

July 6, 2023

Tamara Syrek Jensen, JD
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Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

Re: National coverage analysis for Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Myelodysplastic Syndromes (MDS)

Dear Ms. Syrek Jensen:

On behalf of the American Society of Hematology (ASH), the American Society for Transplantation and Cellular Therapy (ASTCT), the National Marrow Donor Program (NMDP), the Center for International Blood and Marrow Transplant Research (CIBMTR), and Blood and Marrow Transplant Clinical Trials Network (BMT CTN), thank you for initiating the national coverage analysis for Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) for Myelodysplastic Syndromes (MDS) in response to our reconsideration request submitted October 12, 2021.

As the Centers for Medicare & Medicaid Services (CMS) develops the proposed decision memo on this topic, we respectfully request that the clinical studies and scientific evidence outlined in these comments be considered to support the coverage of HSCT for individuals with MDS without the coverage with evidence development (CED) requirement. This evidence includes the studies outlined in our original reconsideration request as well as recent studies and guidelines that have been published in the interim.

Allogeneic HSCT remains the only curative therapy for patients with MDS, a group of blood disorders in which the bone marrow does not produce enough healthy, functioning blood cells. MDS primarily impacts older adults: the median age at diagnosis is 70 years, making Medicare coverage for HSCT essential for patients to have access to this life-saving treatment.

Summary of the Evidence in Support of Removing the CED Requirement

We understand the agency will undertake a comprehensive literature review as a part of the NCA process. In the following sections of our letter, we have provided a synopsis of studies which support coverage of allogeneic HSCT for MDS without the CED requirement.

Summary of Biologic Assignment Trial of Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients 50-75 Years of Age with Advanced Myelodysplastic Syndrome¹

Allogeneic HSCT, widely used in younger MDS patients, is the only curative therapy for MDS. While transplantation outcomes among selected older patients with MDS are like younger patients with MDS, early transplantation for older patients is infrequently offered since the relative benefits of HSCT over non-HSCT therapy have not been well defined in this patient group. The goal of this

¹ Nakamura R, Saber W, Martens MJ, et al. Biologic Assignment Trial of Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients 50-75 Years of Age with Advanced Myelodysplastic Syndrome. J Clin Onc 2021.

multi-center, biologic assignment study performed by the BMT CTN in older individuals with high-risk MDS was to define the benefit of HSCT over non-HSCT therapy. Specifically, the study compared allogeneic HSCT with DNA hypomethylating therapy or best supportive care in individuals aged 50-75 years with advanced MDS.

To summarize, the study found that overall survival and leukemia-free survival were significantly improved for individuals who had a suitably matched donor in comparison with those who did not have a donor. Half of subjects with a donor were alive 3 years after trial entry compared to only one quarter when a donor was unavailable.

Biologic assignment was to the donor, or no donor group based on the identification of a suitable, HLA-matched related or unrelated donor within 90 days of trial entry. Subjects with an identified donor were expected to undergo transplantation within 6 months, while those without a suitable donor were expected to receive DNA hypomethylating therapy or best supportive care. The primary endpoint of the study was a point comparison of adjusted overall survival at 3 years from study registration. Secondary endpoints included leukemia-free survival at 3 years from study registration, quality of life measured at 6 timepoints, and a cost-effectiveness comparison. Additionally, pre-specified as-treated analyses were performed, analyzing only subjects who received their biologically-assigned therapy.

Three hundred eighty-four subjects in total were accrued at 34 participating centers, with enrollment ending at the end of 2018, when sufficient subjects had been accrued to the no donor arm. Of the 384 subjects, a suitable donor was identified in 260 while no donor was found for 124. Seven subjects died during the 90-day search window and were included in the no donor arm. The donor and no donor arms were well balanced for age, gender, duration of MDS, disease risk and response to prior DNA hypomethylating therapy.

At three years from trial enrollment, overall survival was significantly higher in the donor vs. no donor group, with an absolute improvement of 21.3% (47.9% vs. 26.6%, $p=0.0001$). In a sensitivity analysis, excluding subjects who died or withdrew prior to the end of the search window, no effect on relative outcomes was noted (48.0% vs. 28.1%, $p=0.0004$). **The effect of age on the primary outcome was specifically analyzed, with no difference in the odds ratio (OR) for outcomes when stratified by Medicare age eligibility (age < 65 [OR for survival with donor vs no donor, 2.44] vs age > 65 [OR for survival, 2.962]).** Like overall survival, 3-year leukemia-free survival was significantly better in the donor arm (35.8% vs. 20.6%, $p=0.003$), without a measurable difference in the sensitivity analysis (35.9% vs. 21.8%, $p=0.0074$). **Moreover, no effect of age was noted when stratified by Medicare age eligibility (OR for leukemia-free survival, 2.396 vs 2.206). Thus, the benefit of having a donor/HSCT was clearly observed in the Medicare age group in a similar degree to those treated at age <65.** These findings are consistent with the Atallah, et al 2019 paper summarized below.

In as-treated analyses, only subjects who underwent matched donor transplantation were included in the donor arm, and only those subjects who did not undergo transplantation in the non-donor arm. The differences in outcome in this analysis were greater for both 3-year overall survival (47.4 % vs 16%, $p<0.0001$) and 3-year leukemia-free survival (39.3% vs 10.9%, $p<0.0001$).

Summary of Comparison of patient age groups in transplantation for myelodysplastic syndrome: the Medicare Coverage with Evidence Development study²

The CIBMTR developed an observational study that met CMS' criteria for CED in response to the August 4, 2010, Decision Memo for Allogeneic HSCT for Myelodysplastic Syndrome (CAG-00415N). This prospective, multicenter observational study compared the outcomes of patients aged 55-64 years with patients 65 years and older who received allogeneic HSCT for MDS performed in the United States. The primary outcome was overall survival. Other outcomes included non-relapse mortality, relapse, relapse-free survival, and acute and chronic graft-versus-host disease (GVHD). CIBMTR collected data from all participating HSCT centers and performed the analysis.

From December 2010 to May 2014, 688 patients aged 65 years or older were enrolled in the study, and their outcomes were compared with 592 patients aged 55 to 64 years randomly selected from the population of United States patients treated during the same period. There was no difference in the outcome of the randomly selected sample of patients included in this study compared with the rest of patients aged 55 to 64 years treated during the study period. Twenty-four percent of the patients in the 65 and older group were 70 years or older. The median follow up was 47 months. Other than age, there were no significant differences in patient and disease characteristics between the two age cohorts. About 50% of patients in both groups had an Hemopoietic Cell Therapy-Comorbidity Index (HCT-CI) score of 3 or greater, about 25% had therapy-related MDS; 25% were intermediate risk by the Revised-International Prognostic Scoring System (R-IPSS) and around 30% were high or very high risk by R-IPSS at diagnosis.

Multivariate analysis of overall survival identified high/very high R-IPSS, blasts in bone marrow (bBM) > 11% before HSCT, non-age-adjusted HCT-CI of 4 or greater, and GVHD prophylaxis with calcineurin inhibitor + methotrexate as independently associated with inferior outcome. Age group 65 years or older vs those aged 55 to 64 years had no statistically significant association with mortality with (hazard ratio [HR], 1.09; 95% confidence interval [CI], 0.94-1.27; p=0.23) or without (HR, 1.13; 95% CI, 0.98-1.3; p=0.08) adjustment for excess population-based risk of mortality in the older group.

Multivariate analysis of relapse-free survival demonstrated no significant difference between patients in the 65 years and older age group compared to those 55 to 64 years (HR, 1.14; 95% CI, 0.99-1.31; p=0.07). R-IPSS high/very high, in-vivo T depletion, bBM > 11% before HSCT, conditioning regimen, not being in remission before HSCT and HCT-CI of 4 or greater were associated with worse relapse-free survival.

At 3 years, non-relapse mortality was 28% vs 25% for the patients 65 years and older vs. the 55 to 64 years age group. After adjusting for excess risk of mortality in the general older population in multivariate analysis, there was no statistically significant difference in non-relapse mortality between the 65 years or older group compared to 55 to 64 years group (HR, 1.19; 95% CI, 0.93-1.52; p=0.16). There were no differences in the rates of grades II to IV acute GVHD or chronic GVHD between the two groups.

² Atallah E, Logan B, Chen M, et al. Comparison of patient age groups in transplantation for myelodysplastic syndrome: the Medicare Coverage with Evidence Development study. *JAMA Oncol.* 2020;6(4):486-493. Doi:10.1001/jamaoncol.2019.5140. Published online Dec 12, 2019.

The authors conclude older patients with MDS undergoing allogeneic HSCT have similar overall survival compared with younger patients. The strongest factors associated with survival after allogeneic HSCT were HCT-CI comorbidity score, IPSS-R score and other disease related factors, and GVHD prophylaxis regimen. Chronologic age alone should not be an appropriate selection factor for allogeneic HSCT in patients with MDS.

Summary of Health-related quality of life in reduced-intensity hematopoietic cell transplantation based on donor availability in patients aged 50-75 with advanced myelodysplastic syndrome³

The BMT CTN study 1102, described above, was a multicenter, biologic assignment trial based on matched donor availability in adults aged 50-75 with higher risk de novo MDS who were candidates for reduced-intensity conditioning (RIC) alloHCT. The study described in this paper evaluated the quality of life of participating patients through the comparison of patient-reported outcome (PRO) scores between study arms. Between January 2014 and November 2018, 384 subjects with a median age of 66.7 years and age range of 50.1 to 75.3 enrolled at 34 centers.

The PRO trajectories for both arms of the study were similar with most decreasing or stable from baseline to six months and improving thereafter, demonstrating that the survival advantage associated with donor availability and alloHCT in this older population did not come at the cost of worse QOL. Baseline PRO scores were the most consistent independent predictors of subsequent quality of life (QOL) outcomes and survival after controlling for clinical and patient-level factors.

This study was an important piece of work that highlighted the importance of using PROs to define the benefits of treatment. While other studies focus on diverse clinical outcomes, this study chose to “understand how patients feel and function” as an important benefit of treatment. With this understanding patients and clinicians will be better equipped to make decisions about undergoing curative treatment for MDS.

Summary of Guidelines

The findings from the studies described above have been incorporated into clinical practice guidelines used to determine whether HSCT is appropriate in patients with MDS. The ASTCT guideline, *Hematopoietic Cell Transplantation in the Management of Myelodysplastic Syndrome: An Evidence-Based Review from the American Society for Transplantation and Cellular Therapy Committee on Practice Guidelines⁴*, recommends that allogeneic HSCT be offered to patients with advanced MDS (IPSS int-2 or high risk) (Grade A, Level 1++) and should be implemented efficiently during the course of disease, and recommends referral to HSCT consultation for all patients with MDS, to provide a detailed understanding of allogeneic HSCT and an individualized risk assessment. The guideline states that age alone is not sufficient to restrict HSCT eligibility and forgo potential curative therapy (Grade B, Level 1++). The guideline also discusses “lower risk MDS” and recommends: “most patients with lower-risk MDS who undergo HCT have a disease- or patient-related variable that the treating physician deems of high clinical concern” and “there may be scenarios in which HCT is performed in

³ Cusatis R, Martens MJ, Nakamura R, et al. Health-Related Quality of Life in Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients Aged 50-75 with Advanced Myelodysplastic Syndrome: BMT CTN 1102. *Am J Hematol*, 2021.

⁴ DeFillip Z, Ciurea SO, Cutler C et al. Hematopoietic Cell Transplantation in the Management of Myelodysplastic Syndrome: An Evidence-Based Review from the American Society for Transplantation and Cellular Therapy Committee on Practice Guidelines. *TCT* 29; 71-81, 2023

IPSS lower-risk disease (e.g., younger patients with transfusion-dependent disease despite best supportive care or those with multiple or adverse somatic mutations).”

Additionally, the guidelines for MDS by the National Comprehensive Cancer Network (NCCN)⁵ states: “For patients who are transplant candidates, an HLA-matched sibling or HLA-matched unrelated donor can be considered. Results with HLA-matched unrelated donors have improved to levels comparable to those obtained with HLA-matched siblings. With the increasing use of cord blood or HLA-haploidentical related donors, HCT has become a viable option for many patients. High-dose conditioning is typically used for younger patients, whereas RIC for HCT is the strategy in older individuals.” The specific therapeutic diagrams from the guideline for higher-risk MDS (IPSS-R intermediate-, high-, very high-risk disease) places HSCT as one of the first line treatment options for patients considered as HSCT candidates, and for lower-risk MDS (IPSS-R very low-, low-, intermediate-risk disease), HSCT is recommended for select patients such as those with severe cytopenia.

Additional considerations

Although we have learned much about MDS and its treatment since the last NCD for MDS, it remains true that HCT is the only curative option for this disease. Supportive options have improved, particularly in patients with less aggressive disease, but a substantial proportion of patients over age 65 are eligible for and can be cured by HCT.

Risk stratification systems for MDS are rapidly evolving. The latest revision of the IPSS, the IPSS-M⁶ incorporates important molecular mutations in the prognostic model and is dynamic to account for changes in patients over time and treatment. There are additional models including a personalized prediction model for MDS⁷ and EuroMDS⁸ which also provide important prognostic information. Each of these risk stratification systems have not only improved risk prediction, but they have also up-classified substantial proportions of patients to more aggressive disease categories. We believe this evolution of prognostic models will limit the ability to clearly define a group of patients at such low risk that HCT should not be considered a potential treatment option, especially in a way that is durable and does not need to be addressed frequently. For this reason, we recommend coverage that is not limited by disease classification within MDS.

Finally, there continues to be expanding utilization of ‘alternative’ graft sources/donors with improving outcomes to reduce HLA barriers and increase access to HCT for more Americans, especially for racial/ethnic minorities who are less likely to find an HLA-matched donor⁹. This includes continued use of cord blood and expanding use of mismatched unrelated donors and

⁵ Greenberg PL, Stone RL, Al-Kali A, et al. NCCN Clinical Practice Guidelines in Oncology for Myelodysplastic Syndromes Version 1.2023. National Comprehensive Cancer Network, Inc. 2023. All rights reserved. www.nccn.org. Accessed June 26, 2023.

⁶ Bernard E, Tuechler H, Greenberg PL et al. Molecular International Prognostic Scoring System for Myelodysplastic Syndrome; NEJM Evid 2022.

⁷ Nazha A, Komrokji R, Meggendorfer M, et al. Personalized Prediction Model to Risk Stratify Patients with Myelodysplastic Syndromes. J Clin Oncology 2021; 39:3737.

⁸ Bersanelli M, Travaglino E, Meggendorfer M, et al. Classification and Personalized Prognostic Assessment on the Basis of Clinical and Genomic Features in Myelodysplastic Syndromes. J Clin Oncol 2021; 39:1223.

⁹ Auletta, J, Kou J, Chen, M et al. Real-World Data Showing Trends and Outcomes by Race and Ethnicity in Allogeneic Hematopoietic Cell Transplantation: A Report from the Center for International Blood and Marrow Transplant Research. Transplant Cell Ther 2023.

haploidentical family donors. We believe it is appropriate to provide coverage for patients with MDS agnostic of the donor source, which is consistent with the statements in the current practice guidelines from the ASTCT and NCCN.

In conclusion, ASH, ASTCT, NMDP, CIBMTR, and BMT CTN submit this comment letter to support full coverage of allogeneic HSCT for individuals with myelodysplastic syndromes and the removal of the CED requirement currently tied to coverage for HSCT for individuals with MDS. Additionally, we have provided all published evidence in support of this recommendation in Appendix A.

Thank you for your consideration of our comments. Should you have any questions or require more information, please contact Suzanne Leous, American Society of Hematology's Chief Policy Officer, at sleous@hematology.org or 202-292-0258.

Sincerely,

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Appendix A: Literature outlining clinical evidence which supports eliminating the CED requirement

Nakamura R, Saber W, Martens MJ, et al. Biologic Assignment Trial of Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients 50-75 Years of Age with Advanced Myelodysplastic Syndrome. *J Clin Onc* 2021.

Atallah E, Logan B, Chen M, et al. Comparison of patient age groups in transplantation for myelodysplastic syndrome: the Medicare Coverage with Evidence Development study. *JAMA Oncol*. 2020 ;6(4) :486-493.

Cusatis R, Martens MJ, Nakamura R, et al. Health-Related Quality of Life in Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients Aged 50-75 with Advanced Myelodysplastic Syndrome: BMT CTN 1102. *Am J Hematol*, 2021.

DeFillip Z, Ciurea SO, Cutler C et al. Hematopoietic Cell Transplantation in the Management of Myelodysplastic Syndrome: An Evidence-Based Review from the American Society for Transplantation and Cellular Therapy Committee on Practice Guidelines. *TCT* 29; 71-81, 2023

Greenberg PL, Stone RL, Al-Kali A, et al. NCCN Clinical Practice Guidelines in Oncology for Myelodysplastic Syndromes Version 1.2023. National Comprehensive Cancer Network, Inc. 2023. All rights reserved. www.nccn.org. Accessed June 26, 2023.

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Nazha A, Komrokji R, Meggendorfer M, et al. Personalized Prediction Model to Risk Stratify Patients with Myelodysplastic Syndromes. *J Clin Oncology* 2021; 39:3737.

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Auletta, J, Kou J, Chen, M et al. Real-World Data Showing Trends and Outcomes by Race and Ethnicity in Allogeneic Hematopoietic Cell Transplantation: A Report from the Center for International Blood and Marrow Transplant Research. *Transplant Cell Ther* 2023.