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TO THE EDITOR:

Increased incidence of hematologic malignancies in SCD after HCT in adults with graft failure and mixed chimerism

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Two population studies reported an increased risk of hematologic malignancies in patients with sickle cell disease (SCD) compared with the general population.[1,2] Hematopoietic cell transplantation (HCT) is curative for SCD; however, many adults cannot tolerate myeloablative conditioning because of preexisting organ damage. Therefore, we aimed to induce mixed chimerism using nonmyeloablative conditioning.[3] The human leukocyte antigen (HLA)–matched sibling donor (MSD) approach has been efficacious, with 85% SCD-free survival and minimal graft-versus-host disease.[4] Because <15% of patients have an HLA-MSD,[5] we expanded the approach to the haploidentical setting, albeit initially with a high graft rejection rate.[6] Herein, we report the incidence of all hematologic malignancies, including therapy-related myeloid neoplasms (TRMNs), in our patients with SCD who underwent nonmyeloablative allogeneic peripheral blood HCT between September 2004 and December 2020.

All protocols were approved by the National Heart, Lung, and Blood Institute Institutional Review Board (ClinicalTrials.gov identifier NCT00061568, NCT02105766, NCT00977691, or NCT03077542), and all subjects gave written informed consent. Patients undergoing HLA-MSD HCT received alemtuzumab, 300 cGy total body irradiation (TBI), and sirolimus with or without pentostatin and oral cyclophosphamide (PC) preconditioning (Table 1). Patients who underwent haploidentical HCT received alemtuzumab, 400 cGy TBI, and sirolimus with or without posttransplant cyclophosphamide (up to 100 mg/kg) and PC preconditioning. The patients' hematologic malignancy status and clinical course were obtained by reviewing their medical records.

Of our 120 patients who underwent allogeneic HCT for SCD, 81 received HLA-MSD and 39 received haploidentical HCT. The median (range) of their ages was 31 (10-64) and 32 (19-51) years, respectively. Eight patients aged between 19 and 53 years at HCT developed hematologic malignancies between 4 months and 9 years post-HCT (Table 1); all except 1 had homozygous SCD. Five received HLA-MSD and 3 received haploidentical HCT. Five developed aggressive TRMN, all deceased: 3 acute myeloid leukemia and 2 myelodysplastic syndrome. All 5 patients developed TRMN in the setting of persistent autologous hematopoiesis: 4 patients rejected their grafts, and 1 had low donor myeloid chimerism levels associated with the return of SCD.[7,8] Three living patients with mixed chimerism developed other hematologic malignancies: 1 T-cell acute lymphoblastic leukemia, 1 chronic myeloid leukemia, and 1 mantle cell lymphoma (Table 1).

The incidence of hematologic malignancies using our allogeneic regimen is compared with 3 other cohorts in Table 2. Starting with the cohorts that employed one of our conditioning regimens, 2 patients developed TRMN on HLA-MSD protocols, with incidence ranging from 1.8% to 4.2% and follow-up ranging from 4.0 to 9.1 years after HCT. Our HLA-MSD protocol adopted in Chicago, IL, and Riyadh, Saudi Arabia, is also shown: 1 of 64 patients (1.6%) developed TRMN with a median follow-up of up to 4 years.[4] Three of 21 patients (14.3%) developed TRMN on our original haploidentical HCT protocol at a median follow-up of 8.4 years. On the newer haploidentical HCT protocol, which includes PC preconditioning, no patients have developed TRMN, with a median follow-up of 2.6 years. Of note, 1 patient received haploidentical HCT in the study as part of both protocols (Table 2).

The higher incidence of TRMN in our patients (5 of 120 patients [4.2%]) is comparable to the rate of TRMN development 3 to 5.5 years after gene therapy with myeloablative busulfan for SCD (2 of 47 patients [4.3%], aged 25-42 years).[9-11] In contrast, a large multicenter study based on data reported to the Center for International Blood and Marrow Transplant Research included 908 patients with SCD: 74% were aged <18 years, and 53% received myeloablative conditioning with a goal of full donor chimerism. In addition, 61% had HLA-MSD, and 15% had haploidentical donors. The incidence of TRMN was much lower (2 of 908 patients [0.22%]; Table 2).[12] In addition, a recent French study included 234 patients with a median age of 8.4 years who underwent myeloablative HLA-MSD HCT.[13] Although 79 patients (34%) developed mixed chimerism, no TRMN was reported, with a median follow-up of just <8 years.

Others have reported a higher risk of hematologic malignancies in patients with SCD who do not undergo HCT.[1,2] In 6423 patients with SCD compared with the general population with 27 years of data, individuals with SCD were 1.7 times more likely to develop hematologic malignancies.[2] However, only

Table 1. Demographic and clinical information for patients with SCD who developed hematologic malignancies after allogeneic HCT

Patient No.	SCD type	Age at HCT, y/sex	SCD comorbidities	HCT type	TBI dose, cGy	PC	PT-Cy dose, mg/kg	Cytos pre-HCT	Day of graft failure	Malignancy	Time of malignancy dx post-HCT, y	Cytos and bone marrow blasts at malignancy dx	DMC at dx	DLC at dx	Current status
1	HbSS	37/male	Recurrent VOC Chronic pain	HLA matched	300	No	0	Normal	183	MDS	2.5	Complex <5%	0	0	Dec
2	HbSS	19/male	Priapism ACS	HLA matched	300	No	0	Normal	N/A	CML	3.5	46XY, t(2, 9, 22), *BCR/ABL1* p210 fusion <5%	39	59	Alive
3	HbS-β^0thal	53/male	TRV 3.2 m/s	HLA matched	300	No	0	ND	N/A	MCL	9	Monosomy 13, 11q deletion and t(11;14) <5%	89	73	Alive
4	HbSS	34/male	TRV 2.5 m/s Priapism ACS Recurrent VOC	HLA matched	300	Yes	0	Normal	74	AML	0.33	Complex 15%-20%	16	18	Dec
5	HbSS	39/female	Silent infarct ACS TRV 2.8 m/s SCD-associated liver disease	HLA matched	300	Yes	0	Normal	N/A	T-cell ALL	3	46XX, t(9:22)[18]/46,XY[2] *BCR/ABL1* p190 fusion 93%	30	25	Alive
6	HbSS	37/male	Stroke CRI Recurrent VOC	Haplo	400	No	100	Normal	73	MDS	2	Complex <5%	0	0	Dec
7	HbSS	20/female	Recurrent VOC ACS SCD-associated liver disease Chronic pain	Haplo	400	No	100	Normal	90	AML	5.5	Complex 20%	0	0	Dec
8	HbSS	44/female	ESRD pHTN Diastolic dysfunction	Haplo	400	No	0	Normal	7 mo	AML	5	7q deletion 10%-15%	0	0	Dec

ACS, acute chest syndrome; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CRI, chronic renal insufficiency; Dec, deceased; DLC, donor lymphoid chimerism; DMC, donor myeloid chimerism; dx, diagnosis; ESRD, end-stage renal disease; Haplo, haploidentical; HbS-β^0thal, compound heterozygosity for hemoglobin S and β 0 thalassemia; HbSS, homozygous SCD; MCL, mantle cell lymphoma; MDS, myelodysplastic syndrome; N/A, not applicable; ND, not done; pHTN, right heart catheterization-documented pulmonary hypertension; PT-Cy, posttransplant cyclophosphamide; t, translocation; TRV, tricuspid regurgitant velocity; VOC, vaso-occlusive crises.

Table 2. Comparison of hematologic malignancy incidence for patients transplanted using our regimens vs other conditioning regimens

	NHLBI HLA matched			NHLBI haploidentical		Gene therapy	French group	CIBMTR
Conditioning	Alemtuzumab 300 cGy TBI	Pentostatin/Cy alemtuzumab 300 cGy TBI	(Chicago, IL, and Riyadh, Saudi Arabia) alemtuzumab 300 cGy TBI	Alemtuzumab 400 cGy TBI ± PT-Cy	Pentostatin/Cy alemtuzumab 400 cGy TBI PT-Cy	Busulfan	Cy ± ATG busulfan	Cy ± ATG busulfan (mostly)
No. enrolled in study	57	24	64	21*	19*	47	234 (79 with mixed chimerism long-term)	908†
TRMN (MDS, AML), No. (%)	1 (1.8)	1 (4.2)	1 (1.6)‡	3 (14.3)	0	2 (4.3)	0	2 (0.22)†
Hematologic malignancies (including TRMN), No. (%)	3 (5.3)	2 (8.3)	1 (1.6)‡	3 (14.3)	0	2 (4.3)	1 (0.4)	3 (0.33)†
Median time to hematologic malignancy development, y	3.5	1.7	3	5	N/A	4.3	6	1
No. deceased from hematologic malignancies	1	1	0	3	0	2	?	?
Graft status	1 Graft failure, 2 mixed chimerism	1 Graft failure, 1 mixed chimerism	1 Graft failure	3 Graft failure	N/A	Group A	?	?
Median follow-up, y	9.1	4.0	4	8.4	2.6	?	7.9	2.1-3.9
Therapeutic goal	Mixed chimerism	Mixed chimerism	Mixed chimerism	Mixed chimerism	Mixed chimerism	Gene-corrected autologous HSPCs	Full donor chimerism	Full donor chimerism

AML, acute myeloid leukemia; ATG, antithymocyte globulin; CIBMTR, Center for International Blood and Marrow Transplant Research; Cy, cyclophosphamide; HSPC, hematopoietic stem and progenitor cells; MDS, myelodysplastic syndrome; N/A, not applicable; NHLBI, National Heart, Lung, and Blood Institute; PT-Cy, posttransplant cyclophosphamide; TRMN: therapy-related myeloid neoplasm.

*One patient was transplanted on study for both protocols.

†Two patients transplanted at the NHLBI and who developed therapy-related myeloid neoplasms were included with the NHLBI studies and are not included herein.

‡Incidence of hematologic malignancies and median duration of follow-up are reported from the time of article publication.

31 patients with SCD developed hematologic malignancies over 141 752 person-years (0.021 per 100 person-years). And, 18 individuals without SCD were expected to develop hematologic malignancies over that time frame when controlled for age, sex, race, and ethnicity (0.013 per 100 person-years). Therefore, although the relative risk of hematologic malignancies is higher in SCD, the absolute risk is low. In contrast, 8 of our patients developed hematologic malignancies over 844 person-years (0.94 per 100 person-years). Thus, the rate of hematologic malignancy is ≈45 times higher following HCT for SCD using our approach compared with those with SCD who do not receive curative therapy.

Notably, others have reported adults with graft failure after nonmyeloablative allogeneic HCT for SCD subsequently developing aggressive TRMN.[14,15] Still, the incidence of hematologic malignancies, particularly aggressive TRMN, is higher than expected in our patients after nonmyeloablative allogeneic HCT. Multiple potential reasons exist: First, compared with the Center for International Blood and Marrow Transplant Research and French studies, our patients are older with severe SCD-related complications; both factors have been implicated in increasing the risk of leukemia in individuals with SCD.[2] Second, our patients receive TBI vs chemotherapy-based conditioning and peripheral blood stem cells rather than bone marrow as the hematopoietic cell source. Third, our patients receive alemtuzumab rather than antithymocyte globulin, and per protocol, many remain on prolonged immunosuppression due to mixed chimerism. Last, the goal of our allogeneic HCT regimen has traditionally been mixed chimerism instead of full donor chimerism.

TRMN, arising from autologous hematopoiesis, is a known risk following chemotherapy, radiation, or both,[16-18] with rates of 5% to 10% reported following autologous HCT.[19-22] DNA sequencing of pretreatment samples in those who later developed TRMN after chemotherapy or radiotherapy for solid tumors,[17,18] or after autologous HCT for lymphoma[21] or multiple myeloma,[22] has shown the etiology to most commonly involve the expansion of preexisting clones containing *TP53* during such therapy. The TRMN rates of 5% to 10% following autologous HCT are similar to the 4% rate of hematologic malignancies found in our cohort and following gene therapy for SCD. We recently reported that 2 of our patients with pathogenic *TP53* mutations at TRMN diagnosis had the same *TP53* mutation at baseline,[23] in the context of persistent autologous hematopoiesis. Furthermore, 2 older patients who developed TRMN following gene therapy for SCD were in the first group of the bluebird bio study, where the cell dose was low, and the patients did not experience sufficient therapeutic benefit.[10,11] We postulate that the incidence of hematologic malignancies is higher in older individuals undergoing regenerative hematopoiesis from preleukemic autologous cells exposed to genotoxic HCT conditioning.[9] Interestingly, in younger patients, despite mixed chimerism following myeloablative conditioning, the French study did not report TRMN.[13]

Currently, available data are insufficient to test for potentially preleukemic clones to reassure patients that they will not develop a TRMN, but this is an active area of research. In the interim, patients with SCD should be alerted about the risk of hematologic malignancies after curative therapy, particularly in adults following autologous approaches or allogeneic HCT, which results in mixed chimerism. Furthermore, the decision to move forward should be based on a benefit/risk assessment that includes the risk of dying early from SCD itself.

In conclusion, we report an increased incidence of hematologic malignancies after allogeneic HCT for SCD. Given a likely etiology is selective pressure placed on autologous preleukemic clones in adults with severe disease, we have shifted the therapeutic goal of future regimens for this adult population from mixed chimerism to full donor chimerism. We do not have sufficient evidence to deduce that TBI-based regimens create an added risk for TRMN at this time. However, more evaluation and long-term follow-up are necessary to establish clinical and genetic risk factors and the incidence of hematologic malignancies after all types of curative therapies for SCD.

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Authorship

Contribution: R.A.L., D.M., and L.W.D. performed the data analyses and wrote the manuscript; E.M.L., W.C., and M.M.H. assisted with data collection and reviewed the manuscript; C.S.H. designed the study, analyzed the data, and reviewed the manuscript; and C.D.F. designed the study, analyzed the data, and wrote the manuscript.

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Footnotes

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