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Patients' perspectives on oral decitabine/cedazuridine for the treatment of myelodysplastic syndromes/neoplasms

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Abstract

Background: Hypomethylating agents (HMAs) are guideline-recommended treatment for higher-risk myelodysplastic syndromes/neoplasms (MDS). However, *a prior* survey of patients with MDS reported challenges with intravenous (IV) and subcutaneous (SC) HMA therapies, including pain related to treatment administration and interference with daily activities; most patients also indicated a preference to switch to an oral therapy if one were available.

Objectives: This study evaluated the perspectives of US patients with MDS receiving oral decitabine/cedazuridine (DEC-C), an alternative to IV/SC HMAs.

Methods: An online survey was conducted among adult patients with MDS in the United States (10 November 2022 to 5 December 2022) who had filled a prescription for oral DEC-C between 2021 and 2022.

Results: A total of 150 patients completed the survey; 61% were aged ⩾60 years and 63% were male. Of these, 123 (82%) were still receiving oral DEC-C, and 27 (18%) had stopped oral DEC-C treatment. Half (50%) of patients had received oral DEC-C for ⩾6 months. The majority reported that treatment was convenient (83%) and that they were satisfied with treatment (86%). Most patients also reported very little/no interference with regular daily activities (82%), social activities (78%), and productivity (78%). When queried about negative impacts on quality of life (QOL), treatment side effects were the most commonly reported (30% of respondents). Among patients who had previously received IV/SC HMAs ($n = 91$), most agreed that oral DEC-C interfered less with daily life (91%) and had experienced improvement in QOL (85%) compared with previous treatment; 91% reported that oral DEC-C reduced the number of times they needed to travel to a healthcare facility.

Conclusion: Survey results suggest very little/no impact on regular daily activities and improved QOL with oral DEC-C relative to IV/SC HMAs, highlighting the potential for oral DEC-C to reduce the treatment burden associated with parenteral HMA therapy.

Keywords: hypomethylating agents, myelodysplastic syndromes, oral decitabine and cedazuridine, patient perspectives, quality-of-life

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Introduction

Myelodysplastic syndromes/neoplasms (MDS) are a heterogenous group of myeloid cancers characterized by inadequate bone marrow hematopoiesis and a variable risk of progression to acute myeloid leukemia (AML).[1,2] As of 2020, the estimated age-adjusted prevalence rate of MDS in the United States was reported as 3.4 cases per 100,000 individuals, with 60,041 individuals living with the disease.[3] Most patients with MDS are older adults; median age at diagnosis is approximately 77 years, and the incidence

increases greatly after the age of 70 years. Higher incidence of the disease is also observed among males compared with females (58% *versus* 42%).[3] MDS is associated with a broad range of symptoms including fatigue, shortness of breath (dyspnea), bruising and bleeding easily, and frequent infections, which impose a significant burden on patients with negative consequences to quality of life (QOL).[4–6]

Guidelines and recommendations for the treatment of MDS vary across countries worldwide.[2,7,8] In the United States, hypomethylating agents (HMAs) are recommended for the treatment of adult patients with higher-risk MDS (HR-MDS) and are also often used at lower doses in patients with lower-risk MDS (LR-MDS) after failure of other options,[7] while in Europe, HMA therapy is recommended for HR-MDS but not endorsed for LR-MDS.[2,8] Until recently, the only approved HMAs were decitabine (approved for MDS in the United States and Canada but not Europe) and azacitidine.[8–10] Decitabine is administered *via* intravenous (IV) infusion either every 8 hours for 3 days every 6 weeks or daily for 5 days every 4 weeks, and azacitidine is administered *via* IV infusion or subcutaneous (SC) injection daily for 7 days every 4 weeks.[9,10] Guidelines recommend at least 4–6 cycles of HMA therapy to elicit response in the absence of progression or until unacceptable toxicity.[7,9,10] Although clinical trials have demonstrated clear improvements in response rates with decitabine and azacitidine treatment, compared with conventional and supportive care,[11–13] real-world studies have shown that parenteral HMAs are substantially underutilized in clinical practice.[14,15] In retrospective claims analyses conducted in the United States between 2010 and 2020, it was reported that 44%–65% of patients with HR-MDS did not receive IV/SC HMA therapy.[14–17] Furthermore, among patients who received IV/SC HMAs, 44% were non-persistent with therapy, discontinuing before four cycles of therapy or having a gap of 90 days or more between consecutive HMA cycles.[14,16,17]

Underuse of HMA therapy has been associated with worse survival outcomes. In a real-world analysis in the United States, patients who were persistent with HMAs had higher overall survival (13.8 months) compared with those who were non-persistent (9.5 months) and with those not receiving HMAs (3.8 months).[14] HMA underuse is also associated with a burden on healthcare resource utilization (HCRU), with higher total per-patient-per-month healthcare costs reported among patients who were non-persistent with HMAs compared with those who were persistent ($18,039 *versus* $13,893).[16–18] Previous studies on patients' experiences with IV/SC HMA therapy have highlighted the treatment burden associated with parenteral HMA administration.[19,20] In a prior survey conducted in the United States, patients reported pain and anxiety before and during IV/SC HMA therapy, interference with daily activities, and logistical challenges related to IV/SC administration of HMAs.[19] Around 70% of patients in previous surveys also indicated they would prefer to switch to an oral treatment if one were available.[19,20]

Oral decitabine/cedazuridine (DEC-C) was approved in July 2020 by the US Food and Drug Administration and in Canada and subsequently Australia, for the treatment of intermediate and high-risk MDS groups as defined by the International Prognostic Scoring System.[21–23] Oral DEC-C is a fixed-dose combination of decitabine, a nucleoside metabolic inhibitor, and cedazuridine, a cytidine deaminase inhibitor, which increases systemic exposure of decitabine.[21] Oral DEC-C has shown similar pharmacokinetic exposure and response rates to IV/SC HMAs, thereby providing an alternative to parenteral HMA treatment,[12,13,21] which offers the potential to reduce patient burden through self-administration of therapy at home compared with parenteral administration in the clinical setting.[9,10,21,24] However, while patients' experiences with IV/SC HMAs have been documented in prior studies,[19,20] there are limited data on the treatment experiences of patients receiving oral DEC-C therapy to date.

This study aimed to evaluate the perspectives of patients with MDS receiving oral DEC-C in US clinical practice, as an alternative to IV/SC HMAs, by examining patients' views on convenience and satisfaction with treatment, impact on daily activities and QOL, and overall experience with oral DEC-C treatment compared with other HMA therapies.

Methods

Study design and sampling

This was a non-interventional web-based survey study of patients with MDS living in the United

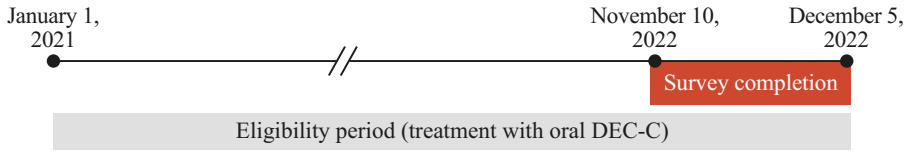

Figure 1. Patient survey design.
DEC-C, decitabine/cedazuridine.

States, conducted between 10 November 2022 and 5 December 2022 (Figure 1). Hematologists and oncologists were asked to screen and recruit eligible patients within their practice, based on information available in patients' chart records. Patients were eligible if they had filled a prescription for oral DEC-C during the eligibility period (1 January 2021 to 5 December 2022), were aged 18 years or older, and were residents of the United States. Patients also had to be fluent in English, with the ability to read and write. The demographics of the respondents were monitored to ensure that the survey cohort mirrored the diversity of the actual MDS patient population. Institutional Review Board exemption was received for this project as risk was minimal; all patients were required to provide online consent for participation in the web-based survey and those unwilling to provide consent were excluded. The reporting of this study conforms to the Checklist for Reporting Results of Internet E-Surveys statement (Supplemental Material S1).

Survey design

The online survey was programmed using Alchemer software (Alchemer LLC). It comprised a 25-item questionnaire, which included 23 fixed-response questions and 2 free-text questions (Supplemental Material S2), and the estimated completion time of the survey was 15 min. The survey included screening questions designed to confirm eligibility, followed by questions on patient demographics. The remaining questions focused on patients' experiences with oral DEC-C and included items on treatment convenience, treatment satisfaction, and ease of receiving oral DEC-C. Patients were also asked if they had taken IV/SC treatments for MDS, and those who had received prior HMAs were required to complete further questions about their experience with oral DEC-C compared with previous IV/SC HMA therapies. Two free-text questions were also included in the survey to assess how oral DEC-C impacted upon patients' QOL, either positively or negatively.

Data management and analysis

Patient responses were analyzed descriptively; continuous variables were summarized as means and standard deviations and categorical variables were summarized as percentages. Demographics and treatment patterns were assessed for the full patient cohort and responses on patients' treatment experience were analyzed for the full cohort and also for patient subgroups, according to those who were still receiving oral DEC-C and those who had stopped receiving oral DEC-C.

Results

Patient demographics and treatment patterns

Of the 162 patients who were approached to complete the survey, 12 were excluded (5 who did not meet the inclusion/exclusion criteria and 7 who did not complete the survey in full). Among the 150 respondents who met the eligibility criteria and fully completed the survey, 61% were aged 60 years or over and 63% were male (Table 1). Most respondents (71%) reported being White or Caucasian, 18% African American or Black, and 7% Asian. At the time of the survey, 82% of patients stated they were still receiving oral DEC-C and 18% had stopped treatment. Duration of treatment ranged from 1-20 months and half the patients (50%) reported taking oral DEC-C for 6 months or more. Overall, almost two-thirds of patients (61%) reported receiving IV/SC HMAs prior to oral DEC-C treatment (Table 1), and within the eligibility period (2021–2022), 15% and 7% of patients reported receiving IV and SC azacitidine, respectively, and 1% reported decitabine use.

Convenience and satisfaction with oral DEC-C

Most patients (83%) reported that oral DEC-C treatment was convenient or extremely/very

Table 1. Demographics and treatment patterns among respondents ($N = 150$).

Characteristics	All respondents ($N = 150$), *n* (%)
Age range, years	
20–29	1 (1)
30–39	9 (6)
40–49	22 (15)
50–59	26 (17)
60–69	70 (47)
70–79	20 (13)
80–89	2 (1)
Male	94 (63)
Race[a]	
African American or Black	27 (18)
Asian	11 (7)
White or Caucasian	106 (71)
Other/prefer not to answer	9 (6)
Urban/rural	
Rural (<50,000 people in community)	19 (13)
Suburban (50,000–149,999 people in community)	81 (54)
Urban (≥150,000 people in community)	49 (33)
Don't know	1 (1)
Currently receiving oral DEC-C	
Yes	123 (82)
No	27 (18)
Duration of treatment, months	
1	3 (2)
2	13 (9)
3	23 (15)
4	22 (15)
5	14 (9)
≥6	75 (50)
Received IV/SC HMAs prior to oral DEC-C	
Yes	91 (61)
No	59 (39)
HMAs received during (2021–2022)	
Oral DEC-C	150 (100)
Azacitidine (IV)	22 (15)
Azacitidine (SC)	10 (7)
Decitabine	2 (1)

[a]Participants could be included in ≥1 category; therefore, percentages do not add up to 100%.
DEC-C, decitabine/cedazuridine; HMA, hypomethylating agent; IV, intravenous; SC, subcutaneous.

convenient [Figure 2(a)], and 86% reported that they were satisfied or very satisfied with oral DEC-C treatment [Figure 2(b)].

Impact of oral DEC-C treatment on daily activities

Respondents reported minimal impact from oral DEC-C treatment on activities of daily living. Most patients reported very little or no interference from oral DEC-C treatment on their regular daily activities (82%), social activities (78%), and overall productivity, which included work activities, volunteer activities, or hobbies (78%; Figure 3). For respondents who were aged 70 years or older, 64% reported very little or no interference with their overall productivity ($n = 14$). For respondents who were younger than 70 years, 80% reported very little or no interference with their overall productivity ($n = 103$).

When asked in a free-text question to explain how oral DEC-C had impacted their QOL, either positively or negatively, 'side effects' was the most commonly used term among patients (mentioned by 30% of respondents; $n = 45$) when describing a negative impact from oral DEC-C on QOL.

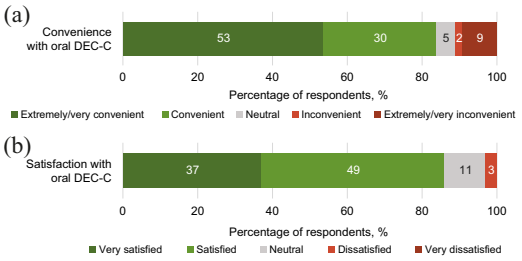

Figure 2. Convenience (a) and satisfaction (b) with oral DEC-C treatment (*N* = 150).
Some percentages do not add up to 100% due to rounding.
DEC-C, decitabine/cedazuridine.

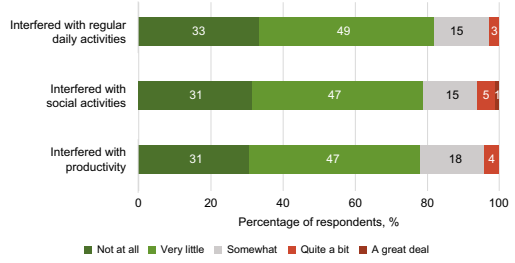

Figure 3. Impact of oral DEC-C treatment on respondents' daily activities (*N* = 150).
Some percentages do not add up to 100% due to rounding.
DEC-C, decitabine/cedazuridine.

Comparison of oral DEC-C treatment with prior IV/SC HMAs

Among the patients who had received IV/SC HMAs prior to receiving oral DEC-C (*N* = 91), most reported a positive treatment experience with oral DEC-C. Most patients in this group strongly agreed or agreed that oral DEC-C interfered less with daily life (91%) and made it easier to cope with the disease (75%) compared with IV/SC HMAs (Figure 4). Most patients also strongly agreed or agreed that oral DEC-C helped them be independent (86%) and reduced the number of encounters at a healthcare facility (91%). When asked to compare oral DEC-C with prior IV/SC HMA treatments received, most respondents felt a personal benefit from taking oral DEC-C (79%) and experienced an improvement in QOL from treatment (85%). Most respondents were also glad they switched to oral DEC-C from previous IV/SC HMA treatment (89%; Figure 4).

Patients' treatment experience with oral DEC-C, stratified according to patients who were still receiving or had stopped receiving oral DEC-C at time of survey

The majority of patients reported a positive experience with oral DEC-C treatment, regardless of whether or not they were still receiving treatment at the time of the survey. While positive responses were more frequent among patients still receiving oral DEC-C compared with those who had stopped treatment, more than 75% of patients who had stopped treatment reported convenience with oral DEC-C treatment, and more than half of patients also reported satisfaction with treatment and minimal impact on regular daily activities (Supplemental Material S3).

Discussion

To our knowledge, this is the first study reporting patients' experiences with an oral HMA for MDS in the real-life setting. Patients reported convenience and satisfaction with oral DEC-C treatment with very little or no negative impact on regular daily activities. Oral DEC-C treatment also reduced the number of times needed for patients to travel to healthcare facilities. Patients who had received prior IV/SC HMAs felt a personal benefit and improvement in QOL from receiving oral DEC-C, relative to IV/SC HMA treatment. Notably, most patients who had previously received IV/SC HMAs expressed satisfaction with the switch to oral DEC-C.

Results from this survey of patients with MDS receiving oral DEC-C may be considered alongside previous results from surveys of patients with MDS receiving IV/SC HMAs. These prior studies have reported a significant treatment burden and interference with daily activities associated with IV/SC HMA use.[19,20] A patients' perspectives survey reported that only half of patients (56%) found IV/SC HMA treatment convenient, and approximately one-third of patients felt that IV/SC HMA treatment interfered 'a great deal' and 'quite a bit' with their regular daily activities (32%) and social activities (30%).[19] This study also revealed the time burden imposed on patients receiving IV/SC HMAs, with almost half of patients (42%) needing to travel for at least 1 h to a treatment center to receive parenteral therapy.[19] Notably, 70% of patients in this survey indicated

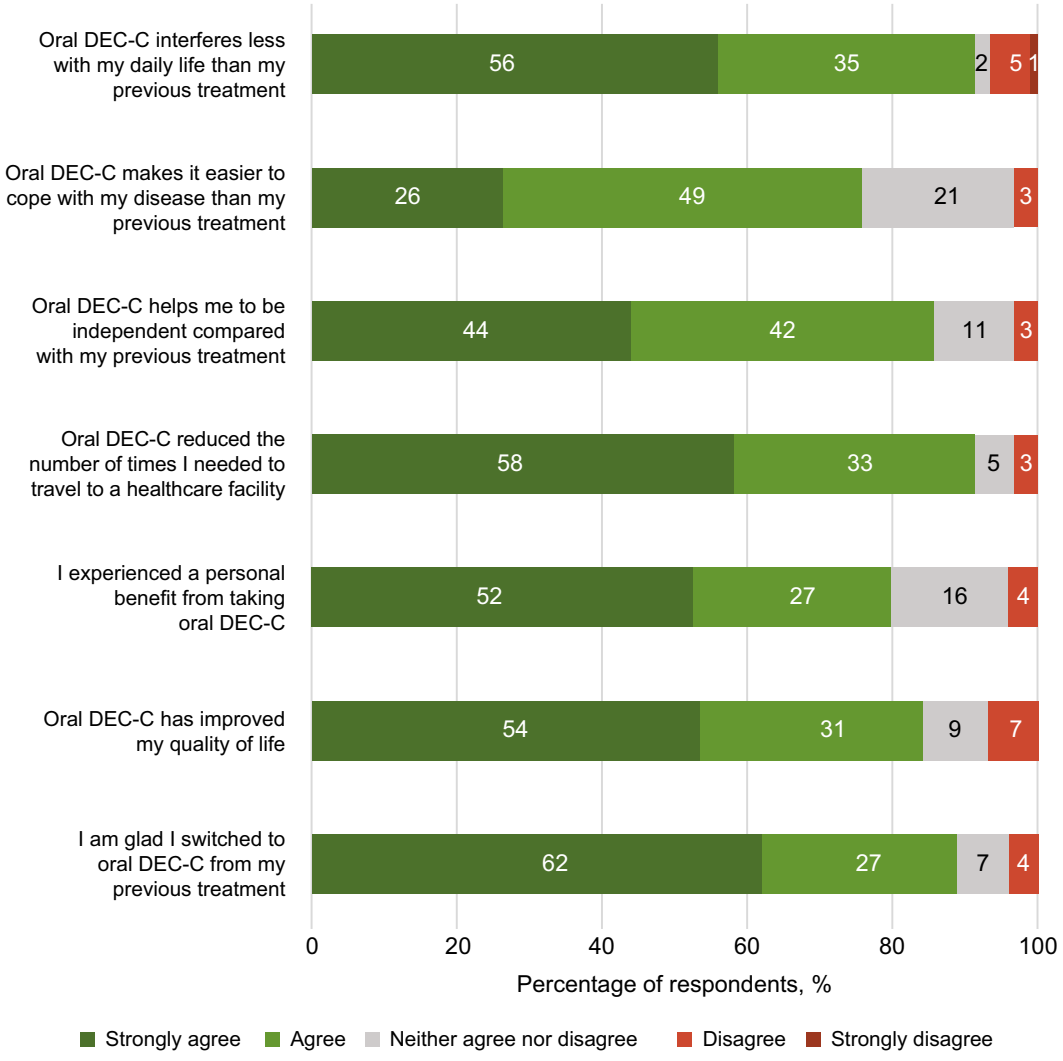

Figure 4. Patient experience with oral DEC-C in comparison with IV/SC HMAs (*N* = 91).
Some percentages do not add up to 100% due to rounding.
DEC-C, decitabine/cedazuridine; HMAs, hypomethylating agents; IV/SC, intravenous and subcutaneous.

they would prefer to switch to an oral treatment.[19] Similarly, a discrete choice experiment identified frequency and duration of visits to healthcare facilities and mode of administration as key drivers of treatment preference among patients with MDS.[20] Assuming the same risk of AML transformation, level of fatigue, and number of visits for treatment, 77% of respondents indicated preference for an oral HMA option if it were available.[20] Patients' preferences for HMA should be considered in treatment decision-making.

From the time of diagnosis, patients with MDS experience substantial disease burden and significantly reduced health-related QOL, compounded with restrictions in mobility and, compared with population norms, increased anxiety and depression.[6,25] A recent prospective analysis of patient-reported outcomes among a large cohort of patients with newly diagnosed MDS revealed clinical implications with physical functioning, fatigue, and dyspnea in more than half of patients assessed, in advance of receiving treatment and/or interventions.[6] In addition, MDS is associated with considerable treatment burden as a majority of patients also require red blood cell and platelet transfusions to manage cytopenias.[26,27] Studies have shown that transfusion dependence negatively impacts QOL; in a survey of patients with MDS requiring red blood cell transfusions,

patients reported interventions that reduced visits to the clinic would improve QOL.[26,27] In this survey, patients receiving oral DEC-C reported an improvement in QOL and a personal benefit from oral DEC-C treatment. These improvements in QOL with oral DEC-C are noteworthy as they are in contrast to the anxiety associated with IV/SC HMA treatment and interference with social and daily activities reported by patients in a previous survey.[19]

Overall, the findings from the current study are consistent with other studies conducted among patients with other cancer types, including breast, lung, ovarian, and colorectal cancers, in which a majority of patients have reported preference for oral *versus* parenteral therapy.[28–31] In those studies, patients stated that convenience, the ability to receive treatment at home, and flexibility in the treatment schedule were key attributes associated with their preference for oral treatment.[28,29] Other factors reported that support oral therapy included increased autonomy, previous issues with IV treatment and anxiety over IV lines and needles, and preference for receiving medication outside of the clinic.[28,31] While some physicians and patients may have concerns that the disease may be more difficult to manage with oral medication due to reduced hospital visits and medical supervision,[32] most patients who participated in the current and prior surveys reported that oral treatment made it easier to cope with the disease.[28,31]

In particular, a reduction in the number of hospital visits has been identified as a positive attribute contributing to preference for oral *versus* IV/SC therapy in patients with MDS and with other types of cancer.[20,28] Time toxicity, a measure of the time spent in coordinating care and visiting healthcare facilities (including travel and treatment times, seeking urgent care for side effects, hospitalization, and follow-up tests), is increasingly gaining traction as a metric to determine the appropriate cancer treatment for patients.[33–35] A recent survey study among oncologists identified waiting to receive infusion, waiting for a physician, and labs and scans as the top three sources of time toxicity.[36] As patients with MDS receiving IV/SC HMAs are required to visit healthcare facilities between 3 and 7 times a month for HMA treatment, often in addition to red blood cell and platelet transfusions,[9,10,26,27] a reduction in the frequency of visits due to self-administration of oral DEC-C has the potential to improve time toxicity for patients with MDS. Ongoing studies measuring the time toxicities associated with oral DEC-C and IV/SC HMA therapies will provide meaningful insight into the time burden experienced by MDS patients and further quantify the impact of receiving oral DEC-C at home compared with IV/SC HMAs in the clinic.

A concern among healthcare practitioners is treatment adherence to oral medication, and data on adherence to oral agents are limited.[32,37] Prior and ongoing real-world data on MDS patients receiving oral DEC-C and IV/SC HMAs may help dispel these concerns, as results suggest similar or improved compliance with oral DEC-C compared with IV/SC HMA therapy and trends toward improved persistence at 6 months and beyond.[38,39] Ongoing analysis of real-world treatment patterns will further determine adherence and persistence among patients receiving oral DEC-C *versus* IV/SC HMA treatment.

Previous studies have demonstrated that adherence and persistence with HMA treatment may be associated with reduced HCRU in the long term.[16,18] While the survey did not evaluate HCRU and costs incurred by patients receiving oral DEC-C *versus* IV/SC HMAs, treatment with oral DEC-C at home could potentially reduce HCRU and related costs, while maintaining efficacy, due to fewer visits to healthcare facilities compared with parenteral HMA therapy. Reduced visits to healthcare facilities with oral DEC-C treatment could also potentially lead to savings in travel costs for patients and caregivers and costs related to work absenteeism and lost wages as observed in studies conducted in other disease areas.[40–42] Studies evaluating HCRU and costs and persistence with oral DEC-C and IV/SC HMAs are ongoing to assess the economic benefit of oral DEC-C over parenteral HMA therapy.

This study provides the first descriptive patient-centric report of treatment experience with oral DEC-C for MDS in the United States. The survey also includes higher participation of African American or Black patients, a racial group typically underrepresented in cancer clinical trials, than the prior surveys in MDS (18% *versus* <13%), thus improving the generalizability of

these results.[43] However, certain limitations should be considered for this study. There is the potential for selection bias, as use of an online survey may favor the pool of participants toward a younger, more technologically proficient population; hematologists and oncologists who were responsible for offering the survey to patients could also introduce further bias. Costs and financial considerations for patients and insurance coverage information, which would also introduce selection bias, were not addressed in this study. Furthermore, 39% of patients surveyed had not received prior IV/SC HMAs, which may introduce bias to some of the survey responses (for questions that included the full cohort), as these patients would not have had a point of comparison for their experience with oral DEC-C treatment. It is also noteworthy that patients with a positive experience may be more likely to respond to the survey. In addition, the respondents self-reported treatment history, which was not confirmed by physicians or medical records. MDS severity was also not specified among patients in this survey, as the inclusion criteria did not differentiate between HR-MDS or LR-MDS patient groups; however, it is expected that most of the study population had higher-risk disease based on treatment. Reasons for treatment discontinuation were also not captured in this survey, and further research on the reasons underlying decisions to stop treatment is warranted. Finally, the differing provisions in non-US health systems and variability in home care delivery feasibility of injectable HMAs will limit the application of these results to other countries.

Conclusion

This US-based study is the first to describe patient experience with an oral HMA for MDS. Patients reported oral MDS treatment to be convenient and reported high levels of satisfaction. Patients reported very little or no impact on regular daily activities, improved QOL, and a reduction in the amount of travel required to healthcare facilities with oral DEC-C relative to IV/SC HMA treatment. These findings add to the body of evidence suggesting the potential for oral DEC-C to enhance QOL and to alleviate the treatment burden and time toxicity associated with parenteral HMA therapy. Future analyses comparing time toxicity including healthy days at home, treatment adherence, and real-world effectiveness among patients receiving oral DEC-C *versus* IV/SC HMAs will provide insights for patients and clinicians in treatment decision-making.

Declarations

Ethics approval and consent to participate

Institutional Review Board exemption was received for this project as risk was minimal. All patients were required to provide online consent for participation in the web-based survey, and those unwilling to provide consent were excluded.

Consent for publication

Not applicable.

Author contributions

Amer M. Zeidan: Conceptualization; Writing – review & editing.

Kate Perepezko: Conceptualization; Data curation; Formal analysis; Methodology; Validation; Writing – review & editing.

Tehseen Salimi: Conceptualization; Writing – review & editing.

Terri Washington: Conceptualization; Writing – review & editing.

Robert S. Epstein: Conceptualization; Writing – review & editing.

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Competing interests

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Incyte, Agios, Servier, Boehringer-Ingelheim, Novartis, Astellas, Daiichi Sankyo, Geron, Taiho, Seattle Genetics, Otsuka, BeyondSpring, Takeda, Ionis, Amgen, Janssen, Genentech, Epizyme, Syndax, Gilead, Kura, Chiesi, ALX Oncology, BioCryst, Notable, Orum, Mendus, Zentalis, Schrodinger, Regeneron, Syros, and Tyme; and has served on clinical trial committees for Novartis, Gilead, Syros, BioCryst, Abbvie, ALX Oncology, Kura, Geron, and Celgene/BMS. KP is an employee of CorEvitas LLC, paid consultants to Taiho Oncology, Inc. TS and TW are employees of Taiho Oncology, Inc. RSE is an employee of Epstein Health; holds leadership positions in Illumina, Veracyte, Fate Therapeutics, Tasso, and Diadem; and has received consulting fees and/or equity from TriAxia Health, Health Rhythms, Tasso, Avalon Healthcare, Halozyme, Merck, Janssen, Radius Health, G1 Therapeutics, and Taiho Oncology, Inc.

Availability of data and materials

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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