TO THE EDITOR:

High incidence of suicidal ideation in a series of patients with sickle cell disease after hematopoietic stem cell transplantation

Adrienne D. Mishkin,1,2 Stephanie G. Cheung,3 Alison Hoffman,1 Elizabeth J. Leimbach,2 Simon Dosovitz,3 and Markus Mapara1

1Blood and Marrow Transplantation and Cell Therapy Program, Division of Hematology & Oncology, Columbia University Irving Medical Center, New York, NY; 2Department of Psychiatry, Columbia University Irving Medical Center, New York, NY; and 3Department of Psychiatry, New York University Langone Medical Center, New York, NY

Sickle cell disease (SCD) is a risk factor for reduced quality of life (QOL), low self-esteem, hopelessness, depression, anxiety, and cognitive impairment.1,2 Estimates of lifetime prevalence of clinical depression in patients with SCD range from 22% to 50% vs overall 13.2% in the United States.1,3 Chronic pain is in a bidirectional relationship with depression, with up to 85% of pain sufferers developing depression4 and depression increasing the risk of developing pain5 and chronic pain increasing the rate of death by suicide.6 Suicidal ideation (SI) and suicide attempts (SAs) are noteworthy phenomena even among patients diagnosed with depression. In general population, estimates of 1-year incidence of SI for younger adults are 6.6% among 18- to 25-year-olds and 4.0% among 26- to 49-year-olds.7 Among people with major depressive disorder, the 1-year incidence rises to 26.3%.7 Depression in SCD is understudied. One study found a 29% lifetime prevalence of SI and 8% lifetime prevalence of SAs among patients with SCD.6 Depression in SCD correlates with poorer adherence, increased days of pain, severity of pain, emergency room visits, and transfusions.1,2,10 Hematopoietic cell transplantation (HCT) is the only cure for SCD.11 In adult patients, stable engraftment and reversal of SCD symptoms are achieved in over 90% of patients receiving matched related donor grafts, with success depending on variables including age, donor type, and conditioning regimen.11 There are very few studies about QOL and none about clinical depression or suicidality in patients with SCD undergoing HCT. However, patients with cancer undergoing HCT report poor QOL, depression, and SI and have an increased rate of death by suicide for years following transplant.12-14 We noted a frequent clinical complaint of SI in our adult patients with SCD and present this case series of SI after HCT.

The Columbia University Institutional Review Board approved this retrospective chart review. Electronic medical records (EMRs) were reviewed to identify all patients diagnosed with SCD who underwent HCT at the Columbia University Medical Center from 2014 to July 2018. We collected demographics, basic transplant data, duration of the initial stay, number of readmissions, and readmission diagnoses from the EMRs. Two psychiatrists (S.M.D. and E.J.L.) independently reviewed all relevant EMRs for 1 year after transplantation. All psychiatry notes explicitly included suicide assessments as part of the standard of care. All episodes of SI or behavior, as evidenced by patient reports, patient-observed behavior, or family report, were identified by our research team. Each patient record was classified by the presence or absence of SI and SA and by the number of days of SI. Each identified episode of SI was classified utilizing the Columbia Classification Algorithm of Suicide Assessment (C-CASA), which categorizes levels of suicide risk and has been found to have excellent inter-rater reliability.15 The C-CASA was applied retrospectively in chart review to classify the intensity of all SI or SA events.15,16 We assessed the incidence of SI in patients with SCD after HCT, compared these rates with their histories of depression, and assessed the demographic and clinical differences between suicidal and nonsuicidal groups. We analyzed by the Fisher exact test (categorical covariates) and Wilcoxon rank sum (continuous variables).
Of the 14 adult patients who were included in the study, 7 were men and 7 were women. Eight were of African or Afro-Caribbean descent, and 6 were of Hispanic descent. Seven patients received matched related donor cells, 6 unrelated donor cells, and 1 had a genetically modified autologous transplant. Successful stable engraftment defined by chimerism and the absence of vaso-occlusive crises was achieved in all 14 patients and 0 had chronic graft-versus-host disease. Hemoglobin S levels decreased either to 0% or equilibrated with the Hemoglobin S trait level of the donor in all patients. Length of stay ranged from 32 to 71 days.

The patients underwent psychosocial clearance by a clinical social worker (14) and a psychiatrist (13). Nine patients had a clinical history of depression, SI, or both. We categorized the patients into binary groups of any history of depression or SI or no history. All 14 patients were psychiatrically stable, with neither SI nor acute major depressive episode at the time of transplant; 4 were on antidepressants. All patients with a psychiatric history were actively followed up by a team psychiatrist (A.D.M.) and all patients had continuous access to psychiatric care (Table 1).

Six patients (42.9%) reported an SI and 1 had an SA within 1 year after HCT, and all patients who reported an SI had a C-CASA classification of “suicidal ideation.” None of the patients died or engaged in other self-injury. There was no relationship between suicidality and gender, age, race, or donor type (Table 1). Of the 5 patients with no history of depression, SI, or SA, none (0%) had an SI in the year after transplantation. Of the 9 patients with any history of depression, SI, or SA, 6 (66.7%) expressed an SI after transplantation. The association between history of depression, SI, or SA with posttransplant SI was highly significant (odds ratio = ∞; P = .0301). Having a history of depression or suicidality before transplantation was associated with an increased number of total pain-related readmissions after transplantation (mean [range], 1.333 [0-3] vs 0 [0-0]; P = .0304) (Table 2).

We found a 43% rate of SI in our case series of patients with SCD in the post-HCT year across age, race, gender, and donor type, despite 100% engraftment. This is higher than that reported in studies on the SI incidence for either SCD or depression.7 There are no published data on SI rate in post-HCT SCD. Contributions may include severe SCD correlating with opting for HCT, worse pain, increased medically related stress immediately after transplantation, and the isolation required during HCT. Given that chronic pain continues for more than a year after transplantation,17 a longer follow-up might reveal an initial period of increased suicidality followed by improvement.18 It concerns us greatly that some patients psychiatrically deteriorated after HCT. Having a history of depression or suicidality correlated with pain readmissions. Our findings raise the question of whether patients are sufficiently emotionally prepared for the post-HCT year, during which pain and depression are likely to continue.

This 14-patient case series was exploratory. The sample size was too small to compare by age, disease burden, and other factors that may be critical. Additional limitations include the retrospective chart review design and the lack of quantitative psychometric scales at evaluation. A retrospective review methodology increases the risk of undercounting events and the total rate of SI might even be higher. We had no available control group and a comparable psychiatric follow-up for non-HCT patients was not uniformly available. There may be unique characteristics about our program, or the patients it attracts and accepts, given the presence of a dedicated niche psychiatrist, which further decreases its generalizability. Strengths included the duration of follow-up, integrated team, thorough review, the inclusion of inpatient and outpatient

| Demographics and transplant details | No post-HCT SI (N = 5) | History of depression or SI (N = 9) | No post-HCT SI (N = 8) | Post-HCT SI (N = 6) |
|-------------------------------------|------------------------|----------------------------------|-----------------------|---------------------|
| **Demographics and transplant details** | Age, mean (range), y | 27.8 (22-35) | 27.4 (18-44) | 27.9 (18-35) | 28.8 (22-44) |
| Gender, n (% of N) | F | 2 (40) | 5 (55) | 4 (50) | 3 (50) |
| | M | 3 (60) | 4 (44) | 4 (50) | 3 (50) |
| **Ethnicity, n (% of N)** | African descent | 4 (80) | 4 (44) | 5 (62.5) | 3 (50) |
| | Hispanic descent | 1 (20) | 5 (55) | 3 (37.5) | 3 (50) |
| **HCT-CI, mean (range)** | 4.4 (3-7) | 4.8 (3-6) | 4.4 (3-7) | 5 (3-6) |
| **Psychiatric history** | History of MDD, SI, or both, n (% of N) | 0 (0) | 9 (100) | 3 (37.5) | 6 (100) |
| | On psychiatric treatment at SCT, n (% of N) | 0 (0) | 4 (44) | 1 (12.5) | 3 (50) |
| **Donor type, n (% of N)** | Matched related, n (% of N) | 4 (80) | 3 (33.3) | 5 (62.5) | 2 (33.3) |
| | Matched unrelated, n (% of N) | 1 (20) | 5 (55) | 3 (37.5) | 3 (50) |
| | Modified auto, n (% of N) | 0 (0) | 1 (11) | 0 (0) | 1 (16.7) |
| | Acute GVHD maximum grade, mean (range) | 1.6 (0-3) | 0.6 (0-3) | 1.3 (0-3) | 0.6 (0-3) |
| | Chronic GVHD, n (% of N) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

GHVD, graft-versus-host disease; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; MDD, major depressive disorder; SCT, stem cell transplant.
There is insufficient research in SCD supporting specific screening, management, and monitoring practices, potentially exacerbating disparities in care. Given longstanding inequities in clinical care and biomedical research for people of African and Afro-Caribbean descent, patients with SCD, and especially those facing multiple layers of inequities, we consider ongoing work in this area to be vital. Our findings require formal prospective consideration for the evaluation of major depression, SI, and SA in post-HCT SCD. We provisionally recommend thorough, universal, and required screening for depression and SI in patients with SCD anticipating transplant and that transplant programs have psychiatrists available for ongoing support.

**Contribution:** A.D.M. designed the research and wrote the manuscript; S.G.C. managed and analyzed the data; A.H. participated in background research and wrote the manuscript; E.J.L. and S.M.D. collected the data; and M.Y.M. participated in data analysis and interpretation, and wrote the paper.

**Conflict-of-interest disclosure:** The authors declare no competing financial interests.

**ORCID profiles:** A.D.M., 0000-0003-4872-7260; S.G.C., 0000-0001-9796-2932.

**Correspondence:** Adrienne Mishkin, Department of Psychiatry, Columbia University Medical Center, 622 W 168th St, PH Center, New York, NY 10032; email: adm2172@cumc.columbia.edu.

**References**

1. Hasan SP, Hashmi S, Alhassen M, Lawson W, Castro O. Depression in sickle cell disease. *J Natl Med Assoc.* 2003;95(7):533-537.
2. Pecker LH, Darbari DS. Psychosocial and affective comorbidities in sickle cell disease. *Neurosci Lett.* 2019;705:1-6.
3. Belgrave FZ, Molock SD. The role of depression in hospital admissions and emergency treatment of patients with sickle cell disease. *J Natl Med Assoc.* 1991;83(9):777-781.
4. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med.* 2003;163(20):2433-2445.
5. Currie SR, Wang J. More data on major depression as an antecedent risk factor for first onset of chronic back pain. *Psychol Med.* 2005;35(9):1275-1282.
6. Racine M. Chronic pain and suicide risk: a comprehensive review. *Prog Neuropsychopharmacol Biol Psychiatry.* 2018;87(pt B):269-280.
7. Han B, McKeon R, Gfroerer J. Suicidal ideation among community-dwelling adults in the United States. *Am J Public Health.* 2014;104(3):488-497.
8. Edwards CL, Green M, Wellington CC, et al. Depression, suicidal ideation, and attempts in black patients with sickle cell disease. *J Natl Med Assoc.* Nov 2009;101(11):1090-1095.
9. Levenson JL, McClish DK, Dahman BA, et al. Depression and anxiety in adults with sickle cell disease: the PiSCES project. *Psychosom Med.* Feb 2008;70(2):192-196.
10. Adam SS, Flahiff CM, Kamble S, Telen MJ, Reed SD, Castro LM. Depression, quality of life, and medical resource utilization in sickle cell disease. *Blood Adv.* 2017;1(23):1983-1992.
11. Lucarelli G, Isgro A, Soda, et al. Hematopoietic SCT for the Black African and non-Black African variants of sickle cell anemia. *Bone Marrow Transplant.* 2014;49(1):1376-1381.
12. Wells KJ, Booth-Jones M, Jacobsen PB. Do coping and social support predict depression and anxiety in patients undergoing hematopoietic stem cell transplantation? *J Psychosoc Oncol.* 2009;27(3):297-315.

---

### Table 2. Depression, SI, length of stay, and readmissions

| History of MDD or SI | Posttransplant SI (N = 6) | No posttransplant SI (N = 8) | Total (N = 14) | P value |
|----------------------|---------------------------|-----------------------------|---------------|---------|
| History of MDD or SI | 6                         | 3                          | 9             | .310    |
| No history of MDD or SI | 0                      | 5                          | 5             | OR = ∞ (.9494, ∞) |
| Mean LOS, d          | 36                        | 52.25                      | 45.29         | .0515   |
| Median (Q1,Q3)       | 34 (33,25,38,25)          | 51.5 (36,67,75)            | 37,75 (35,25,65,25) |
| Mean readmissions, d | 3.25                      | 3.25                      | 3.14          | .7938   |
| Median (Q1,Q3)       | 3.5 (1,5,4,75)            | 2.5 (1,75,3,26)            | 3 (1,25,4)   |
| Mean readmissions for pain, d | 1.17        | 0.63                      | .86           | .5632   |
| Median (Q1,Q3)       | 0.5 (0,2,5)               | 0 (0,1)                   | 0 (0,1)      |

**LOS, length of stay; OR, odds ratio.**
13. Nakamura ZM, Nash RP, Quillen LJ, Richardson DR, McCall RC, Park EM. Psychiatric care in hematopoietic stem cell transplantation. Psychosomatics. 2019;60(3):227-237.

14. Tichelli A, Labopin M, Rovo A, et al. Increase of suicide and accidental death after hematopoietic stem cell transplantation: a cohort study on behalf of the Late Effects Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Cancer. 2013;119(11):2012-2021.

15. Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA’s pediatric suicidal risk analysis of antidepressants. Am J Psychiatry. 2007;164(7):1035-1043.

16. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatr. 2011;168(12):1266-1277.

17. Darbari DS, Liljencrantz J, Ikechi A, et al. Pain and opioid use after reversal of sickle cell disease following HLA-matched sibling haematopoietic stem cell transplant. Br J Haematol. 2019;184(4):690-693.

18. Han J, Holden CC, Ahluwalia AY, et al. Chronic opioid use can be reduced or discontinued after haematopoietic stem cell transplantation for sickle cell disease. Br J Haematol. 2020;191(3):e70-e72.

19. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. JAMA. 2014;312(10):1033-1048.