Bone Marrow Transplantation (2014) **49,** 440–442

www.nature.com/bmt

ORIGINAL ARTICLE

A clofarabine-based bridging regimen in patients with relapsed ALL and persistent minimal residual disease (MRD)

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In patients with relapsed ALL, minimal residual disease (MRD) identified prior to allogeneic hematopoietic cell transplantation (HCT) is a strong predictor of relapse. We report our experience using a combination of reduced-dosing clofarabine, CY and etoposide as a 'bridge' to HCT in eight patients with high risk or relapsed ALL and pre-HCT MRD. All patients had detectable MRD (>0.01%, flow cytometry) at the start of therapy with all eight achieving MRD reduction following one cycle. The regimen was well tolerated with seven grade 3/4 toxicities occurring among four of the eight patients. Five patients (62.5%) are alive, one died from relapse (12.5%) and two from transplant-related mortality (25%). The combination of reduced-dose clofarabine, CY and etoposide as bridging therapy appears to be well tolerated in patients with relapsed ALL and is effective in reducing pre-HCT MRD.

Bone Marrow Transplantation (2014) **49,** 440–442; doi:10.1038/bmt.2013.195; published online 9 December 2013

Keywords: ALL; MRD; pediatric; transplantation; clofarabine; leukemia

INTRODUCTION

Improvements in the treatment of children with ALL have resulted in 5-year OS approaching 90%.[1] However, those with relapsed disease continue to respond poorly to traditional salvage approaches, with survival rates hovering around 35–40%.[2] Although allogeneic hematopoietic cell transplantation (HCT) in children with relapsed ALL has the ability to overcome resistant disease and cure some patients, relapse remains a significant barrier to success. Recent studies show that identifying minimal residual disease (MRD) prior to HCT is the strongest predictor of treatment failure.[3–8] Whether eliminating MRD prior to HCT will influence post-HCT outcomes, particularly with regard to reducing relapse, has not yet been established. However, this approach is not without risks, as additional chemotherapy in patients who have already achieved remission could lead to toxic complications that may preclude proceeding to HCT or increase peri-transplant toxicity. Also, in prolonging the time to HCT for further chemotherapy, patients may lose their state of remission and increase their disease burden, rather than decrease it. Despite these uncertainties, there is a strong sense among the pediatric oncology and transplant communities that attempts to eliminate MRD prior to HCT are warranted.[9]

Clofarabine, a novel purine nucleoside analog granted accelerated FDA approval in 2004 for pediatric relapsed/refractory ALL, has reported promising results as a single agent or part of a multi-drug regimen with cyclophosphamide (CY) and etoposide.[10–12] Although clofarabine combinations have shown encouraging rates of CR in heavily pre-treated relapsed/refractory patients,[11,12] significant toxicities exist that appear to be dose dependent.[13] In an attempt to reduce and/or eliminate pre-HCT MRD without inducing significant toxicities, we treated eight consecutive patients with reduced dosing of clofarabine, CY and etoposide. The goal of this therapy was to 'bridge' patients to HCT. This case series describes the impact of this bridging therapy approach on toxicity, clearance of MRD and transplantation outcomes in children with relapsed ALL and pre-HCT MRD.

MATERIALS AND METHODS

This bridging regimen was selected specifically for patients with relapsed or very high-risk ALL who had received a median of 3 (range, 2–3) blocks of prior re-induction/consolidation therapy and were proceeding to HCT in morphologic remission but with persistent disease identified by multiparameter flow cytometry (>0.01% leukemia). This report of a case series as determined by the participating institution's review boards did not meet the regulatory definition of research and institution's review board's review as it is a discussion of a course of therapy for a small group of patients with all data de-identified and therefore the patient's permission to use the data was not required. The goal of the therapy was to safely reduce or eliminate MRD in patients without causing significant toxicity and with all patients proceeding to HCT following this course of therapy. Eight patients meeting the above characteristics were treated at our institutions between 2011 and 2013 (Table 1). The median age was 12.5 years (range, 23 months to 20 years). Three patients were evaluated for HCT in CR1 for persistent MRD (Patients 2, 3, 6), three patients had early BM relapses and were in CR2 at the time of HCT with persistent MRD (Patients 1, 4, 5), one patient had a late marrow relapse and in CR2 at the time of HCT with persistent MRD (Patient 8) and the remaining patient (Patient 7) had Ph chromosome positive ALL (CR2) with persistent MRD after failing a prior HCT in CR1.

The bridging regimen was developed to reduce the overall toxicity that had been previously reported using clofarabine at 40 mg/m^2 and CY at 440 mg/m^2 [11] through a dose reduction of both of these agents to 30 and 300 mg/m^2, respectively and yet retain the efficacy of this three-drug regimen. While there were mild variations in the bridging therapy dosing based on treating physician discretion, all patients received the three-drug regimen of clofarabine (20–30 mg/m^2 i.v.), CY (300–340 mg/m^2 i.v.) and etoposide (100 mg/m^2 i.v.) for days 1–5. Treatment-related toxicities were

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Received 1 July 2013; revised 6 September 2013; accepted 21 October 2013; published online 9 December 2013

Table 1. Patient characteristics

Patient	*Age*	*Cytogenetics*	*Pre-therapy MRD (%)*	*# Prior therapy courses*	*Post-therapy MRD (%)*	*Clof/Cy/Etop dosing (mg/m²)*	*Graft source*	*Time to HCT (days)*	*Grade 3/4 toxicities*[a]	*Disease status*
1	14 years	del 6	0.18	3	NED	30/340/100	UCB	43	None	Alive
2	23 months	t(4;11q23), *MLL-R*	0.06	3	NED	1/10/3.3[b]	UCB	88[c]	None	Alive
3	17 years	i(7), gain 17p	3.00	3	NED	30/300/100	MSD, PBSC	69	F/N, transient RI, tenosynovitis	Alive
4	5 years	t(11q23;19), *MLL-R*	1.40	3	NED	30/300/100	MUD, BM	41	None	Relapsed/Alive
5	7 years	-X, t(7;11q23)	0.28	2	0.02	30/300/100	UCB	53	Mandibular osteomyelitis	TRM
6	18 years	IKAROS del *loss of CDKN2A*	0.93	3	NED	30/340/100	DUCB	64	Sinusitis, rash (cheeks)	TRM
7	11 years	t(9;22) *Ph+*	0.14	2	0.07	20/340/100	UCB	53	None	Relapsed/Died
8	20 years	47, XY (+21)	0.11	2	NED	30/300/100	MUD	201[d]	Zoster	Alive

Abbreviations: DUCB = double umbilical cord blood; F/N = fever and neutropenia; MSD = matched sibling donor; MUD = matched unrelated donor; NED = no evidence of disease; RI = renal insufficiency; TRM = transplant-related mortality; UCB = umbilical cord blood. [a]Common terminology criteria for adverse events version 4.0. [b]Dosing was in mg/kg. [c]This patient received a second course of bridging therapy while MRD negative as they awaited donor collection for HCT. [d]This patient received ALL maintenance type therapy after bridging treatment and MRD negative secondary to developing zoster and unable to go directly to HCT.

graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0.

RESULTS

This bridging regimen was well tolerated overall with 8/8 patients able to proceed to HCT within a median of 53 days (range, 41–201) from completing the five-day cycle. All patients had evidence of MRD (>0.01%, flow cytometry) prior to bridging treatment. Six (75%) patients became MRD-negative (<0.01% leukemia) after a single course of treatment with the remaining two patients achieving significant reduction of their MRD (0.28%→0.02% and 0.14%→0.07%, respectively). There were seven grade 3/4 toxicities occurring among four patients: one grade 4 (mandibular osteomyelitis) and six grade 3 toxicities (sinusitis, rash, fever/neutropenia, achilles tenosynovitis, zoster and transient renal insufficiency). Importantly, none of the toxicities precluded patients from ultimately proceeding to HCT, however the patient who developed zoster (Patient #8) was delayed due to this infection after achieving MRD negativity with the bridging treatment and received oral chemotherapy (6-mercaptopurine and MTX) while awaiting recovery of the zoster. The median time to neutrophil recovery (ANC >500/μL) for the eight patients was 23.5 days (range, 16–37) from the start of the clofarabine-based regimen and a median of 33 days (range, 17–45) to achieve an ANC >1000/μL.

At the time of this report, four patients (50%) are alive without disease with a median of 217 days from HCT (range, 84 to 360), two patients died without disease (day 37 and 140), one patient died of disease (day 94) and one patient relapsed (day 106) but remains alive. EFS at 1 year for the eight patients was 44% (95% CI 6–81) (Figure 1) with a median EFS time of 140 days post HCT.

There have been two cases of relapse in this cohort of patients. One occurred in a Ph chromosome positive patient (Patient 7) who received the bridging therapy, but remained with persistent MRD prior to HCT, which incidentally was a reduced intensity conditioning regimen and the patient's second HCT. The second relapse occurred in a patient with *MLL* gene rearrangement (Patient 4) who achieved MRD negativity post bridging therapy but subsequently relapsed 106 days post HCT. This patient then received another course of the clofarabine-based bridging regimen resulting in elimination of his disease becoming MRD-negative (4%→<0.01% by flow cytometry) and proceeded to chimeric Ag receptor T-cell therapy.

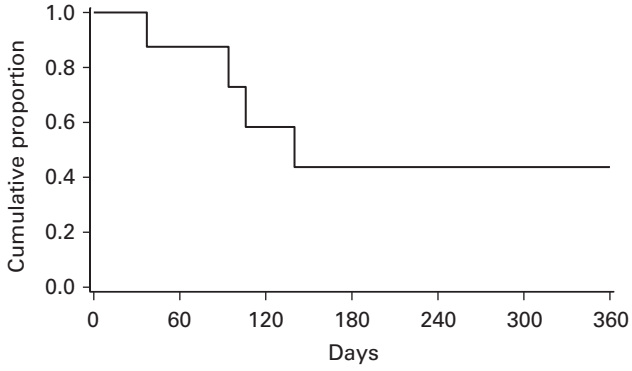

Figure 1. The probability of EFS at 1 year was 44% (95% CI 6–81).

DISCUSSION

Outcomes for patients with relapsed ALL continue to be poor, particularly for patients who have MRD prior to allogeneic-HCT.[3–8] Although consolidative therapy with HCT can cure some patients with persistent MRD,[7,14,15] most studies suggest that the majority of these patients will relapse post HCT.[3,6–8] The idea that leukemia-free survival would be improved if pre-transplant MRD can be eliminated has scientific rationale, but the theory has not been formally tested. Whether pre-HCT MRD represents a patient who is inadequately treated, or one who has underlying high-risk biology that is predetermined to fail HCT, is currently unknown. In this case series, we demonstrate that lower doses of clofarabine, CY and etoposide can reduce pre-HCT MRD (eliminating MRD in 75% of patients), maintaining a limited toxicity profile, and successfully bridge patients to allogeneic-HCT. Alternative approaches to bridging therapies may include immunotoxins (for example, moxetumomab pasudotox targeting CD22) or bi-specific T-cell engagers (for example, blinatumomab targeting

CD19/CD3) which would be more selective and potentially more tolerable than traditional chemotherapy options.

Although this report is small in scope but typical for a case series, the results are promising and show the possibility of MRD being a reversible risk factor and less of a biomarker for predefined treatment failure since our pre-HCT MRD-positive patients behaved more like MRD-negative patients after receiving bridging therapy with a relatively low relapse rate of 25%. This relapse rate is strikingly less than what would be predicted for pre-HCT MRD positive patients (relapse rate of 50–60%), and more in line with patients who were MRD-negative.[3,4,6–8] Further study of this bridging therapy combination is necessary to characterize the toxicities, as well as the ability to reduce/eliminate MRD prior to HCT and ensure that leukemia-free survival remains improved. Based on this anecdotal experience, a pilot study using this bridging regimen has been opened at the University of Minnesota for patients (ages 0–60 years) with ALL or AML proceeding to HCT who are in morphologic remission but have evidence of persistent disease identified by flow cytometry. Results from this study as well as others will be critical in providing further data regarding the feasibility and efficacy of this approach for patients with acute leukemia and persistent MRD prior to HCT.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Children's Cancer Research Fund (MJB, MRV) and the University of Minnesota Pediatric Leukemia Program supported this work.

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