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REVIEW

Health-related quality of life of patients with acute myeloid leukemia and myelodysplastic syndromes/neoplasms treated with decitabine: a systematic literature review

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Abstract

Decitabine, including its new oral formulation (decitabine-cedazuridine, DEC-C), is commonly used in AML and MDS, particularly in older or unfit patients. While its clinical efficacy and tolerability are well documented, evidence regarding patient-reported outcomes (PROs) and health-related quality of life (HRQoL) remains limited. We conducted a review of the available literature on PROs in patients with AML and MDS treated with decitabine, with the aim of evaluating its impact on HRQoL, symptom burden, and patient preferences. A systematic literature search of PubMed up to October 2024 identified studies evaluating HRQoL or PROs in adult AML and/or MDS patients receiving decitabine, regardless of study design. Ten studies met the inclusion critera. Decitabine-based regimens were associated with preservation of HRQoL compared with intensive chemotherapy and improvements in fatigue and physical functioning versus best supportive care. In patients with AML, baseline HRQoL scores were found to be predictive of survival outcomes. Surveys consistently indicated strong patient preference for oral DEC-C due to reduced treatment burden and greater convenience, though longitudinal data remain limited. In conclusion, currently available HRQoL evidence for decitabine provides meaningful insight to guide further research. Findings from patient surveys and the availability of decitabine in both intravenous and oral formulations emphasize new treatment aspects that can be effectively captured through PROs. Their systematic integration may help uncover critical issues such as symptom burden, adherence, and patient priorities, ultimately fostering more patient-centered care.

Keywords Myelodysplastic syndrome · Acute myeloid leukemia · Decitabine · Quality of life · Patient reported outcomes

Introduction

Acute myeloid leukemia (AML) and myelodysplastic syndromes/neoplasms (MDS) are clonal disorders of myeloid hematopoiesis that mostly affect the elderly and have poor prognoses [1, 2]. Over the past decade, the development of hypomethylating agents (HMAs) has reshaped the therapeutic landscape for patients with these diseases by offering a less toxic alternative compared to intensive chemotherapy (IC) [3].

More recently, low-intensity induction strategies incorporating decitabine have shown encouraging results both in younger and older fit patients with AML [4–7]. Although not yet part of standard practice, these approaches are under investigation as safer alternatives to IC, with the goal of

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minimizing early treatment-related toxicity while preserving remission outcomes and maintaining therapeutic trajectory toward allogeneic hematopoietic stem cell transplantation (alloSCT) [4–6]. The availability of oral decitabine/cedazuridine (DEC-C) represents a significant step forward in the treatment of AML and MDS, by significantly reducing logistical and physical burdens associated with parenteral HMA administration [8–10]. However, the introduction of oral anticancer therapies may also introduce some challenges associated with the mode of administration that are to be considered. For example, as seen in the treatment of other hematologic malignancies, such as chronic myeloid leukemia (CML), adherence to oral therapy is critical to maximize clinical response [11], and there is a complex interplay between HRQoL, symptom burden and adherence to therapy [12–14].

Oral DEC-C is a promising option because it achieves the same systemic exposure as intravenous (IV) decitabine while offering the convenience of oral administration [9, 10, 15]. Clinical studies have reported anti-leukemic activity and tolerability profile consistent with IV decitabine, supporting its use especially in older or unfit patients. Recent data on DEC-C combined with venetoclax indicated preserved activity without significant interaction, opening the perspective of a fully oral regimen for unfit AML patients [7, 16].

While growing clinical evidence supports the efficacy and safety of decitabine-based regimens [17–20], limited evidence exists on HRQoL and other patient-reported outcomes (PROs). In this review, we aim to describe the existing literature on PROs in patients with AML and MDS treated with decitabine, to summarize current knowledge in this area. We also discuss directions for integrating patient-centered outcomes into future clinical decision-making and trial design.

Materials and methods

Identification of relevant studies

We conducted a systematic literature search in PubMed to identify studies including AML and/or MDS patients treated with decitabine, published until October 2024. The following search criteria were used: ("quality of life" OR "health related quality of life" OR "health status" OR "health outcomes" OR "patient outcomes" OR "depression" OR "anxiety" OR "emotional" OR "social" OR "psychosocial" OR "psychological" OR "distress" OR "social functioning" OR "social wellbeing" OR "patient reported symptom" OR "patient reported outcomes" OR pain OR fatigue OR "patient reported outcome" OR "PRO" OR "PROs" OR "HRQL" OR "QOL" OR "HRQOL" OR "symptom distress" OR "symptom burden" OR "symptom assessment" OR "functional status" OR sexual OR functioning) and ("decitabin*" OR "hypomethylat*" OR "demethylat*" OR "ASTX727") AND (myelodysplastic OR myelodysplasia OR leukemia OR leukaemia). The PubMed filter "Clinical Study" was applied. Only studies published in English were considered.

Additional studies were identified through manual searches of reference lists from the selected articles and through direct communication of clinical experts in the field. If multiple publications from the same study were available during the review period, relevant data were extracted from all related publications. The search strategy and selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [21].

Selection criteria

Articles were included if they involved adult patients with AML and/or MDS and decitabine treatment (alone or as part of treatment approach). We selected studies that assessed HRQoL or other PROs, satisfaction with care, treatment adherence, or patient preferences for treatment (e.g., oral vs. intravenous administration). Studies were excluded if they evaluated PROs but focused on hypomethylating agents other than decitabine (regardless of route of administration) or without specifying population size of patients receiving decitabine. Review articles, conference abstracts, or case reports or protocol presentation papers were excluded due to their lack of detailed information or results. Studies were included regardless of the study design and survey-based studies were also considered.

Before beginning the literature search, a predefined coding schema for data extraction was developed (LC, FE). The data extraction form included various information on (1) basic study characteristics (i.e., type and acronym of study, study locations, multicenter study [y/n]); (2) clinical details (i.e., type of hematologic disease [AML/MDS], patient's age and sex, number of patients, types of treatments); (3) PRO assessment characteristics (i.e., PRO measure/s used); (4) main PRO findings. Eligibility assessment and data extraction for each study was performed manually and independently by two reviewers (SP and LC). Any discrepancies were resolved through discussion and re-examination of the original articles until consensus was reached.

Results

The literature search identified 196 records, published until October 2024, that were screened for eligibility. Of these, we retrieved a total of 14 papers comprising 10 unique studies [4, 22–34]. Details of the search strategy and selection process of the articles included in this review are reported in Fig. 1.

Of the 10 studies included in this review, five included patients with AML and five with MDS. Overall, there were five randomized controlled trials (RCTs), two prospective investigational studies and three online surveys. Eight eligible studies (80%) were multicenter and the remaining two were single-center studies from the US. The majority of the studies ($n=8$, 80%) enrolled ≥ 100 patients. In nearly all cases ($n=9$; 90%) more than half of participants were male, while in only one (10%) there was a predominance of female. Median age of patients in studies identified ranged from 63 to 76.2 years. The two most frequently used PRO instruments were the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC-QLQ-C30) ($n=5$; 50%) and the Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu) Questionnaire ($n=2$; 20%). Considerable heterogeneity across key study characteristics, including study design, patient populations, treatment strategies, PRO measures, and the timing of HRQoL assessments, limited comparability among the included studies.

Overview of PRO findings in AML patients treated with decitabine

The extracted data regarding study design, population, treatment and PRO assessment from studies on AML patients receiving decitabine are presented in Table 1. Of the five studies reporting AML patients' perspective on decitabine-based therapies, three were RCTs and two prospective trials. In the first RCT, the DECIDER trial [22], no benefit in HRQoL was seen after adding valproate and/or ATRA to decitabine in newly diagnosed AML patients older than 60 years not qualifying for or not consenting to intensive approaches. However, this HRQoL result was constrained by the small number of patients included in the analysis (61 AML patients eligible for PRO analysis vs. 200 AML patients for clinical outcome analysis).

In the second RCT, the AML2002 trial, baseline HRQoL data from all randomized arms (decitabine plus talacotuzumab versus decitabine alone) were pooled for analysis [26]. While, the formal efficacy interim analysis of this study indicated that the addition of talacotuzumab to decitabine did not improve clinical outcomes in older patients with AML (no clinically meaningful or statistically significant differences in CR, OS were observed between the two arms) [27], the pooled baseline HRQoL analysis highlighted the prognostic significance of several FACT-leu

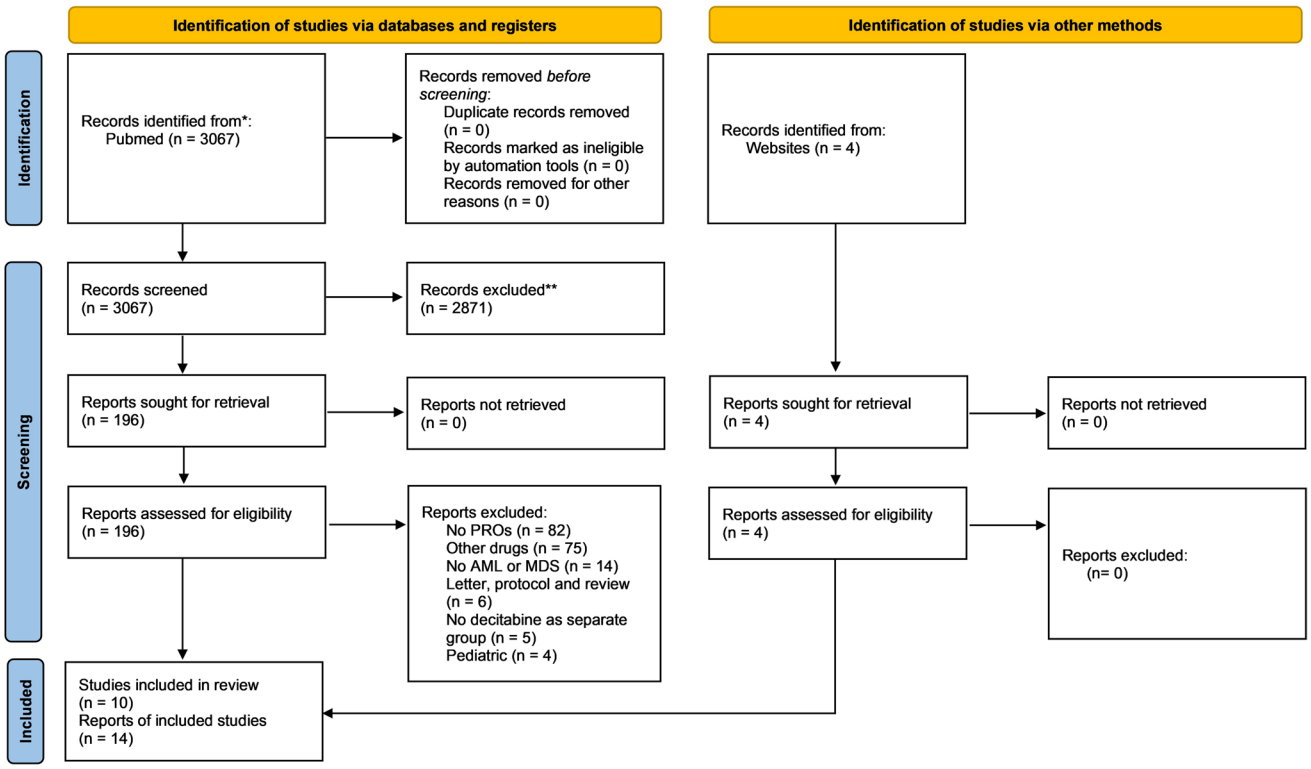

Fig. 1 PRISMA 2020 flow diagram of articles selection process [21]

Table 1 Overview of AML studies on decitabine with a PRO assessment

AML										
Author, Year	Type of study	Study acronym*	Study locations	Multicenter study (Yes/ No)	Sample Size (*n*)	Age of patients (Median (range), years) §	Sex (Male/ Female, *n*, %)	Treatment outline	PRO assessment	Main PROs findings
Lübbert et al. 2020 [22] Grishina et al. 2015 [23]	Observer-blind, longitudinal, prospective, phase 2 RCT with a 2×2 design	DECIDER trial	Germany	Yes	200	Median (range): 76 (61–92)	Male: 128 (64%) Female: 72 (36%)	DEC vs DEC+VPA vs DEC+ATRA vs DEC+ VPA+ATRA	EORTC QLQ-C30	No positive effects of VPA and ATRA on HRQoL were observed across 9 scales and 6 single items of the EORTC QLQ-C30.
Ritchie et al. 2022 [24] Roboz et al. 2018 [25]	Open-label, longitudinal, prospective study (derived from CALGB 11002 Alliance RCT)	CALGB 361101	US	Yes	96	Median (range): 72.7 (60.6–92.4)	Male: (69.8%) Female: (30.2%)	DEC vs DEC+V	EORTC QLQ-C30, MOS, OARS, patient-rated KPS, number of self-reported falls in the past 6 months.	Lower baseline EORTC global health status/QoL scores were independently associated with shorter OS, dependence in instrumental activities of daily living and cognitive impairment predicted 6-month mortality.
Peipert et al. 2022 [26] Montesinos et al. 2022 [27]	Open-label, two-part, longitudinal, prospective, phase 2/3 RCT	AML2002	Australia, US, Israel, Taiwan, Europe (Spain, France, Germany, Italy, Poland, Sweden, Turkey, UK, The Netherlands)	Yes	309	Median (range): 75 (51–92)	Male: 166 (53%) Female: 143 (47%)	DEC vs DEC + Talacotuzumab	FACT-Leu	Prognostic significance of several FACT-Leu scales, especially the PWB for OS in older, unfit patients with AML treated with DEC

Table 1 (continued)

AML										
Author, Year	Type of study	Study acronym*	Study locations	Multicenter study (Yes/ No)	Sample Size (*n*)	Age of patients (Median (range), years) §	Sex (Male/ Female, *n*, %)	Treatment outline	PRO assessment	Main PROs findings
Im et al. 2024 [28]	Open-label, prospective, phase 2 trial	_	US	No	44	Median (range): 76.2 (67.1–87.5)	Male: 25 (57%) Female: 19 (43%)	DEC+ara-C and DEC	FACT-Leu	No change in PRO outcomes was observed between baseline and the end of cycle 1
Efficace et al. 2024 [29] Lübbert et al. 2023 [4]	Open-label, longitudinal, prospective, phase 3 RCT	EORTC-1301 (EORTC-GIMEMA-GMDS-SG)	Europe (Belgium, The Netherlands, Germany, France, Lithuania, Italy, Croatia, Bulgaria, Portugal)	Yes	549	Frequencies, n (%): 60–64= 131 (23.9%) 65–69= 231 (42.1%) ≥ 70= 187 (34.1%)	Male: 318 (58.1 %) Female: 229 (41.9%)	DEC+alloSCT vs IC +alloSCT	EORTC QLQ-C30; EORTC QLQ-ELD14	Primary scales: Fatigue, pain, burden of illness, and physical or role functioning. Short term (2 months): Patients in the DEC arm had a significantly lower risk of HRQoL deterioration compared with the IC arm. Long term (6–12 months): No significant differences in the risk of HRQoL deterioration between treatment arms. After allo-HSCT: Patients treated with DEC did not experience clinically meaningful HRQoL deterioration, whereas deterioration was observed in patients treated with IC compared to baseline.

AML acute myeloid leukemia; *ara-C* Cytarabine Arabinoside; ATRA All-Trans Retinoic Acid *DEC* Decitabine; *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; *EORTC QLQ-ELD14* EORTC QLQ-Elderly Module; *FACT-Leu* Functional Assessment of Cancer Therapy-Leukemia; *HRQoL* Health related Quality of Life; *KPS* Karnofsky Performance Status; *MOS* Medical Outcomes Survey; *OARS* Older Americans Resources and Services; *OS* overall survival; *IC* intensive chemotherapy; *alloSCT* allogeneic stem cell transplantation; *PRO* patient-reported outcome; *PWB* FACT-Leu Physical Well-Being; *RCT* randomized controlled trial; *US* United States; *V* Bortezomib; *VPA* Valproic Acid

*In this column we reported also study acronym whenever available. §In this column we reported median age and range. If these were not available, frequencies (percentage) for age class were reported

scales, especially the Physical Well Being (PWB), for overall survival (OS) in older, unfit patients with AML treated with decitabine [26]. The PWB score of FACT-Leu reflects key elements of health status of older patients including physical and role functioning, fatigue, pain, somatic symptoms and side effects of treatment. The PWB score strong association with OS supported its potential use as a complementary tool to better characterize functional status in older patients with AML or to complement established disease-risk stratification systems.

In the third RCT, EORTC-1301 (EORTC-GIMEMA-GMDS-SG) trial, fit patients aged 60 years or older with newly diagnosed AML were randomized to receive either decitabine or IC (3 + 7 scheme), both followed by alloSCT, when feasible. At 2 months, the risk of HRQoL deterioration was lower in the DEC arm than in the 3 + 7 arm; 76% vs. 88%; odds ratio, 0.43 (P = .003). In a subgroup analysis of those who received transplantation, HRQoL declined from baseline to post-alloSCT (i.e. 100 days after transplantation) in both arms but clinically meaningful deterioration (of at least 10 points) was observed only in the 3 + 7 arm in some key HRQoL domains. This HRQoL benefit of decitabine, together with comparable long-term outcomes (e.g.,OS) and similar alloSCT rates, has been interpreted to support the use of decitabine as a de-escalation and non-chemotherapeutic strategy for fit older AML patients eligible for alloSCT [4, 29].

Of the two prospective studies, the CALGB 361,101 trial focused on longitudinal HRQoL and geriatric assessment in older, unfit patients with newly diagnosed AML who received decitabine plus bortezomib or decitabine alone as part of the CALGB 11,002 RCT. The main PRO finding of this analysis was the strong association between lower baseline EORTC QLQ-C30 global health status/QoL score and inferior OS, as documented in both univariate and multivariate analyses. However, the limited number of patients remaining on study after cycle 4 of decitabine-based treatment precluded a reliable comparative PRO analysis [24]. The recent single-arm trial investigating an induction regimen of one or two cycle of decitabine followed by low dose continuous infusion of cytarabine infusion (100 mg/m^2 for 4 days), reported no significant change in HRQoL from baseline up to end of first cycle in a small cohort of older patients with newly diagnosed AML [28].

Overview of PRO findings in MDS patients treated with decitabine

The key data on study design, population, treatment, and PRO assessment from studies on MDS patients treated with decitabine are presented in Table 2. Of the five studies reporting MDS patients' perspective on decitabine-based therapy, two were RCTs and three online surveys. The first RCT observed that patients with IPSS int-1 or higher MDS, who were receiving decitabine alone reported better HRQoL scores than those receiving best supportive care (BSC). Sustained HRQoL benefits included several domains of EORTC QLQ-C30: global health status, fatigue, and dyspnea. However, decitabine treatment in this study was limited up to two cycles after complete remission achievement, which may have hindered the detection of greater benefits from a longer treatment duration [30].

Another large RCT in high-risk MDS patients confirmed HRQoL advantage of decitabine over BSC: patients receiving decitabine reported significant improvements in fatigue and physical functioning, with a borderline improvement in global health status and no change in dyspnea (measured with EORTC QLQ-C30). However, the decline in HRQoL compliance during follow-up was a limitation to the generalizability of the results [31].

Of the three online surveys, one describes the burden of parenteral/IV hypomethylating agents (HMAs) treatment in terms of logistical challenges (e.g. timely administration of scheduled cycles, time toxicity linked with time spent in coordinating care including travel to hospital and waiting times) and treatment related inconveniences (e.g. pain or discomfort, interference with daily and social activities) [32]. It was completed by 141 adult MDS patients or caregivers (as proxies) in the US who received HMAs within 6 months of the survey (i.e., azacitidine, n = 104, 73% or decitabine n = 28, 27%). The majority of respondents preferred oral treatment, believing it would cause less disruption to their lives than infusion, it would make coping with their disease easier, and it could help to maintain the treatment schedule [32]. Another online survey aimed to identify patient's priority on treatment benefits, risks, and administration burden using a discrete-choice experiment (DCE). It involved 187 MDS patients or caregivers from the US and Canada, of whom 39 (21.2%) had been treated with decitabine. AML transformation risk and fatigue severity were key drivers in patients' decision making and they were valued more than the number of the visit or mode of administration or duration of visit. In addition, survey results showed a marked preference for oral formulations among patients [33]. More recently, an online survey of adult patients with MDS who were receiving oral DEC-C in US clinical practice, as an alternative to IV/SC hypomethylating agents reported high levels of satisfaction with oral treatment with very little or no negative impact on regular daily activities [34].

Table 2 Overview of MDS studies on decitabine with a PRO assessment

MDS									
Author, Year,	Type of study	Study locations	Multicenter study (Yes/ No)	Sample Size (n)	Age of patients (Median (range), years) *	Sex (Male/Female, *n*, %)	Treatment outline	PRO assessment	Main PROs findings
Kantarjian et al. 2006 [30]	Open-label, longitudinal, prospective, phase 3 RCT	US	Yes	170	Median (range): 70 (30–85)	Male: 116 (68%) Female: 54 (32%)	DEC vs BSC	EORTC QLQ-C30	Patients treated with DEC reported statistically superior HRQoL compared with BSC in the following scales: global QoL/health status, fatigue, and dyspnea scales. There were statistically significant changes from baseline during cycles 2 and 4 for patients receiving DEC vs BSC
Lübbert et al. 2011 [31]	Open-label, longitudinal, prospective, phase 3 RCT	Europe (Austria, Belgium, Czech Republic, Croatia, Germany, Italy, the Netherlands, Switzerland, Turkey)	Yes	233	Median (range): 70 (60–-90)	Male: 149 (64%) Female: 84 (36%)	DEC vs BSC	EORTC QLQ-C30	Patients in the DEC arm reported a significant improvement in their fatigue and physical functioning, with borderline improvement of global health status, whereas no apparent effect was found for dyspnea
Zeidan et al. 2022 [32]	Online survey	US	Yes	141	Median (range): 63 (20–89)	Male= 65 (46.1%) Female= 76 (53.9%)	AZA or DEC in the previous 6 months	Online survey including sociodemographic, treatment-related items, symptoms, treatment convenience and satisfaction, interference with daily and social activities, oral treatment perception, CDC's Healthy Day, ZBI -12 for caregivers	Participants commonly reported pain/discomfort associated with IV/SC DEC or AZA administration. About one-third of patients reported inconvenience, while most noted that treatments interfered with daily or social activities. Most participants indicated they would prefer oral treatment to IV/SC therapies.
Zeidan et al. 2022 [33]	Online survey	US, Canada	Yes	184	Median (range): 69 (27–91)	Male: 93 (50.5%) Female: 91 (49.5%)	DEC, DEC-C, AZA, all types of treatments	Semi-structured interviews and an online survey including sociodemographic items, experience with the disease and treatment, attribute descriptions and comprehension checks, and the DCE choice tasks	Patient's key drivers of treatment preferences were related to clinical outcomes (i.e. reducing AML risk and fatigue severity). Participants preferred oral to parenteral mode of administration, and desired a lower visit-related burden (fewer and shorter visits)
Zeidan et al. 2024 [34]	Online survey	US	No	150	Frequencies, n (%): 20–59= 58 (39%) 60–69= 70 (46%) ⩾ 70= 22 (15%)	Male: 94 (63%) Female: 56 (37%)	Oral DEC-C between 2021 and 2022	Online survey including 25 items, with 23 ad hoc fixed-response questions and 2 free-text questions	Most patients reported a positive experience with oral DEC-C with very little or no negative impact on daily activities. Most patients who had previously received other HMAs expressed satisfaction with the switch to oral DEC-C.

AML acute myeloid leukemia; *AZA* Azacitidine; *BSC* Best Supportive Care; *CDC* Centers for Disease Control and Prevention; *DCE* Discrete Choice Experiment; *DEC* Decitabine; *DEC-C* Decitabine/Cedazurine; *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; *HMAs* Hypomethylating agents; *HRQoL* Health related Quality of Life; *IV* intravenous; *PRO* patient-reported outcome; *RCT* randomized controlled trial; *SC* subcutaneous; *US* United States; *ZBI-12* Zarit Burden Inventory 12-item

*In this column we reported median age and range. If these were not available, frequencies (percentage) for age class were reported

Discussion

Since its FDA approval in 2006, decitabine has been widely adopted in both clinical trials and real-world practice; yet, nearly two decades later, data on HRQoL and PROs associated with decitabine treatment in patients with AML and MDS remain limited. In this review, we found that few randomized studies described tangible HRQoL benefits of decitabine beyond survival. In MDS, two RCTs comparing decitabine monotherapy with BSC demonstrated improvement in selected HRQoL domains, with fatigue emerging as a consistently improved dimension [30, 31]. In AML, decitabine used as bridging therapy in older patients eligible for alloSCT was associated with a lower short-term risk of HRQoL deterioration compared to standard IC [29]. Findings from the same trial also suggested a potential advantage of decitabine in post-alloSCT HRQoL outcomes over IC. These observations are particularly relevant in the management of older patients, in whom treatment intensity must be carefully balanced against its impact on functional status and perceived well-being [35–37]. Decitabine's more favorable HRQoL profile (compared to standard care) may therefore be a critical factor in guiding clinical decision-making, especially when survival outcomes are comparable or when preserving functionality and autonomy may be as important as extending survival.

Beyond its role as a treatment outcome, HRQoL has also shown prognostic value for overall survival. In elderly patients with newly diagnosed AML who were treated with decitabine, two studies highlighted that baseline HRQoL can complement comorbidity and geriatric assessments by better capturing symptom burden at the time of treatment initiation [24, 26]. These studies used different questionnaires and therefore identified different predictive scales and score (i.e. global health status scale of EORTC QLQ-C30, physical well-being scale of FACT-G, FACT-Leu Trial Outcome Index and FACT-Leu total score), but their findings converged on the idea that HRQoL may reveal aspects of patient vulnerability and functional reserve that are not fully captured in conventional risk models such as genetic mutations. Although these findings require further validation, the integration of HRQoL into clinical decision-making may enable more personalized care and better treatment alignment with patient goals and values. These insights gain further importance in light of the recent revision to the ELN risk classification tailored to patients receiving less-intensive therapies such as decitabine [38]. As treatment paradigms continue to evolve, refinement of risk stratification tools might be warranted to eventually reflect the growing role of patient-centered outcomes [39].

Patient preferences regarding treatment route and treatment decision-making have also been explored. There are evidence that suggest that patients with MDS reported high level of satisfaction with the oral formulation of decitabine (DEC-C) and identified specific burdens associated with intravenous administration [32, 34]. However, no similar information is available in patients with AML. Patients with MDS also expressed interest in being actively involved in treatment decisions and prioritized outcomes such as reducing fatigue and minimizing the risk of AML evolution [33]. While survey data suggest active patient engagement among those receiving decitabine, other evidence indicates that patient involvement in decision-making may be more limited in broader real-world populations. In fact, a large international observational study involving 280 higher-risk MDS patients at diagnosis reported that a passive role in decision-making was common and associated with lower hemoglobin levels [40]. However, differences in study design, patient populations and timing limit direct comparisons between the two sets of data: the surveys focused on patients treated with decitabine or other HMAs, whereas the observational study on patients at diagnosis regardless of treatment requirement.

Among the issues reported by patients treated with decitabine, survey data highlighted time toxicity as a relevant and often overlooked burden. Although the concept of time toxicity, defined as the time patients spend receiving or managing treatment (including travel and waiting times) [41], remains underreported in clinical trials and rarely addressed in routine care, it may significantly impact patient well-being and treatment adherence. In the case of IV decitabine, time toxicity is largely inherent to the treatment schedule and not easily modifiable in routine practice. While evidence remains scarce, one retrospective study reported voluntary discontinuation of HMA therapy due to personal or financial reasons [42], which could indirectly relate to the broader concept of treatment burden, including time toxicity. Recently, time toxicity has been proposed as an important dimension in the evaluation of cancer care to support more informed, patient-centered decisions and help clinicians and patients to better balance life prolongation and the impact of treatment on HRQoL [43, 44].

Experience from other hematologic malignancies suggested that PROs can meaningfully inform treatment evaluation, particularly in the context of emerging oral targeted therapies [45–47]. The growing availability of oral agents for MDS and AML holds the promise of improving HRQoL by reducing the burden of clinic visits and infusions and enabling home-based treatment. However, oral cancer therapy also introduces distinct challenges, particularly regarding adherence, toxicity monitoring, and patient engagement [48, 49]. Unlike IV or subcutaneous cancer therapies that require hospital administration, oral regimens place greater responsibility on patients, which may impact treatment continuity and effectiveness. Research in CML has consistently shown that adherence to tyrosine kinase inhibitors is a key determinant of therapeutic outcomes [11,

50–52]. Poor adherence is influenced by multiple factors, including patient-, clinician-, treatment-, and healthcare system–related determinants, with drug-related adverse events representing the most common driver of intentional non-adherence [11, 53, 54]. Because treatment-related symptoms are frequently underestimated by clinicians [55, 56], monitoring of HRQoL in clinical routine can provide valuable additional insights to symptom burden, enabling early identification of patients at risk for suboptimal adherence. Evidence from hematologic and solid tumor settings indicates that systematic PRO monitoring can improve patient–clinician communication, enhance symptom management, and support adherence, ultimately contributing to better clinical outcomes [13, 57]. For example, in newly diagnosed patients with CML, PRO monitoring improved communication and symptom management, contributing to high adherence and favorable early molecular responses [13]. Similarly, in women with early breast cancer, the use of electronic PROs to individualize follow-up care significantly reduced the number of consultations required, without compromising adherence, HRQoL, or patient satisfaction [57]. These findings highlight the broad potential of PRO integration to optimize symptom management, sustain adherence, and ultimately improve the quality and effectiveness of cancer care. However, to date, no investigational studies of oral decitabine-cedazuridine, either as monotherapy or in combination, have reported longitudinal HRQoL data. In contrast, the inclusion of HRQoL data in key trials of venetoclax- and ivosidenib- based regimens in AML provided valuable insight on how treatment affect patients beyond survival. HRQoL data from Viale-A/C and AGILE trials further supported the tolerability and acceptability of these treatments and can help guide treatment decisions in elderly or unfit AML patients [58, 59].

This review has several limitations. Although we adopted a comprehensive search strategy using the PubMed database, it is possible that we missed some eligible studies. The use of predefined filters (e.g., "clinical study") might have reduced the number of records retrieved. However, manual screening of references and citations likely helped mitigate this risk. A recent work [60] on decitabine and HRQoL also documented the paucity of data in this area. The studies included in this review were highly heterogeneous in design, patient populations, treatment strategies, and PRO measures, which limit cross-study comparability and generalizability. Nevertheless, this review offers a focused synthesis of the current evidence on PROs of patients with MDS and AML treated with decitabine, and highlights directions for future research. No PRO data is currently available for oral DEC in AML, which limits the ability to determine whether the potential advantages of the oral formulation translate into measurable benefits from the patient perspective.

The therapeutic landscape of older AML patients has profoundly changed with the advent of venetoclax-based regimens, and the introduction of oral DEC-C may further expand this shift toward less intensive and potentially fully oral treatment strategies [16]. Such approaches may reduce hospital visits and inpatient stays while lowering healthcare costs related to drug administration, central venous catheters, and infection management [61]. However, despite these promising clinical and economic implications, no HRQoL data for oral DEC-C is yet available. Future studies are warranted to assess whether fully oral regimens can also translate into measurable improvements in patients' HRQoL and treatment experience.

Author contributions L.C. and S.P. contributed to literature search, data extraction, designed the tables and figure, and wrote the first manuscript. F.E. contributed to study conceptualization, supervision, literature search, data extraction, and editing of the manuscript. A.V., R.P., M.L. and M.B. provided guidance, and reviewed the manuscript for accuracy, clarity, and relevance. All authors contributed to critical review of the manuscript.

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Data availability The raw data supporting the conclusions of this article are available upon reasonable request to the corresponding author.

Declarations

Competing interests M.B. serves as the Editor-in-Chief of Annals of Hematology. F.E. has consultancy or advisory role for AbbVie, Incyte, Novartis, FibroGen, GlaxoSmithKline (GSK), and Jazz Pharmaceuticals, and has received research grant (institution) from Daiichi Sankyo and Otsuka, all outside the submitted work. A.V. reports grants or contracts from Jazz Pharmaceuticals, AstraZeneca, and AbbVie. A.V. has received consulting fees from Jazz Pharmaceuticals, AbbVie, Servier, Istituto Gentili, Bristol Myers Squibb, Pfizer, Astellas, Otsuka, Janssen, and Daiichi Sankyo. A.V. has also received honoraria from Servier, Jazz Pharmaceuticals, AbbVie, Otsuka, Pfizer, Astellas, Astex, and Janssen, and support for attending meetings and/or travel from Servier, Janssen, AbbVie, Daiichi Sankyo, and Pfizer, all outside the submitted work. F.E., M.L., and A.V. are authors of some of the studies included in this review. The authors declare that they have no other relevant financial or non-financial interests related to the content of this article.

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