relapse with deaths due to non-relapse as competing risk events. All surviving participants without relapse were censored at the time of the last follow-up for CIN of relapse. Statistical analyses were performed with R Software version 2.15.1 (R Core Development Team, Vienna, Austria).

RESULTS

Patients and treatment

Fifteen patients with high-risk hematologic malignant neoplasms were enrolled and received therapy on the study at St. Jude Children's Research Hospital between March 2009 and July 2011. The patient characteristics are summarized in Table 1. Eight of the 15 patients were receiving a second transplant as a result of the persistence ($n = 1$) or recurrence ($n = 7$) of their disease, despite their having received a prior allogeneic transplant. These patients had received their first transplant at a median of 18 months before enrollment (range, 6–45 months). Two patients had received their initial HCT from a matched sibling donor, four from a matched unrelated donor, one from a mismatched unrelated cord-blood donor, and one from a mismatched related donor. The average blast percentage in the pretransplant bone marrow aspirate of the patients with leukemia was 20% by morphology (range, 0%–90%). Of the four patients who were in their first complete remission (CR) at the time of transplant, one experienced initial induction failure but entered remission after a fourth induction course. The other three patients had therapy-related leukemia after receiving prior sarcoma therapy.

Hematopoietic recovery

All 14 patients who received a transplant experienced rapid and complete donor engraftment. The median times to neutrophil and platelet engraftment were 11 days (range, 9–13 days) and 16 days (range, 13–25 days), respectively (Fig. 1). All patients exhibited donor chimerism of more than 99% in their post-engraftment bone marrow aspirate. No patient received a progenitor cell boost, and no patient received a donor leukocyte infusion for mixed chimerism or secondary graft failure.

Determination of MTD and DLT

The first three patients enrolled on the study received clofarabine at dose level 1 ($40 \text{ mg/m}^2/\text{dose} \times 5 \text{ doses}$). None of these patients experienced a DLT, which allowed dose escalation to level 2 ($45 \text{ mg/m}^2/\text{dose} \times 5 \text{ doses}$). The first patient enrolled at dose level 2 experienced a DLT starting on day 24 after transplant. The rapidly progressive pulmonary failure in this patient was confirmed on autopsy to be pulmonary VOD (grade V). After the next two patients had received transplants at this dose level without experiencing a DLT, an additional

three patients were enrolled for a total of six patients on dose level 2. Because only one of the six patients on dose level 2 experienced a DLT, the MTD was not reached and the dose was escalated to dose level 3 (50 mg/m²/dose × 5 doses). As there were no plans to escalate above dose level 3, six patients were enrolled at this dose. The fifth patient enrolled at dose level 3 experienced a DLT (capillary leak syndrome, grade IV) after receiving a single dose of clofarabine. This patient was unable to proceed with a transplant while enrolled on the study as a result of their poor clinical condition. No other patient experienced a DLT at this dose level. Therefore, the MTD for clofarabine in combination with thiotepea and melphalan in a CD3⁺-depleted haploidentical donor transplant was not reached.

Regimen-related toxicity and GvHD

All 15 patients enrolled on the study experienced AEs of at least grade III, with one of the patients experiencing an AE of maximum grade IV and two others experiencing AEs of maximum grade V. Table 2 summarizes the most common and notable toxicities observed in this study. There was no apparent association between the toxicities observed and the escalation of clofarabine dosing.

Fever and mucositis were the most common nonhematologic toxicities observed. Thirteen of the 15 patients (86.7%) experienced a transient rise in transaminases (grade I–II: n=7; grade III: n=6), all of which resolved spontaneously. Five patients developed a rash (grade I–II: n=3; grade III: n=2), but none of them had classic hand/foot syndrome. Two patients developed peripheral neuropathy (grade II and III in one each) at 2 weeks and 2 months post transplant, respectively, and both responded well to gabapentin therapy. Only one patient (on dose level 2) with a prior history of anoxic brain injury developed central nervous system toxicity (grade II encephalopathy), characterized by confusion and somnolence on day +81 after transplant, which completely resolved within a few days with supportive care. This contrasts with the severe neurologic impairment seen with fludarabine toxicity [34]. No other significant neurotoxicity was observed in this study.

Three patients met the criteria for hepatic VOD. VOD was diagnosed in one patient on dose level 2 (patient #8, grade III) on day 8 post transplant. The total bilirubin of that patient peaked at 4 mg/dL and recovered fully with defibrotide therapy. A second patient on dose level 2 (patient #9, grade III) met the criteria for VOD more than 4 months after transplant. The VOD did not resolve after a course of defibrotide treatment, and this patient subsequently died of multiple organ failure. The hepatic dysfunction was at least partially related to a known *Bacillus* infection and GvHD. A third patient on dose level 3 (patient #14, grade III) met the criteria for hepatic VOD 19 days after receiving a single dose of clofarabine and experiencing capillary leak syndrome. The etiology of the clinical signs of VOD in this patient was in part cardiogenic, although the signs resolved during defibrotide treatment.

Of the 14 patients who proceeded to transplant, four developed grade II–IV GvHD (grade II: n = 3; grade IV: n = 1). Five patients developed chronic GvHD (transitional in three cases, de novo in two other cases); four were limited and one extensive (skin only) GvHD. None of the survivors has active GvHD.

Outcomes

The 14 patients who received a transplant had an OS of $25.7\% \pm 12.3\%$ at 2 years post transplant (Fig. 2A). Four patients remain alive more than 5 years post transplant. Three of the four long-term survivors received clofarabine at dose level 3, and three of the four were in remission at the time of transplant (Table 3). One long-term survivor (patient #11) experienced relapse at day +189 but remains alive and in remission after two subsequent transplants.

Recurrent/refractory disease was the most common cause of treatment failure. The primary cause of death in eight of the 10 patients who expired was recurrent/refractory disease. One patient did not achieve remission, and a further eight patients experienced relapse at a median of 133 days after transplant (range, 33–383 days) (cumulative incidence of relapse/progression: $64.3\% \pm 2.0\%$ at 2 years) (Fig. 2B). The patient who did not proceed to transplant because they developed capillary leak syndrome eventually stabilized and received an allogeneic transplant 3 months later, but they eventually died of progressive disease.

Transplant-related death occurred in two patients, both of whom received level 2 clofarabine dosing. The first patient experienced a DLT and eventually died on day +53 as a result of pulmonary VOD. The second patient died of multiple organ failure on day +184, after a complicated disease course that included grade IV acute GvHD and multiple infections.

DISCUSSION

Allogeneic HCT remains the recommended therapeutic approach for relapsed and refractory malignant hematologic neoplasms [35]. However, many patients are unable to receive further myeloablative chemotherapy or a subsequent HCT because of their poor clinical status, accumulated toxicities from previous therapy, and resistant disease burden [5,6,10–16]. Outcomes remain poor in those patients who do receive allogeneic HCTs for refractory or resistant malignant hematologic neoplasms, with disease relapse and treatment-related mortality occurring in more than 40% of patients and long-term LFS being less than 30%, even in contemporary studies [5,10–16]. We developed a novel reduced-intensity regimen by substituting clofarabine for fludarabine in our well-established T cell-depleted, haploidentical HCT backbone and explored the MTD of clofarabine in this regimen. A similar conditioning regimen consisting of clofarabine, thiotepe, and melphalan was also recently described by investigators from Memorial Sloan Kettering Cancer Center (MSKCC), where 18 patients who had experienced relapse after undergoing an earlier HCT received a matched related or unrelated donor HCT [36]. In the MSKCC series, most of the included patients were older than 18 years and clofarabine was administered at 20–30 mg/m²/dose for 5 days—a dose lower than those used in this phase I study.

Clofarabine undergoes phosphorylation intracellularly [37] and inhibits DNA synthesis and repair in its triphosphate form [37,38]. It also directly induces apoptosis by altering the mitochondrial transmembrane potential and the subsequent release of cytochrome c, apoptosis-inducing factor (AIF), apoptosis protease-activating factor 1 (Apaf-1), and caspase 9 [39]. Inhibition of DNA synthesis and induction of apoptosis are believed to be

mechanisms underlying the potent anticancer activity of clofarabine. Adding clofarabine to melphalan and thiotepe potentiates their antileukemic and myeloablative properties without creating an overlapping toxicity profile. Fludarabine is a critical component of successful submyeloablative regimens because of its immunosuppressive properties, and it has been suggested that clofarabine is even more immunosuppressive than fludarabine [28,29]. The combination of thiotepe and clofarabine with OKT3 induced sufficient immunosuppression for engraftment to be seen consistently at each dose level, indicating that clofarabine facilitates reliable engraftment of T cell–depleted haploidentical donor cell grafts in this patient population.

Clofarabine in combination with thiotepe and melphalan was well tolerated at doses higher than previously reported in this heavily pretreated and high-risk population. Despite the inclusion of heavily pretreated patients on the study, only two (13%) died of treatment-related causes, which is comparable to the 11% treatment-related mortality reported in a cohort of patients from MSKCC who underwent matched-donor HCT with a similar conditioning regimen [36]. The most common toxicities noted were those typically seen after allogeneic transplant, such as fever, nausea, and pain. Transient elevation of transaminases is a common clofarabine-induced toxicity [27] and was seen in almost all the patients included in this study; however, grade III elevation of transaminases was seen in only 40% of patients in our cohort, as compared to almost 80% of patients who experienced grade III or IV elevation of transaminases in the MSKCC study [36]. There was no apparent dose effect on the incidence or severity of this or any other toxicity. Other toxicities previously associated with clofarabine, such as neuropathy, hand/foot syndrome, and renal insufficiency, were not seen to any significant degree in the study patients [30]; neither was there any significant neurotoxicity attributable to clofarabine. Hepatic VOD did occur in three patients, but this incidence is clinically acceptable and expected in this heavily pretreated group. Two patients experienced a DLT: one patient on dose level 2 and one after receiving only a single dose of clofarabine on dose level 3. The MTD was not reached in this study.

Unfortunately, the relapse rate remained very high despite the use of clofarabine in this regimen. Being in remission at the time of transplant is associated with improved leukemia-free survival [5] and, fortuitously, more patients on dose level 3 in this cohort were in CR at the time of transplant, which may account for the appearance of better disease control in those patients. Not surprisingly, only one of the eight patients with active chemoresistant disease at the time of transplant is a long-term survivor, indicating that regimen intensification with the substitution of clofarabine is not sufficient to overcome this well described poor prognostic factor. Notably, three of the six patients who underwent a transplant while in CR have survived.

In conclusion, the use of clofarabine at 50 mg/m²/day for 5 days (for a cumulative dose of 250 mg/m²) in combination with two alkylating agents, thiotepe and melphalan, was well tolerated in this heavily pretreated patient population. The regimen was effective in facilitating full engraftment with T cell–depleted HLA-mismatched related donor grafts. There is some suggestion that higher doses of clofarabine exerted more disease control than did lower doses, but an additional study in a larger group of patients will be needed to

adequately explore this possibility. We conclude that clofarabine should be administered at 50 mg/m²/day when combined with thiotepe and melphalan to treat children with high-risk hematologic malignant neoplasms who are undergoing a hematopoietic cell transplantation.

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Figure 1.
Neutrophil and platelet engraftment after transplant.

Figure 2. Event-free survival, leukemia-free survival, and overall survival (A) and cumulative incidence of relapse (B) after transplant.

TABLE 1

Patient and transplant characteristics

Age		
Median (range)	9 y 8 m	(1 y 11 m–18 y 0 m)
Sex		
Male	9	(60%)
Female	6	(40%)
Race		
Caucasian	9	(60%)
Non-Caucasian	6	(40%)
African	3	
Asian	1	
Mixed	2	
Disease		
ALL	5	(33%)
B cell	4	
T cell	1	
AML	7	(47%)
de novo	3	
Therapy related	3	
MDS related	1	
Mixed phenotype	2	(13%)
Burkitt lymphoma	1	(7%)
Disease stage		
CR1	4	(27%)
Subsequent CR	2	(13%)
Active relapse	8	(53%)
Induction failure	1	(7%)
Transplant		
First	7	(47%)
Second	8	(53%)
HLA match status (n of 6) *		
3	11	(79%)
4	2	(14%)
5	1	(7%)
Donor *		
Father	7	(50%)
Mother	6	(43%)
Uncle	1	(7%)

Donor CMV status*		
Positive	9	(64%)
Negative	5	(36%)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CMV, cytomegalovirus; CR, complete remission; MDS, myelodysplastic syndrome.

* HLA match status, Donor and Donor CMV status is only shown for the 14 patients who underwent transplantation (One patient did not undergo transplantation).

TABLE 2

Distribution of common and notable toxicities at different dose levels

	Dose level 1 N = 3	Dose level 2 N = 6	Dose level 3 N = 6*	Total N = 15*
Fever	3	6	5	14 (93%)
Mucositis	2	5	4	11 (73%)
Pain	1	5	4	10 (67%)
Bacteremia	1	5	2	8 (53%)
ALT elevation (Grade III)	1	4	1	6 (40%)
Vomiting	3	3	1	7 (47%)
Hypoxia	1	3	2	6 (40%)
Rash	1	4	0	5 (33%)
Hepatic VOD	0	2	1	3 (20%)
Neuropathy	0	1	1	2 (13%)
Pulmonary VOD	0	1 [#]	0	1 (7%)
Capillary leak	0	0	1 [#]	1 (7%)
Renal failure	0	1	0	1 (7%)

The numbers indicate the number of patients who experienced the toxicity.

* One patient received only a single dose of clofarabine.

[#] Dose-limiting toxicity.

ALT, alanine aminotransferase.

TABLE 3

Specific patient characteristics and outcomes

UPN	Disease	Stage	Pre-HCT disease (%)		# HCT	DLT	Outcome, cause of death if deceased
			Morphology	MRD			
Dose level 1							
1	Burkitt	Relapse 1	N/A	N/A	1	No	Deceased, relapse
2	AML-M7	Relapse 1	89	89	2	No	Deceased, relapse
3	T ALL	Relapse 2	78	64	2	No	Deceased, relapse
Dose level 2							
4	AML-M4	Relapse 2	88	85	2	Yes	Deceased, TRM
5	Mixed phenotype	Relapse 1	90	90	1	No	Deceased, relapse
6	AML-M7	Relapse 1	45	25	2	No	Deceased, relapse
7	tx-Pre-B ALL	CR1	3	<0.01	1	No	Deceased, relapse
8	Pre-B ALL	Relapse 2	76	>90	2	No	Alive
9	Pre-B ALL	CR3	NED	N/A	2	No	Deceased, TRM
Dose level 3							
10	MDR-AML	PIF	10	7	1	No	Deceased, relapse
11	Mixed phenotype	CR1	NED	<0.1	1	No	Alive
12	tx-AML	CR1	NED	N/A	1	No	Alive
13	tx-AML	CR1	1	<0.01	1	No	Deceased, relapse
14*	tx-AML	Relapse 2	14	17	2	Yes	Deceased, relapse
15	Pre-B ALL	CR2	NED	N/A	2	No	Alive

* Received only a single dose of clofarabine and did not proceed to transplant because of poor clinical condition.

DLT, dose-limiting toxicity; NED, no evidence of disease; MDR-AML, MDS-related AML; MRD, minimal residual disease; PIF, primary induction failure; tx-AML, treatment-related AML; tx-Pre-B ALL, treatment-related Pre-B cell ALL; UPN, unique patient number.