Cancer Management and Research

Elevate Series

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ORIGINAL RESEARCH

Experiences with Higher-Risk Myelodysplastic Syndromes and Improving Patient-Centered Treatment Decision-Making: A Qualitative Study of Patients, Caregivers, and Providers

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Purpose: Research on treatment experiences and decision-making in higher-risk myelodysplastic syndromes (HR-MDS) remains limited, with most studies employing quantitative approaches. This study employed qualitative research methods to further explore patients', caregivers', and providers' experiences with HR-MDS and treatment decision-making.

Patients and Methods: Exploratory, qualitative web-based focus groups and interviews were conducted between April-May 2023 amongst US-based patients with HR-MDS, caregivers for a patient with HR-MDS for ≥3 months, and board-certified oncologists and/or hematologists who treated ≥5 patients with HR-MDS in the past year. Recruitment was facilitated by a survey vendor and the MDS Foundation using convenience sampling. De-identified transcripts were analyzed using constant comparative analysis to identify key themes.

Results: A total of 8 patients, 6 caregivers, and 18 providers participated. Providers described challenges conveying the HR-MDS diagnosis to patients, while patients and caregivers reported lacking information regarding the condition, prognosis, and available treatment options. Providers discussed the lack of HR-MDS treatment options. Patients and caregivers were primarily concerned with treatment efficacy and ability to improve quality of life. While patients, caregivers, and providers expressed interest in shared decision-making (SDM), implementation of SDM can be influenced by the patient's age, level of education, and health literacy. Treatment barriers included lack of treatment options, insurance coverage, lack of information sharing, and access to treatment centers. High levels of caregiver burden were reported, with caregivers having to sacrifice their social lives, assume financial responsibility, and execute the daily management of the patient.

Conclusion: Findings highlight key challenges in HR-MDS including the complexities surrounding HR-MDS education and communication. Patient-centered approaches incorporating cognitively appropriate education and decision aids, and provision of supportive services are needed to improve patient-centered treatment decision-making in HR-MDS. Future research should build upon these findings amongst the broader HR-MDS population and explore practical approaches to facilitate patient-provider communication.

Keywords: myelodysplastic syndromes, communication, shared decision-making, treatment burden, qualitative research, treatment decision-making

Introduction

Myelodysplastic syndromes (MDS) are a group of conditions characterized by the disruption of healthy blood cell production in the bone marrow, impacting between 60,000 to 170,000 persons in the United States (US).[1] The incidence of MDS ranges from 12,000 to 20,000 cases per year in the US and more commonly affects people over the age of 65 and males, with a median age at diagnosis of 71–76 years.[1–3]

MDS is characterized by a deficiency in one or more types of blood cells (eg red cells, white cells, platelets) and about 1 in 3 patients with MDS progress to acute myeloid leukemia (AML).[4] The National Comprehensive Cancer Network (NCCN) further classifies MDS by prognosis using the Revised International Prognostic Scoring System (IPSS-

Received: 1 August 2024
Accepted: 11 April 2025
Published: 24 June 2025

R), where doctors assign a risk score to patients with MDS based on their prognostic factors including the percentage of blasts (immature cells) in the patient's bone marrow, chromosomal abnormalities, and blood cell counts. Based on these factors, patients are categorized as either having lower-risk MDS (LR-MDS) or higher-risk MDS (HR-MDS).[5] Patients falling into the LR-MDS group, include very low (IPSS-R score of ≤1.5), low (IPSS-R score of >1.5–3.0), and some low end intermediate risk (IPSS-R score of >3.0–4.5), while HR-MDS patients include those with medium to high end intermediate risk (IPSS-R score of >3.0–4.5), high (IPSS-R score of >4.5–6.0), or very high-risk disease (IPSS-R score of >6.0).[6] Anywhere from 25% to 43% of patients living with MDS are categorized as having HR-MDS which is associated with lower rates of survival – ranging from 0.8 to 3 years - and a higher probability of developing AML.[2,4]

Clinical treatment goals for patients with HR-MDS are primarily to improve clinical response through symptom management and alleviation, slow or halt disease progression, and improve quality of life and overall survival.[7] However, current treatment options for MDS are limited and depend on individual patient characteristics including patient's risk classification, fitness, goals, preferences, caregiver and social support, and eligibility for hematopoietic cell transplant (HCT).[7] Treatment limitations for HR-MDS are further exacerbated due to the high prevalence of HR-MDS in elderly populations, where elderly patients often have complicated cytogenetics that make them both ineligible for HCT or unlikely to perform well if HCT is administered. Therefore, for patients who are not HCT candidates, treatment options consist primarily of hypomethylating agents (HMAs), and symptom minimization through transfusion and medication support; however, for patients with HR-MDS, responses to HMA therapy are limited and HMA treatment, particularly intravenous and subcutaneous therapy, imposes a significant burden on patients and their caregivers due to the intense administration regimens and other administration-related impacts.[7–9]

Moreover, due to the heterogenous presentation of HR-MDS amongst patients, there has been little overall innovation within the disease field beyond improving symptomatology through transfusion support, the use of growth factors, and minimizing disease related infections.[10,11] With limitations surrounding treatment options and treatment eligibility for patients with HR-MDS, supportive measures are often used to help minimize hospitalizations and improve patients' overall quality of life over the course of the disease treatment and monitoring.[11,12]

Previous studies have demonstrated an interest amongst patients with MDS in having a shared or active role in their treatment selection, as patients with MDS who engage in shared decision-making (SDM) and active treatment engagement experience lower levels of treatment related anxiety and higher overall treatment satisfaction.[13,14] In addition, when engaged in SDM, caregivers play an important role in advocating for the patients' needs and reinforcing the patients' preferences leading to better care for the patient.[15] However, current research suggests that patients with MDS, and their caregivers, have a limited understanding of their disease and treatment options, perhaps driven by older age and overall poor health literacy, which highlights a significant gap in communication that impedes patients' abilities to be involved in the treatment decision-making process.[13,16,17] A lack of patient-provider communication can lead to treatment decisions that do not align with patient goals.[18] This can be exacerbated by research suggesting that patients with MDS who feel distressed have lower health literacy, difficulty asking physicians questions, and lower satisfaction with information given to them about their MDS.[14]

In order to move towards a more holistic, SDM approach in the MDS treatment space, patient, caregiver and provider preferences and experiences need to be further elicited to better understand the factors that are most important to each group. Although recent research has highlighted the need for empirical studies on patient-centered approaches in HR-MDS,[19] research on the treatment decision-making process remains limited. Further, while previous studies have described the impacts of MDS more broadly,[20–24] these studies have largely employed quantitative approaches. As such, they have hardly captured the treatment experiences and the disease impacts amongst patients with HR-MDS, as well as their caregivers. To address this gap, this study sought to explore patients', caregivers', and hematology and oncology providers' perspectives on and experiences with HR-MDS, including the diagnostic experience, treatment decision-making, disease and treatment-related burden, and treatment barriers and facilitators, using qualitative focus groups and individual interviews. The hope is that this study highlights key experiences of HR-MDS patients, caregivers, and providers, which in turn outlines a patient-centered approach for engaging in SDM, as well as the importance for educational and support resources that accommodate the technological abilities and educational levels of the HR-MDS patient and caregiver populations.

Methods

Study Design and Participants

This non-interventional, exploratory qualitative study incorporated semi-structured focus groups and interviews conducted separately among US-based: (i) patients with HR-MDS, (ii) caregivers for patients with HR-MDS, and (iii) board-certified oncologists and/or hematologists managing patients with HR-MDS. Qualitative research methods are particularly appropriate for investigating subjective impressions that may not be captured in other ways. The research team used both deductive and inductive coding and analytic approaches on these data. Deductive analysis includes establishing elements of a coding scheme that reflect key domains outlined in the research objectives and theories and frameworks applied to the research question. Inductive analysis, on the other hand, uses coding derived from the data rather than from a priori theoretical or research questions. A grounded theory approach was used to code and analyze the qualitative data from each population of interest.[25] Grounded theory, which is a widely used approach to developing hypotheses and theories in qualitative research, was used within this process of inductive coding and allowed the team to develop hypotheses and theories through systematic data collection and analysis. Frequently associated with a grounded theory approach, the research team used concurrent data collection and analysis, often referred to as constant comparative analysis, which allows for the emergence and refinement of key themes from the data.[25]

Participant Recruitment

Patients with HR-MDS and caregivers of patients with HR-MDS were recruited to participate in a web-based focus group. Healthcare providers were recruited to participate in individual web-based interviews. Specifically, oncologists, hematologists, and hematologist-oncologists were recruited as these are the primary provider types responsible for treatment of HR-MDS. A third-party research vendor (Sago) identified and recruited participants from their existing proprietary US-based panels of patients, caregivers, and providers created and maintained for research purposes. These research panels were developed using a broad range of in-person and online sources to ensure a diverse and nationally representative panel composition. Additionally, the MDS Foundation partnered with the study team to identify and recruit potential patient and caregiver participants from their constituency.

Using convenience sampling, email study invitations that included a link to the web-based screener and background survey (Appendix 1) were sent by Sago and the MDS Foundation to potential participants. The invitations outlined the aims of the study and described study participation details. Interested participants completed the screener to determine study eligibility prior to focus group or interview scheduling. All recruitment was conducted in a double-blind manner such that the study sponsor did not know the identities of the participants, and the identity of the study sponsor was not shared with participants.

Patients were eligible to participate if they self-reported a diagnosis of HR-MDS (ie, IPSS-R intermediate, high, or very high) or self-reported a diagnosis of MDS with an unknown risk category and reported receiving treatment(s) specific to HR-MDS. Patients were excluded if they were currently enrolled in a clinical trial for MDS. Caregivers were eligible if they were a primary, informal caregiver who provided at least 3 months of unpaid care over the past year for a patient with a self-reported diagnosis of HR-MDS or has received at least one prior treatment regimen specific to HR-MDS and was not currently enrolled in a clinical trial.

Providers were required to be a board-certified oncologist, hematologist, or hematologist-oncologist with at least 2 years of experience post-residency practicing in a community or academic setting that spends at least 50% of time per week providing direct patient care. Providers must have treated at least 5 patients with HR-MDS in the past 12 months and prescribe treatment (eg, HMA, chemotherapy) and/or supportive care (eg, blood transfusions, ESAs) for patients with HR-MDS.

All participants were required to be ≥18 years of age, proficient in English, a resident of the US, provide consent, and be able to participate in a web-based interview and/or focus group. Prior to any data collection, an independent institutional review board (Advarra) reviewed study materials and granted the study exemption (Pro00069879).

Procedures and Data Collection

Prior to participating in the web-based focus group or interview, participants completed a brief online background survey (Appendices 1-3) consisting of the screener questions to determine eligibility and a few additional questions to collect

demographic characteristics (eg, gender, race, ethnicity). Eligible participants who completed the background survey and provided informed consent were scheduled to complete a focus group or interview.

Of 3463 patients, 71 caregivers, and 48 providers that were screened, 11 patients, 19 caregivers, and 24 providers met the study eligibility criteria. Among eligible participants, 3 patients, 4 caregivers, and 6 providers did not complete a focus group or interview (eg, no show, cancelled) resulting in a final study sample of 8 patients, 6 caregivers, and 18 providers. A total of 2 patient focus groups (n=4, n=3) and 2 caregiver focus groups (n=2, n=3) were conducted. Due to scheduling challenges, individual interviews rather than focus groups were conducted for 1 patient and 1 caregiver. All providers completed individual interviews.

Focus groups and in-depth interviews were conducted via Zoom between April and May 2023 by a member of the study team (MCM) with graduate training (PhD) and experience in qualitative research methods. Another member of the study team was present to observe and take field notes (NL, NP, CC). The focus groups and interviews lasted approximately 90 minutes and 60 minutes, respectively. All focus groups and interviews were audio-recorded and transcribed verbatim. Verbal informed consent was obtained from all individual participants at the start of the interview or focus group and permission was obtained to record the discussion.

Three separate, but complementary semi-structured interview guides (Appendices 4–6) were developed to facilitate the discussions with patients, caregivers, and providers, respectively. The development of the discussion guides was informed by a targeted literature review and feedback from a partner patient advocacy organization (MDS Foundation). The discussion guides covered a range of topics including the HR-MDS diagnostic experience, treatment history and preferences, treatment decision-making, experience with and impacts of treatment-related side effects, disease and treatment-related burden, barriers to treatment, and relationships between caregivers and patients and their providers.

Data Analysis

Demographic, health history, and clinical practice characteristics collected in the background survey were analyzed using descriptive statistics. De-identified focus group and interview transcripts were imported into Dedoose (version 9.0.62), a qualitative data analysis software, to facilitate coding and analysis. Data were analyzed in multiple stages using constant comparative analysis to identify and generate emergent themes across the transcripts.[25] First, members of the research team (MCM, NL, NP, CC) developed an initial coding framework based on topics covered in the semi-structured discussion guides. Next, the research team applied the initial coding framework to a subset of transcripts and met to review the codes to identify any emergent themes and further refine and clarify the coding dictionary. The final coding framework was then applied to the entire set of transcripts. Three members of the research team independently coded the transcripts (NL, NP, CC) and a fourth member (MCM) reviewed the data to confirm inter-coder agreement. Individually coded transcripts were aggregated and synthesized to identify overarching themes and key concepts across participants using constant comparative analysis. Lastly, the research team assessed patient and caregiver codes and emergent themes for congruence and incongruence and determined that the data could be pooled. Throughout the iterative data collection and coding process, the study team also individually and collectively generated analytic memos where initial interpretations were captured, as well as provided a place to house researcher reflexivity. Memos addressed codes, theory, research questions, tasks, or other elements in the study.

Reflexivity was considered throughout data collection and analysis by examining research team members' assumptions and potential biases and utilization of researcher triangulation. Members of the research team (MCM, NL, NP, CC) independently reviewed and interpreted the data and regularly discussed findings to help reduce individual bias and strengthen the reliability of the results. Given this was an exploratory study and sample sizes were small, formal assessment of data saturation was not conducted.

Results

Participant Characteristics

Providers

Interviews were completed with 18 providers (mean age = 52.6 years, 78% male, 50% Asian, 50% urban; Table 1). Provider participants primarily worked in partnership practices (33%), specialty group practices (33%), and academic medical centers (17%) and most treated an average of more than 10 patients with HR-MDS in the past year (61%).

Table 1 Provider Demographic and Practice Related Characteristics

Characteristics	N = 18
Age, mean (SD, range)	52.6 (10.1, 39–70)
Gender, n *(%)*	
Male	14 (77.8)
Female	4 (22.2)
Race, n *(%)*	
Asian	9 (50.0)
White or Caucasian	8 (44.4)
Two or more races	1 (5.6)
Hispanic, Latino, or Spanish Origin, n *(%)*	
Yes	2 (11.1)
No	16 (88.9)
Practice geographic area, n *(%)*	
Urban	9 (50.0)
Suburban	7 (38.9)
Rural	2 (11.1)
Number of years in practice, n *(%)*	
6–10 years	6 (33.3)
11–15 years	4 (22.2)
16–20 years	3 (16.7)
More than 20 years	5 (27.8)
Primary specialty, n *(%)*	
Hematology Oncology	15 (83.3)
Oncology	3 (16.7)
Principal practice setting, n *(%)*	
Solo Practice	1 (5.6)
Partnership Practice	6 (33.3)
University/Academic Medical Center	3 (16.7)
National Cancer Institute Designated Cancer Center	1 (5.6)
Specialty Group Practice	6 (33.3)
Multi-Specialty Group Practice	1 (5.6)
Number of patients with MDS treated in the past 12 months, n *(%)*	
11–19 patients	4 (22.2)
More than 20 patients	14 (77.8)
Number of patients with HR-MDS treated in the past 12 months, n *(%)*	
5–10 patients	7 (38.9)
11–19 patients	8 (44.4)
More than 20 patients	3 (16.7)

Note: Provider interviews were conducted between April-May 2023.
Abbreviations: HR-MDS, higher-risk myelodysplastic syndromes; MDS, myelodysplastic syndromes; SD, standard deviation.

https://doi.org/10.2147/CMAR.S482570

Patients and Caregivers

A total of 8 patients participated in a focus group or interview (mean age = 68.1 years, 50% male, 88% White, 88% suburban; Table 2). Most patient participants reported having a high risk IPSS-R score (50%), had been diagnosed with MDS more than 2 years ago (88%), and were not currently receiving treatment (75%).

Table 2 HR-MDS Patient Demographic, Treatment, and Disease-Related Characteristics

Characteristics	N = 8
*Age, mean (*SD, range)	68.1 (6.4, 58–81)
Gender, n *(%)*	
Male	4 (50.0)
Female	4 (50.0)
Race, n *(%)*	
Black or African American	1 (12.5)
White or Caucasian	7 (87.5)
Hispanic, Latino, or Spanish Origin, n *(%)*	
No	8 (100.0)
Residence geographic area, n *(%)*	
Urban	1 (12.5)
Suburban	7 (87.5)
Marital status, n *(%)*	
Married	5 (62.5)
Partnered or living with someone in a marriage-like relationship	1 (12.5)
Separated/Divorced	2 (25.0)
Employment status, n *(%)*	
Employed full-time	1 (12.5)
Retired	7 (87.5)
Highest level of education completed, n *(%)*	
High school graduate or equivalent	2 (25.0)
College graduate	2 (25.0)
Graduate degree or higher	4 (50.0)
Health insurance, n *(%)*	
Medicare	7 (87.5)
Private health plan	1 (12.5)
MDS risk category, n *(%)*	
Intermediate	2 (25.0)
High	4 (50.0)
Very High	2 (25.0)
Time since MDS diagnosis, n *(%)*	
1–2 years ago	1 (12.5)
2–3 years ago	4 (50.0)
More than 3 years ago	3 (37.5)
Has a caregiver, n *(%)*	
Yes	5 (62.5)
No	3 (37.5)
Relationship to caregiver[a], n *(%)*	(n=5)
Spouse/partner	4 (80.0)
Sibling	1 (20.0)
Treatment status[b], n *(%)*	
Currently receiving	2 (25.0)
Previously received, but since stopped	6 (75.0)

(*Continued*)

Table 2 (Continued).

Characteristics	N = 8
*Treatments currently receiving**, n *(%)*	
Decitabine and cedazuridine (Inqovi)	2 (25.0)
Ivosidenib (Tibsovo)	1 (12.5)
*Treatments previously received**, n *(%)*	
Azacitidine (Vidaza)	6 (75.0)
Decitabine (Dacogen)	1 (12.5)
Decitabine and cedazuridine (Inqovi)	2 (25.0)
Cytarabine (Cytosar-U)	2 (25.0)
Venetoclax (Venclexta)	2 (25.0)
Stem cell transplant	3 (37.5)
Other[c]	2 (25.0)
Supportive care status[d], n *(%)*	
Currently receiving	3 (37.5)
Previously received, but since stopped	2 (25.0)
Never received	3 (37.5)

Notes: *Participants could select more than one answer. [a]Only asked to those who reported having a caregiver. [b]Treatment includes hypomethylating agents therapy (eg, Vidaza, azacitidine, decitabine), venetoclax, chemotherapy, immunosuppressive therapy. [c]Other: Neupogen. [d]Supportive care includes blood transfusions, erythropoiesis stimulating agents (ESAs), iron chelation therapy). Patient focus groups and interviews were conducted between April-May 2023.
Abbreviations: HR-MDS, higher-risk myelodysplastic syndromes; MDS, myelodysplastic syndromes; SD, standard deviation.

Additionally, 6 caregivers participated in the study (mean age = 64.3 years, 83% female, 100% White, 83% suburban; Table 3). Most caregiver participants cared for patients with an intermediate risk IPSS-R score (67%) who had been diagnosed more than 2 years ago (67%) and were not currently receiving treatment (83%).

Table 3 Caregiver Demographic Characteristics and HR-MDS Patient Treatment and Disease-Related Characteristics

Characteristics	N = 6
Age, mean (SD, range)	64.3 (4.5, 59–71)
Gender, n *(%)*	
Male	1 (16.7)
Female	5 (83.3)
Race, n *(%)*	
White or Caucasian	6 (100.0)
Hispanic, Latino, or Spanish Origin, n *(%)*	
No	6 (100.0)
Residence geographic area, n *(%)*	
Suburban	5 (83.3)
Rural	1 (16.7)
Marital status, n *(%)*	
Married	6 (100.0)
Employment status, n *(%)*	
Employed full-time	1 (16.7)
Retired	5 (83.3)

(*Continued*)

https://doi.org/10.2147/CMAR.S482570

Table 3 (Continued).

Characteristics	N = 6
Highest level of education completed, n *(%)*	
Some college or technical or vocational school	1 (16.7)
College graduate	3 (50.0)
Graduate degree or higher	2 (33.3)
Relationship to patient, n *(%)*	
Spouse/partner	6 (100.0)
Time spent caregiving over past year, n *(%)*	
3–6 months	1 (16.7)
9–12 months	5 (83.3)
Average time spent providing care (hours/week), mean (SD, range)	22.2 (14.1, 6–40)
Age of patient, mean (SD, range)	65.7 (5.2, 57–75)
Patient's MDS risk category, n *(%)*	
Intermediate	4 (66.7)
High	2 (33.3)
Time since patient's MDS diagnosis, n *(%)*	
1–2 years ago	2 (33.3)
2–3 years ago	1 (16.7)
More than 3 years ago	3 (50.0)
Treatment status[a], n *(%)*	
Currently receiving	1 (16.7)
Previously received, but since stopped	5 (83.3)
*Treatments currently receiving**, n *(%)*	
Decitabine and cedazuridine (Inqovi)	1 (16.7)
*Treatments previously received**, n *(%)*	
Azacitidine (Vidaza)	5 (83.3)
Decitabine (Dacogen)	1 (16.7)
Decitabine and cedazuridine (Inqovi)	1 (16.7)
Cytarabine (Cytosar-U)	1 (16.7)
Venetoclax (Venclexta)	1 (16.7)
Stem cell transplant	2 (33.3)
Other[b]	1 (16.7)
Supportive care status[c], n *(%)*	
Currently receiving	2 (33.3)
Previously received, but since stopped	3 (50.0)
Never received	1 (16.7)

Notes: *Participants could select more than one answer. [a]Treatment includes hypomethylating agents therapy (eg, Vidaza, azacitidine, decitabine), venetoclax, chemotherapy, immunosuppressive therapy. [b]Other: Neupogen. [c] Supportive care includes blood transfusions, erythropoiesis stimulating agents (ESAs), iron chelation therapy. Caregiver focus groups and interviews were conducted between April-May 2023.

Abbreviations: HR-MDS, higher-risk myelodysplastic syndromes; MDS, myelodysplastic syndromes; SD, standard deviation.

Qualitative Findings

The findings from the qualitative analysis are described below and results are separated by providers and patient/caregiver groups for a selection of key themes identified in the patient, caregiver, and provider data. Appendix 7 includes a summary of key themes and sub-themes with some additional exemplar narrative quotes.

Diagnostic Experience and Communication

Providers

Providers reported that patients with HR-MDS are most often referred to them by primary care providers or other

specialists due to the presence of abnormally low blood counts or cytopenias in one of the blood cell lines (eg, red blood cells (RBCs), white blood cells (WBCs), platelets). Once a patient has been referred to them, providers typically perform a full workup including molecular and cytogenetic testing of the bone marrow and peripheral blood. This allows providers to establish the number of blasts present within the patient's bone marrow in order to confirm an MDS diagnosis and use the IPSS-R, the most commonly used prognostication methodology, to determine a patient's risk status. When diagnosing patients with HR-MDS, providers described communicating the diagnosis to a patient as a challenging and ongoing process and reported tailoring their communication about diagnosis to the patient's level of health literacy, current health status, and general demeanor.

> It varies tremendously. The population that I deal with may have as little as a second or third grade education, may be post-doctoral, everything in between. I have to try to gauge it to the level that the individual has. – Provider (suburban, specialty group practice, 20+ years in practice)

Providers discussed seeking equipoise when needing to adequately explain the seriousness of the condition without instilling panic or diminishing hope. Generally, providers spoke about employing a broad communication approach that focuses on describing MDS from a production standpoint, specifically explaining MDS as a disease of the bone marrow that results in inadequate production of blood cells, though the amount of detail conveyed depends on the individual patient. Providers described focusing discussions on the production aspects of MDS and less on the potential for the disease to evolve into cancer. Providers emphasized that explaining to patients that HR-MDS is not cancer – but could become cancer – is challenging. Some providers do not mention "cancer" unless patients explicitly ask or are extremely high risk, while others are very direct about the risk of the disease evolving into acute leukemia.

> A lot of challenges come because of the disease itself…is this cancer or not cancer? Depending on the patient sometimes we struggle to convince that, yes, it is cancer. I think the challenges are mostly at the time of diagnosis and convincing the patient what they have. – Provider (rural, partnership practice, 16-20 years in practice)

Providers also cited some difficulties with directing patients to additional disease and treatment-related information found online, and viewed many patients as not being "tech savvy" and unlikely to be able to easily access information online, perhaps owed to the patients' advanced age.

Patients and Caregivers

While some patients reported that the diagnostic process was straightforward and quick, others reported challenges with delays and misdiagnosis. Specifically, when first diagnosed and during initial conversations about treatment, patients generally reported being provided little information regarding the condition, their prognosis, and available treatment options from their care team, despite having questions and wanting to know more information. Information of interest included potential treatment options and treatment-related side effects, how long they had to live, and how to interpret the MDS risk scale. Further, patients reported receiving limited information and/or not fully understanding the information provided to them and described challenges with not knowing what questions to ask to further their care or participate in treatment decision-making.

With respect to HR-MDS caregivers, some caregivers reported feeling they were provided the information they wanted from the care team regarding diagnosis and relevant treatment options, while others reported being given limited-to-no information, particularly surrounding treatment options and expectations including the overall prognosis and treatment cadence.

> Communication is the only part of his care team that we feel could have improvement. They haven't done a great job of that from beginning to end. We feel that they should have given us better information on the transplant process. They should have given information on what to expect when he started chemo. They should have given us information on how to get the secondary drug. A lot of things we had to find out through Google. – Caregiver (Female, 62 years old, patient IPSS-R: Intermediate, Missouri)

Information of interest for patients and caregivers included the meaning of laboratory values, available treatment options, what to expect during the treatment process, reasons for choosing particular treatments, as well as outcomes data for treatment options. This resulted in information challenges included feeling as if the care team did not have the time to answer all their questions and feeling like the patient did not know the right questions to ask the care team during appointments.

> I had questions, and I think the problem was I didn't feel I was getting the answers from my team at the smaller hospital. I realized I needed—my primary knew questions to ask, but I did not know the proper questions. – Patient (Female, 72 years old, IPSS-R: Very High, Maryland)

Patients and caregivers described looking to the internet to try to find additional information and answers to their questions that were not being answered by their care team. Patients and caregivers generally described a positive and trusting relationship with their care team; however, communication issues were emphasized, including feeling rushed during appointments, not always being able to speak directly with the doctor, and the doctor not being as communicative as they would have liked.

Treatment Decision-Making

Providers

Providers noted that beyond stem cell transplants (SCT), few treatment options exist for patients with HR-MDS, particularly for older patients. While SCT is the only curative treatment option, most patients with HR-MDS are not transplant eligible. Providers described recommending SCT for patients who were younger, had good performance status, and had no major comorbidities. For patients who are ineligible for SCT, HMAs are considered the standard of care; the majority of providers reported using azacitidine as their preferred HMA treatment. Some providers also discussed the use of targeted therapy for patients with actionable mutations (ie, IDH1/2), though it was noted this was the case for only a small percentage of patients with HR-MDS, or use of combination HMA + venetoclax for patients with high blast percentage and/or rapidly progressing disease. Providers described typically recommening supportive care for patients with LR-MDS or for patients with HR-MDS who are elderly, very frail, have poor performance status, have significant comorbidities, lack social support, have limited mobility, or are not interested in receiving treatment. From providers' perspectives, the most important treatment factors patients prioritized were a combination of efficacy (eg, improvement in survival) and the impact of treatment on quality of life (eg, toxicity, frequency of administration/time spent in the office); however, providers noted that patient age impacts these preferences. Older patients were viewed as wishing to avoid aggressive treatment altogether, and as being more concerned about side effects, financial toxicities, and life disruptions (ie, quality of life).

> Older patients—they're more worried about side effects. They're going to be home by themselves, so they're kind of paying more attention to the side effects. Then elderly with limited transportation or also living far way, then the frequency of the treatments—intervals matter to them. They don't want to come every week. They want to come maybe just once a month. – Provider (urban, university/academic medical center, 6-10 years in practice)

Given the already limited treatment options, options for elderly patients are further limited as they were viewed as more reluctant to undergo therapies that might result in more impactful toxicities or that could be financially draining. Younger patients, however, were viewed by providers as prioritizing life extension and showing greater interest in trying more aggressive treatments that could improve survival.

When caring for patients with HR-MDS, providers reported being supportive of SDM and indicated that they incorporate patient preferences into treatment plans when possible. They noted that difficulties comprehending the HR-MDS diagnosis can make elicitation of preferences a challenging process. Additionally, providers reported that patient participation in SDM varies based on patient factors, ability, and interest in involvement. In general, providers viewed patients who were more highly educated and health literate, regardless of age, as more involved and engaged in decision-making. Providers also reported that comorbidities and cognitive issues, which are more prevalent among older patients, can pose challenges to communicating about prognosis and treatment.

> Some patients are more willing and interested than others, but that often comes to the age, personal experience, education, severity of symptoms, and presence of comorbidities. If somebody, let's say, has dementia, you probably will not have or see much of the engagement, for example. – Provider (urban, multi-specialty group practice, 11-15 years in practice)

Patients and Caregivers

When receiving treatment for HR-MDS the most important treatment factors for patients and caregivers included efficacy and quality of life, specifically related to the time commitment of treatment. While patients had some concerns about treatment-related side effects, they felt they could manage experiencing side effects as long as the treatment was working. Some patients reported explicitly declining provider recommended procedures such as SCT due to age considerations, the time required to spend in the hospital, and lack of caregiver support.

In relation to treatment education and support resources, patients and caregivers noted that not being provided adequate information or educational resources about HR-MDS hampered their ability to participate in informed treatment decision-making. While some patients described being involved in the treatment decision-making process, others described not being presented with any treatment options or opportunities for involvement.

> She [doctor] runs the ship, so she tells him what's gonna happen. I'm not really sure it's really a discussion [laughs], or it's more than just, 'Oh, you're gonna do this. This is what you're gonna do now.' – Caregiver (Female, 62 years old, patient IPSS-R: Intermediate, New York)

Patients also expressed interest in having the opportunity to be involved in the treatment decision-making process and being able to ask questions; however, some desired less involvement and preferred to "not know what's going to happen to them".

> Well, the problem is—to be honest with you, I am the kind of person that would rather be left in the dark. My wife is pretty much handling everything for me. She is the knowledge. She reads the book. She does all of this stuff that—I'll do the treatment, I'll do the plan, but I don't wanna know what's gonna happen to me. – Patient (Male, 64 years old, IPSS-R: Intermediate, Missouri)

Overall, a lack of information and education around MDS appeared to limit patients' ability to engage in the treatment decision-making process or even ask their providers questions.

Disease and Treatment-Related Burden

Providers

From the providers' perspective, the most impactful treatment-related side effects to patients were cytopenias, specifically anemia and the associated fatigue, low WBCs, infections, and gastrointestinal toxicities (eg, nausea, vomiting, diarrhea). In concert with the physical impacts of these side effects (eg, feelings of tiredness, lack of energy, shortness of breath, generally not feeling well) providers emphasized the significant impacts of these side effects on patients' quality of life and activities of daily living, including the ability to drive themselves to appointments.

> Obviously, if you are fatigued, you are not able to look after yourself. Your activities of daily living, your instrumental activities of daily living suffer. Your ability to ambulate may be restricted. You may have need for a caregiver. As far as bleeding and bruising goes, obviously, once again, if you are bleeding and bruising, you are requiring often frequent platelet transfusions. [...] That can be a serious quality of life issue. – Provider (urban, university/academic medical center, 20+ years in practice)

Providers also discussed the psychological impact of HR-MDS on patients and patients' feelings of defeat, specifically during the initial phase of treatment when they may feel worse at first due to the treatment initially worsening cytopenias. Lastly, providers described how symptoms of HR-MDS, particularly fatigue, impact patients' functioning, quality of life, and the lives of their caregivers.

> Some patients it's [fatigue] very challenging. They cannot really get out of bed. It's a struggle, daily struggle for—it's hard to counsel them just to do walking. They're just so tired. They don't have extreme cytopenia. You do give transfusions and give ESA, but it's just hard. It impacts their quality of life as well. – Provider (suburban, NCI Cancer Center, 11-15 years in practice)

Patients and Caregivers

When noting the HR-MDS symptoms and side effects, patients discussed the impact HR-MDS symptoms and treatment-related side effects had on their physical and mental functioning including their overall mobility, ability to travel, mental concentration, sleep, and general ability to perform daily activities, such as caring for pets and driving.

> Tremendously. I retired from working. It was hard to concentrate. I gave up driving because I almost got into two really bad car accidents. I'm literally not the same person that I used to be. It is what it is now. – Patient (Female, 66 years old, IPSS-R: Intermediate, Connecticut)

In support of these challenges, caregivers also described the many social sacrifices the patient had to make due to HR-MDS, including the ability to travel abroad, spend time with friends, and engage in their hobbies. The loss of patient autonomy due to HR-MDS was also emphasized by caregivers, including the patient losing the ability to perform daily tasks such as driving, shopping, and housework, while some patients even had to stop working entirely due to the significant side effect impacts from HR-MDS treatments. Caregivers also discussed the impacts of time toxicity related to the patients care and side effect management. Here, caregivers emphasized the disproportionate amount of time the patient and caregiver spend in clinical settings for routine side effect management or due to hospitalization. Patients and caregivers tended to describe scenarios in which HR-MDS dictated much of their daily lives. This was reflected clearly when patients and caregivers described the general emotional and mental toll that HR-MDS has on patients, including the emotional toll of having to come to terms with having an often-terminal disease and contemplating their own mortality due to their HR-MDS diagnosis, fear of running out of treatment options, and worry for the burdens their loved ones will have to face without them after they pass.

> I will tell you that the biggest thing was accepting that I was at the end of the road. There were no more treatments. There were no more clinical trials. That I just had to accept. My local doctor sent me to <institution>, <name> who's one of the world's experts about MDS and was in treatment with her for two to three years. She also agreed there was nothing left to do. Right now, like I said, if I wake up and I open my eyes, this is a good day. I look at it that way. – Patient (Female, 66 years old, IPSS-R: Intermediate, Connecticut)

Caregiver Role and Burden

Patients and Caregivers

Within our study, caregivers were reflected as highly involved in the patients' overall care management and had varying degrees of involvement in treatment decision-making.

> I went to every appointment. I listened, asked questions and, shall we say, was the horse's mouth. My wife wasn't feeling well, and I had kept track of what happened and when, I had a book, and the doctors would mostly talk to me. – Caregiver (Male, 70 years old, patient IPSS-R: Intermediate, Connecticut)

Specifically, caregivers discussed playing a role across several aspects of the patient's care management including managing medications, appointment scheduling, providing transportation, researching treatment options, recording disease and treatment history, and providing general comfort and care, with some caregivers acting as equal partners in treatment decision-making. However, other caregivers discussed playing a more supportive role surrounding patient decision-making.

Due to the patient's HR-MDS and disease progression, caregivers discussed assuming the full management of their household including household chores, handling finances, and shopping. This level of caregiving for someone with HR-MDS negatively impacted caregivers' social lives, specifically, having little free time for social events, and having to frequently cancel plans due to the patient's HR-MDS symptoms, side effects, or treatment scheduling. Caregiving also impacted caregivers' emotional health as caregivers discussed the emotional struggle of coming to terms with the patients' mortality due to their diagnosis. HR-MDS further burdened caregivers and patients financially with the stress of potentially losing their patients income if they were to pass away from HR-MDS. Alongside the caregiver burden felt amongst HR-MDS caregivers, caregivers also described an overall lack of informative resources available for undertaking the role of caregiving for a patient with HR-MDS. However, when caregivers were able to receive support

resources, such as counseling, they helped caregivers become better carers and aided in managing their anticipatory grief of one day losing the patient.

> The one thing that I think about is there's no school that you go to learn how to be a caregiver. I've gone to therapists since this all started, for caregivers and of course for people who are gonna lose a loved one kind of thing, and that's been very helpful for me. – Caregiver (Male, 70 years old, patient IPSS-R: Intermediate, Connecticut)

Caregiver burden, such as the time commitment and personal sacrifice of caring for a patient with HR-MDS, was also described by patients. When discussed, patients often emphasized encouraging their caregiver to continue to pursue their hobbies and take time away from caregiving, to avoid burnout. Similarly, caregivers noted the need for healthy outlets to help manage their caregiver burden. Therapy, exercise, participating in their hobbies, disease outcomes research, and talking to loved ones about their experiences as a caregiver were primary ways in which caregivers reported coping with their caregiver burden.

Treatment Barriers and Facilitators

Providers

One of the primary challenges with treatment for HR-MDS, and the largest unmet need noted by providers, was the lack of available, effective treatment options. Challenges with current treatment options included limited efficacy, time delay to start working, initial treatment toxicity (eg, cytopenia gets worse initially), and difficulties predicting who will respond to treatment. There are also challenges and logistical barriers (eg, transportation) associated with current treatment options due to the frequency of administration and monitoring requirements which is a significant burden and inconvenience to patients and their caregivers. While some providers noted challenges with the overall costs of treatment adding up for patients (eg, copays, deductibles, transportation, lodging), insurance coverage and costs were generally not a significant barrier to treatment, as the majority of patients have Medicare, and most treatments are covered under Part B. However, for oral therapies specifically, there are challenges with insurance coverage and high out-of-pocket costs which have limited its use in clinical practice. Additionally, challenges with treatment of HR-MDS arise due to patient-related characteristics including age, comorbidities, concurrent medications, mobility limitations, health literacy and understanding of treatment options, and patient motivation to pursue treatment.

> I think that the fact these tend to be older patients, motivation is an issue. I think transportation is an issue. Performance status and comorbidity is sometimes an issue. Transfusions in the setting of cardiac disease and heart failure is sometimes an issue. The issue of the reality of the situation with that, which is that if they're not going to transplant, this is a palliative scenario, which I think is difficult for some patients, especially patients who otherwise would come into this feeling totally fine. – Provider (suburban, partnership practice, 6-10 years in practice)

To minimize treatment barriers and facilitate treatment for their patients with HR-MDS, providers discussed the importance of various support services including nurse navigators, social workers, patient assistance programs, and educational materials.

Patients and Caregivers

Primary treatment barriers discussed by patients and caregivers included insurance coverage, lack of information sharing, and access to treatment centers. Insurance barriers were reported by both patient and caregiver participants, noting how insurance barriers impacted the patients' ability to receive specific treatments for HR-MDS. Additionally, the lack of MDS experience by local clinicians resulted in some participants having to travel long distances to receive better care for their HR-MDS at more specialized care centers.

> My biggest barrier, I think, is the fact I live in a relatively small, mid-sized town. To go to <institution>, which is the closest center of excellence, it's a two-and-a-half-hour drive. – Patient (Female, 72 years old, IPSS-R: Very High, Florida)

Specifically, patients discussed how a lack of treatment information, including information about clinical trials, impacted their ability to engage in SDM and acted as a barrier against the patient's ability to make informed decisions surrounding their care.

> I wasn't aware of makin' any decisions on anything. This was just like; this is what we're gonna give you. I didn't know. Probably had I was told that so many people have taken this drug, so many people have taken that drug. We had a better response with the people takin' this one, then I probably would've chosen the one with the higher percentage, but I wasn't given any information. – Patient (Female, 58 years old, IPSS-R: High, Texas)

Other treatment barriers described by patients and caregivers included medication and blood shortages which impacted treatment plans and schedules, and patient's having comorbidities, which further limited the patients' treatment options. Notably, care team responsiveness, proximity to care, and accessible communication channels such as telehealth and online patient portals were viewed as key treatment facilitators by patients and caregivers.

Discussion

Little research on the treatment decision-making process for HR-MDS exists. Of the few studies that have described the broad impacts of MDS all but one have done so quantitatively, and there is a lack of stakeholder insights on treatment experiences and disease impacts amongst patients with HR-MDS, their caregivers, and providers.[19] While our qualitative findings are based on a limited sample of stakeholders, several key findings are worth noting and highlighting for further research. This study revealed some discordance between providers and patients and/or their caregivers around how much education and communication about HR-MDS is appropriate or desired. In addition, limited treatment options for HR-MDS are recognized as a barrier by all stakeholders and caregivers described multiple negative impacts from their caregiving.

This study revealed a complex story about education and communication about HR-MDS, with some discordant beliefs between providers and patients and caregivers. Some patients and caregivers expressed interest in furthering education and communication about available treatment options and a desire to better understand the disease itself. However, because HR-MDS is complicated to explain, providers may oversimplify their descriptions and in so doing, may not provide the requisite information patients need and are seeking. There are few treatment options currently available to patients. With few treatment options available, it becomes challenging for the provider to address the topic with patients and may lead providers to overlook the need to explain the few options available to patients. Some patients and caregivers may not know that they are lacking information about the disease and treatment approaches and may not be equipped to know how to ask pertinent questions. Further complicating the matter, patients may vary considerably in their ability to comprehend health information. These factors create a situation that is perfectly poised to hamper and reduce effective communication and shared treatment decision-making between patients, caregivers, and providers of those with HR-MDS. Our findings are in-line with and provide color to the results of a survey study looking at preference for involvement in treatment decisions among newly diagnosed patients with HR-MDS (Efficace et al).[26] In this study they report that, "decision-making preferences vary among newly diagnosed higher-risk MDS patients. Also, the number of patients who preferred to leave treatment decisions to their physicians (47%) was remarkable." Because of the heterogeneity in patient ability and desire for education and communication about HR-MDS and treatment options, providers need to be reminded of the importance of actively assessing patients' desire and ability to be involved in all aspects of treatment decision-making.

Treatment barriers described by providers centered on limited effective treatment options for HR-MDS, compounded by the struggle providers face with finding suitable treatments that consider age, comorbidities, concurrent medications, mobility limitations, health literacy and understanding of treatment options, and patient motivation to pursue treatment. In Crawford et al's analysis of YouTube videos made by patients or caregivers of patients with AML or other hematologic cancers, they found that the lack of a clearly defined treatment pathway for these conditions created feelings of resentment among patients.[27] Rather, the patients and caregivers we interviewed expressed confusion about the lack of treatment options, perhaps due to the small sample of our study or perhaps those with AML feel a greater sense of urgency for effective treatments than those with HR-MDS. Instead, treatment barriers reported by patients and caregivers in our study tended to be broader, including how although many patients with HR-MDS have treatments that are covered under Medicare Part B, oral therapies were associated with insurance coverage issues and high out-of-pocket costs. Additionally, a lack of MDS experience by local clinicians resulted in some participants having to travel long distances to

receive better care for their HR-MDS at more specialized care centers. Patients also noted how medication and blood shortages—which impact treatment plans and schedules—as well as patient comorbidities further limit treatment options overall.

Similar to the findings of Frank et al's qualitative study on the emotional and support needs of caregivers of patients with HR-MDS,[28] our findings include descriptions of negative impacts to caregivers' social lives, emotional health, and financial state, along with personal sacrifice and time toxicity. In general, caregivers also recognize the need for healthy outlets to help manage the caregiver burden and described making use of therapy, exercise, hobbies, and sharing concerns with loved ones as common coping mechanisms. Ultimately, patients and caregivers viewed care team responsiveness, proximity to care, and accessible communication channels such as telehealth and online patient portals as key treatment facilitators.

Insights gained through this work add valuable knowledge to the literature, furthering the understanding of patient, caregiver, and provider perspectives and experiences with HR-MDS. Additional qualitative and quantitative research should be conducted to confirm and expand upon these findings among patients with HR-MDS and caregivers to people with HR-MDS. In particular, additional qualitative dyad research with patients with HR-MDS and their providers would help to elucidate the complexities of proper education and communication about the diagnosis and treatment approaches for HR-MDS. Further work should explore practical approaches to improving accessible education and communication tools designed to inform and facilitate productive conversations to be used in SDM.

Study Strengths and Limitations

A strength of this study design is the use of qualitative data collection techniques, which enables the capturing of perspectives across a broad spectrum of patients, caregivers, and providers. The methodology allows an in-depth exploration of perspectives and experiences not possible in quantitative surveys. Furthermore, a key strength of this study is the collaborative approach to designing the qualitative discussion guides with input from patients and representatives from a patient advocacy group.

A limitation inherent in most qualitative research designs is external validity. While the study aimed to include participants from a variety of sociodemographic backgrounds, the study results may not apply to all patient, caregiver, and provider experiences. Notably, patient and caregiver participants were predominantly white, educated, retired, and caregivers were predominantly female, which may limit the generalizability of the findings. Additionally, this study was limited to those with English proficiency and those with access and ability to use technology. Furthermore, given recruitment was conducted online via survey panels and a patient advocacy group using convenience sampling methods, and participation was voluntary, selection bias may be present. The patients, caregivers, and providers participating in this study may be more enthusiastic about the study subject or face more challenges than those who chose not to participate. Additionally, the information collected was self-reported, including diagnosis of MDS and risk category, and as such, prone to reporting bias. Efforts were made to reduce this potential, including asking questions specific to the diagnosis and treatment regimen in the eligibility screener. Further, the methodology of this study – focus groups and interviews – discourages potential participants from falsifying diagnoses and treatment experiences as they are expected to describe their treatment journey in detail with the research team.

Conclusion

Our findings provide in-depth insights into patient, caregiver, and provider experiences with HR-MDS and illustrate the complexities of HR-MDS education and communication. Providers described challenges explaining the nuances of an HR-MDS diagnosis which is further complicated by limited treatment options. Meanwhile, patients and caregivers reported feeling underinformed hindering their ability to effectively engage in SDM. Although all stakeholders valued strong patient-provider communication, uncertainty remains around how to best involve patients in HR-MDS treatment decisions, particularly given the variability in patients' ability and desire to engage SDM. As novel therapies emerge and treatment options expand, these results underscore the need for improved patient-centered approaches, such as accessible educational materials to facilitate effective communication and promote patient-centered treatment decision-making in HR-MDS. Additional barriers to treatment of HR-MDS focused on the lack of effective treatment options, the clinical

complexities of treating or receiving care for HR-MDS, patient access to specialized care centers, and insurance coverage. Further, this study highlighted the significant burden HR-MDS places on caregivers and illustrated the importance of the role caregivers play in the HR-MDS treatment journey.

While this study contributed to the limited literature on treatment decision-making in HR-MDS by capturing in-depth perspectives across multiple stakeholder groups, the study included a small sample of self-selected participants thus findings may not be generalizable to all HR-MDS experiences. Future research should further explore perspectives and experiences amongst broader HR-MDS patient and caregiver populations, including patient-provider dyads to better understand communication barriers and facilitators to promote patient-centered care in HR-MDS.

Abbreviations

MDS, myelodysplastic syndromes; US, United States; AML, acute myeloid leukemia; NCCN, National Comprehensive Cancer Network; IPSS-R, Revised International Prognostic Scoring System; LR-MDS, lower-risk MDS; HR-MDS, higher-risk MDS; HCT, hematopoietic cell transplant; HMAs, hypomethylating agents; SDM, shared-decision-making; RBCs, red blood cells; WBCs, white blood cells; SCT, stem cell transplant.

Ethics Approval

The Advarra Institutional Review Board reviewed all study procedures for this non-interventional observational study and granted this study an exemption from ethical approval (Pro00069879). Using the Department of Health and Human Services regulations found at 45 CFR 46.104(d)(2), the IRB determined that this research project was exempt from IRB oversight. As outlined in this regulation, research may be considered exempt when there is minimal risk to participants and identifiable information is protected.

Ethics Statement

All study procedures were performed in accordance with the principles outlined in the Declaration of Helsinki.

Consent to Participate

Informed consent was obtained from all individual participants included in the study. Informed consent included consent for the publication of anonymized responses from participants.

Acknowledgments

The authors thank the patients, caregivers, and providers who participated in this study for sharing their experiences and insights.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded by Gilead Sciences, Inc. The sponsor was involved in the design of the study, the review and approval of the manuscript, and the decision to submit the manuscript for publication.

Disclosure

MCM, NL, and CC are employees of Precision AQ, a consulting firm that received research funding from Gilead Sciences, Inc. in relation to this project. MCM owns equity interest in Precision AQ's parent company, Precision Medicine Group. SGM and NP were employees of Precision AQ when this study was conducted. TZJ and CH are employees of Gilead Sciences, Inc. EJS and NA were employees of Gilead Sciences, Inc. when this study was conducted.

TI was an employee of the MDS Foundation when this study was conducted. KB reports no competing interests. The authors report no other conflicts of interest in this work.

Gilead Sciences, Inc. no longer develops any pharmaceutical drugs or related product for MDS. This research is solely aimed at contributing to a topic that is critical for patient's living with MDS and under-reported in the literature.

The abstract of this paper was presented at the American Society of Hematology Annual Meeting as a poster presentation with interim findings. The poster's abstract was published in "The 2023 Annual Meeting Poster Abstracts" in Blood: https://doi.org/10.1182/blood-2023-181976.

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