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To the editor:

Improved outcomes associated with hematopoietic stem cell transplantation for patients with juvenile myelomonocytic leukemia

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only reported cure for juvenile myelomonocytic leukemia (JMML).[1] However, HSCT outcomes remain suboptimal with only 50% event free survival at 5 years.[1,2] We conducted a retrospective study of 7 consecutive children who were diagnosed with JMML[3] and underwent an allogeneic HSCT at Children's Hospital Los Angeles between 2007 and 2014. Approval was obtained from the hospital's Institutional Review Board and the study was conducted in accordance with the Declaration of Helsinki.

Five patients (Table 1) received pre-HSCT therapy. The median patient age at HSCT was 2.6 years. All patients received backbone conditioning with BuMel; Bu 1 mg/kg dose every 6 hours IV on days −8 to −5 (with therapeutic drug monitoring to achieve overall concentration steady state [CSS] of 800-1000 ng/mL) and Mel 45 mg/m^2 per day IV on days −4 to −2. Two patients who received a 10/10 (HLA-A, B, C, DRB1, DQ) histocompatible related BM graft, were conditioned with BuMel only. One patient who received a 9/10 histocompatible related BM graft received BuMel and Flu 35 mg/m^2 per day IV on days −7 to −4; 1 patient who received a 9/10 MUD graft received BuMel and Alem 12 mg/m^2 IV on day −10 and 20 mg/m^2 on day −9. Methylprednisolone was administered at 2 mg/kg per day in divided doses during the Alem infusion. Three patients who received UCB grafts received BuMel and rATG 2.5 mg/kg per day IV on days −4 to −1. Methylprednisolone was administered at 2 mg/kg per day in divided doses during rATG infusion, and thereafter tapered over 6 weeks. All patients received tacrolimus for graft-versus-host disease (GVHD) prophylaxis. Methotrexate was also administered at 5 mg/m^2 dose on days 3, 6, and 11 to all patients, except UCB recipients. Standard supportive care guidelines were followed.[4]

The median (range) Bu CSS and area under the curve were 884 (560-1096) μg/L and 1293 (819-1601) μmol/L-minute, respectively. The median total nucleated cell count and CD34 cell dose were 4.2×10^8 cells per kg and 3.3×10^6 cells per kg, respectively. The median time to neutrophil engraftment (≥500/mm^3) and platelet engraftment (≥20 000/mm^3) was 20 and 36 days, respectively. Six (85.7%) patients achieved predominant (>95%) donor hematopoietic stem cell engraftment. One patient (#6) who received a UCB HSCT had autologous recovery at day +54; she received a related-haploidentical HSCT on day +105. At 100 days post–haploidentical HSCT, she is alive and in remission, with predominant donor chimerism. Another patient (#2) who received an MMSD HSCT developed grade 4 acute GVHD and later developed severe chronic GVHD, requiring bowel resection. This patient (#2) and patient #4 developed severe sinusoidal obstructive syndrome, which resolved with supportive care. At a median (range) length of follow-up of 25.3 (6-99.3) months, 100% of patients are alive and in clinical remission.

There is currently no standard conditioning regimen for children with JMML undergoing HSCT. In the largest clinical trial of patients with JMML given a uniform conditioning regimen, children received myeloablative doses of Bu (16-20 mg/kg orally over 4 days), cyclophosphamide (120 mg/kg over 2 days), and Mel (140 mg/m^2). The 5-year cumulative incidence of transplant-related mortality (TRM) and leukemia recurrence was 13% and 35%, respectively, and one-third of patients relapsed at a median time of 6 months post-HSCT.[1] Similar TRM and relapse rates were also recently reported among patients with JMML who received a myeloablative regimen of Bu (oral or IV), Mel (total dose 210 mg/m^2), and Flu (patients in our cohort received a total dose of Mel at 135 mg/m^2).[5]

It is possible that our target Bu CSS contributed to improved outcomes (decreased graft failure and TRM compared with prior reports with oral Bu and/or no therapeutic drug monitoring). It is also possible that administration of pre-HSCT chemotherapy to patients with more progressive disease may have contributed to improved outcomes. Among our patients, we did not observe any TRM. The BuMel backbone regimen was used to avoid total body irradiation (and its potential associated late effects especially among younger children who are often diagnosed with JMML). With no TRM and 100% of patients alive and in remission, we believe that BuMel may represent a successful conditioning strategy for patients receiving both conventional and alternative donor HSCT. A prospective clinical trial is warranted to confirm these promising findings.

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Table 1. Patient pre-HSCT characteristics and HSCT and clinical variables

Pt#	Age at Dx	Age at HSCT	WBC ($\times 10^9$/L)	Mono (K/μL)	Plt (K/μL)	HbF (%)	PB blast (%)	BM blast (%)	Pre-HSCT chemo	Cytogenetics mutation	Sex (R/D)	ABO (R/D)	CMV (R/D)	Regimen	Graft type	ANC >500 ($\times 10^9$/L)	Plt >20 (K/μL)	Donor chimerism (%)	F/U (mo)	Alive
1	0.6	0.8	60.0	16.8	89.0	18.0	5.0	8.0	6-MP* Flu, Ara-C *cis*-R	47,XX Extra ring chromosome 3 NF1	F/F	A+/O+	−/M+	BuMel/ rATG	4/6 UCB	16	16	100	99.3	Yes
2	4.0	4.2	30.4	2.4	37.0	52.0	3.0	9.0	None	46,XX None	F/M	A+/O+	−/−	BuMel/Flu	9/10 MMSD	17	93	100	83.9	Yes
3	0.5	1.2	36.3	9.8	44.0	7.7	2.0	6.0	6-MP*	46,XY None	M/F	A+/O+	−/M+	BuMel/ rATG	5/6 UCB	27	133	96	41.9	Yes
4	1.7	2.5	25.3	2.8	110.0	0.5	2.0	3.0	6-MP*	46,XX None	F/F	O+/O+	+/−	BuMel	10/10 MSD	25	49	99	25.3	Yes
5	0.8	3.8	130.0	27.3	43.0	4.8	4.0	5.0	HU* 6-MP	46,XY None	M/F	A+/A+	+/+	BuMel	10/10 MSD	15	18	100	9.1	Yes
6	1.4	2.2	20.0	1.1	19.0	7.6	2.0	3.0	None	46,XX PTPN11†	F/F	O+/O+	−/M+	BuMel/ rATG	6/6 UCB	N/A	N/A	6	7.9	Yes
7	2.5	3.2	38.9	2.0	22.0	42.2	6.0	3.0	6-MP*	46,XY PTPN11†	M/M	B+/B+	+/+	BuMel/ Alem	9/10 MUD	22	23	100	6.0	Yes

ABO, ABO blood group system; Alem, alemtuzumab; ANC, absolute neutrophil count; Ara-C, cytarabine; BM, bone marrow; BuMel, busulfan and melphalan; *cis*-R, cis-retinoic acid; CMV, cytomegalovirus; D, donor; Dx, diagnosis; F, female; Flu, fludarabine; F/U, follow-up; HbF, fetal hemoglobin; HU, hydroxyurea; M, male; MMSD, mismatched sibling donor; Mono, monocyte; MSD, matched sibling donor; MUD, matched unrelated donor; N/A, not applicable; PB, peripheral blood; Plt, platelet; Pt#, patient number; R, recipient; rATG, rabbit antithymocyte globulin; 6-MP, mercaptopurine; UCB, unrelated cord blood; WBC, white blood cell count.

*Pre-HSCT chemotherapy was administered to patients who had progressive/high WBC (≥35K), pulmonary/respiratory compromise, and/or prominent/progressive organomegaly before proceeding to HSCT.

†Somatic mutation.

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Contribution: Q.Z. assisted with data collection and analysis and manuscript preparation; K.M.M. designed the research, analyzed the data, and wrote the manuscript; and N.K. and H.A.-A. developed the treatment regimen, designed the research, analyzed the data, and wrote the manuscript.

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