RESEARCH ARTICLE

Factors implicated in underutilization and poor persistence with hypomethylating agent therapy in myelodysplastic syndromes and chronic myelomonocytic leukaemia in Pakistan

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Abstract

Objective: To assess the clinical and non-clinical factors leading to non-compliance or discontinuation of hypomethylating agent therapy in patients of myelodysplastic syndromes and chronic myelomonocytic leukaemia.

Method: The prospective, observational, cohort study was conducted at the National Institute of Blood Diseases and Bone Marrow Transplantation, Karachi, from January 2022 to January 2024, and comprised patients diagnosed with myelodysplastic syndromes or chronic myelomonocytic leukaemia who were started on a monthly cycle of hypomethylating agent therapy, but either discontinued treatment or suffered from treatment interruption of 60 days or more. Demographics and clinical data was collected from the medical records and a questionnaire-based survey via direct interview with the patients. Data was analysed using SPSS 25.

Results: Of the 39 patients with median age 60 years (interquartile range: 53-70 years), 25(64.1%) were male, 23(59%) had myelodysplastic syndromes, and 16(41%) had chronic myelomonocytic leukaemia. The median number of hypomethylating agent cycles received was 3 (interquartile range: 01-11). Common clinical factors influencing poor persistence to therapy included comorbidities 16(41.0%) and infections 15(38.4%). Among the non-clinical factors, affordability, patients' perception of disease, weak family support, and drug unavailability were commonly associated with non-persistence to therapy, with treatment affordability showing a statistically significant association (p=0.037).

Conclusion: The factors leading to poor compliance related to hypomethylating agent therapy among patients with myelodysplastic syndromes and chronic myelomonocytic leukaemia could be predicted beforehand and addressed to a certain degree through collaborative efforts.

Key Words: Myelodysplastic syndromes, Chronic myelomonocytic leukaemia, Hypomethylating agents.

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Introduction

Myeloid neoplasms are a group of clonal haematological disorders, including myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPNs), chronic myelomonocytic leukaemia (CMML) and acute malignancies such as acute myeloid leukaemia (AML).[1] MDS, now known as myelodysplastic neoplasms (MDNs) as per the new World Health Organisation (WHO) classification, are characterised by peripheral blood cytopenia(s) and bone marrow (BM) dysplasia.[2] CMML has overlapping features of myelodysplasia, proliferation and persistent peripheral blood monocytosis (>1x10^9/L).[3] Both MDS and CMML have high propensity to transform into AML and preponderance in the elderly.[2,3] The WHO updated the diagnostic criteria of MDS and CMML in 2022 and provided classification of the disorders on the basis of blast percentage.[4]

The universally used tools for risk stratification of MDS and CMML are the 2012 revised International Prognostic Scoring System (IPSS-R) and the 2013 CMML-specific Prognostic Scoring System (CPSS), respectively.[5,6] These scoring systems categorise the patients into low, intermediate or high risk on the basis of different clinicohaematological variables that influence the ultimate treatment options offered to the patients.[2,3]

The curative treatment for MDS and CMML is haematopoietic stem cell transplantation (HSCT), but majority of patients are ineligible due to poor performance status owing to advanced age and comorbidities. The United States Food and Drug Administration (FDA) has approved three hypomethylating agents (HMAs) for the management of these disorders; azacitidine, decitabine, and oral

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decitabine with cedazuridine.[2,3] Oral decitabine with cedazuridine is unavailable in Pakistan, so the standard of care remains decitabine or azacitidine. Lenalidomide is recommended in patients of MDS with deletion 5q.[2] Western studies have highlighted the safety and efficacy of HMAs in slowing disease progression and improving quality of life (QOL) in MDS and CMML.[7,8] Despite its safety and efficacy demonstrated in clinical trials, the overall real-world outcome of high-risk MDS and CMML remains dismal in patients using HMAs.[9,10]

Various regional studies have overviewed the use of HMAs in Asian population of MDS and CMML.[11-17] Studies from China reported satisfactory outcome with decitabine and azacitidine in older patients with high-risk MDS; while studies from South Korea showed no benefit of HMAs over best supportive care in MDS.[11-14] Studies from India have also reported the use of HMAs in patients of MDS and CMML.[15,16] A study in Pakistan discussed the use of HMAs in MDS,[17] but no data has been reported so far from Pakistan in CMML to assess the response of HMAs. There are inconsistent results regarding the use of HMAs in CMML. Santini V, et al. showed favourable outcomes with good response and survival advantage, while Coston T, et al. demonstrated suboptimal outcomes (<20%) in patients achieving complete remission with both the drugs in CMML.[8,9] Nevertheless, HMAs remain the only easily available and well-tolerated therapy for MDS and CMML, and is given to patients ineligible for HSCT.[2,3]

An important determinant of the efficacy of HMAs is the compliance with treatment, and it has been observed that non-compliance and under-utilisation of HMAs is a prevalent issue.[10,18-20] The continuous administration of HMAs imparts significant challenge, and consistent use of these drugs is an issue faced by the patients.[10] One study highlighted that the first challenge is the mode of administration, as HMAs are only available in intravenous (IV) formulations; while subcutaneous (SC) and oral formulations of decitabine have recently been developed in the West.[21] Due to the IV route of administration, each cycle of HMAs requires admission to hospital, and eventually leads to complications of IV access.[10] Decitabine is given as IV infusion over one hour for five days every four weeks, and azacitidine is given IV for 5-7 consecutive days in cycles of 4-6 weeks.[22, 23] The cause of non-compliance or discontinuation of HMAs is divided into clinical and non-clinical components, and the side-effects of HMAs are observed as clinical toxicities, including cytopenias, gastrointestinal issues and recurrent infections.[7] Non-clinical causes of non-compliance include poor understanding of disease biology leading to patients refusing treatment, logistical issues like IV infusions, delay or unavailability of HMAs, socioeconomic causes like financial restraints, transport difficulty during frequent hospital visits, and physician discretion.[10,24]

The aforementioned challenges in the administration of and compliance to HMAs have been explored and reported by several Western studies,[18-20] but limited data is available from Asian countries. The need for exploring and correcting these challenges to improve the utilisation of HMAs appears to be essential in other parts of the world. As Jiang Y, et al. highlighted, Asian patients are more prone to MDS.[25] There are few studies on MDS from Pakistan,[26-28] but even these studies did not explore the challenges in compliance with treatment. Furthermore, there are no studies on CMML from Pakistan, and, given the rarity of the disorder, challenges in the administration of HMAs to CMML patients has not been specifically reported by any regional study.

The current study was planned to fill the gap in literature by assessing the clinical and non-clinical factors leading to non-compliance or discontinuation of HMA therapy in MDS and CMML patients.

Patients and Methods

The prospective, observational, cohort study was conducted at the National Institute of Blood Diseases and Bone Marrow Transplantation (NIBD), Karachi, from January 2022 to January 2024, after approval from the institutional ethics review committee. Written informed consent was taken from the participants before the commencement of the study, and the sample was raised using non-probability purposive sampling technique. Those included were MDS and CMML patients who were started on a monthly cycle of HMA therapy, but either discontinued treatment or suffered from treatment interruption of 60 days or more. The diagnosis and classification were based on the revised WHO guidelines.[29] Those excluded were patients with secondary or treatment-related MDS/CMML, those not being a candidate for HMA use, or those who used HMA without interruption or in combination with lenalidomide, and patients who were bridged to transplant.

Baseline characteristics were recorded, including age, medical registration number, gender, residence, education status, family structure, source of financial funding, transfusion dependence and the Eastern Cooperative Oncology Group (ECOG) performance status.[30]

This was followed by a questionnaire-based survey that included questions on non-clinical factors, including personal preference, family dynamics, logistical causes like IV access problems, HMA unavailability, socioeconomic causes (financial restraints, transportation issues, frequent hospital visits, organisational problems) and physician discretion. Clinical factors were recorded from the data collected though medical records, and included comorbid conditions, drug toxicities, infections documented during treatment, transfusion dependence, and disease progression. Underutilisation or termination of HMA therapy was identified, and association with the study variables were explored. All the enrolled patients had either underutilisation of HMA or delays in the administration of due cycle.

Persistence was defined as when patients received >4 cycles of HMAs and suffered from a gap of <90 days. Non-persistence was defined as when patients had a gap of at least 90 days in between cycles or when they received up to 4 cumulative cycles.[31]

Transfusion dependence was documented when an average of two units of packed red blood cells (RBCs) or more were transfused every month for at least three months.[32] Disease progression was noted with an increase in blast counts from baseline and/or transformation to AML. The administration of less than planned cycles of HMAs was termed underutilisation.[10]

Data was analysed using SPSS 25. Descriptive statistics were used to describe patient demographics, disease characteristics, clinical and non-clinical factors influencing treatment, HMA utilisation and poor persistence. Univariate analysis of frequencies and percentages was reported for categorical measures, while median and interquartile ranges (IQRs) were presented for continuous measures. Data normality was checked using the Shapiro-Wilk test. Continuous variables were analysed by using Mann-Whitney U test. Association between categorical variables was explored with chi-square and Fisher's exact test. P<0.05 was considered statistically significant.

Results

Of the 39 patients with median age 60 years (IQR: 53-70 years), 25(64.1%) were male, 23(59%) had MDS, and 16(41%) had CMML. The median number of HMA cycles received was 3 (IQR: 01-11). A total of 36(92.3%) patients received decitabine, and 3(7.7%) were given azacitidine. Based on treatment continuity 13(33.3%) were labelled as persistent and 26(66.7%) as non-persistent. Among the demographic and clinical variables, treatment affordability differed significantly between persistent and non-persistent groups (p=0.037) (Table 1). In comorbids, hypertension was observed in 9(23.0%) followed by Diabetes Mellitus (DM) in 5(12.8%) and Ischaemic heart disease in 2(5.1%) patients. Transfusion dependence, comorbidities and disease progression were more common among non-persistent patients (Figure 1).

Infections affected 15(38.4%) patients, and, of them, 12(80%) had fungal infections.

Among the non-clinical reasons affordability was the leading factor contributing to non-persistence, followed

Table: Patient characteristics and their association with HMA.

Characteristic	Overall (n=39,100%)	Persistent (n=13 ,33.3%)	Non-persistent (n=26 ,66.7%)	p-value
Diagnosis				
MDS, n (%)	23.0 (59.0%)	5.0 (38.5%)	18.0 (69.2%)	0.300
CMML, n (%)	16.0 (41.0%)	8.0 (61.5%)	8.0(30.8%)	
IPSS/CPSS category				
High IPSS/CPSS, n (%)	9.0 (23.1%)	5.0 (38.5%)	4.0 (15.4%)	0.232
Intermediate IPSS/CPSS, n (%)	19.0 (48.7%)	6.0 (46.2%)	13.0 (50.0%)	
Very High IPSS/CPSS, n (%)	11.0 (28.2%)	2.0 (15.3%)	9.0 (34.6%)	
Educational status				
Educated, n (%)	12.0 (30.8%)	6.0 (46.2%)	6.0 (23.1%)	0.160
Uneducated, n (%)	27.0 (69.2%)	7.0 (53.8%)	20.0 (76.9%)	
Family Structure:				
Family strong, n (%)	24.0 (61.5%)	10.0 (76.9%)	14.0 (53.8%)	0.160
Family weak, n (%)	15.0 (38.5%)	3.0 (23.1%)	12.0 (46.2%)	
Financial support:				
Patient expenses, n(%)	16.0 (41.0%)	2.0 (15.4%)	14.0 (53.8%)	0.037
Government-funded, n (%)	22.0 (56.4%)	11.0 (84.6%)	11.0 (42.3%)	
Third-party aid, n(%)	1.0 (2.6%)	0.0 (0.0%)	1.0 (3.9%)	
Age(years) median(ranges)	60.0 (53.0-70.0)	62.0 (54.0-67.0)	60.0 (53.0-70.0)	0.752
ECOG median(ranges)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	2.0 (1.0-2.0)	0.085
Haematological parameters:				
Hb (g/dl) median (IQR)	9.3 (7.4-10.4)	10.0(9.2-10.4)	8.45 (7.3-9.8)	0.180
TLC (x109/L) median (IQR)	5.3 (2.84-40.6)	26.2 (3.52-66)	5.16(2.84-9.25)	0.091
ANC (x109/L) median (IQR)	3.2 (0.8-12.1)	10.4 (0.8-28.6)	1.65 (0.8-5.9)	0.091
Platelet counts (x109/L) median (IQR)	49.0 (33.0-99.0)	52.0 (33.0-96.0)	46.0 (30.0-100.0)	0.800
BM blast (%) median (IQR)	10.0 (6.0-15.0)	10.0 (7.0-12.0)	10.0(5.0-16.0)	0.601

IQR: Interquartile range, Hb: Haemoglobin, TLC: Total leucocytes count, ANC: Absolute neutrophil count, ECOG: Eastern Cooperative Oncology Group, HMA: Hypomethylating agents, MDS: Myelodysplastic syndromes, CMML: Chronic myelomonocytic leukaemia, IPSS: International prognostic scoring system, CPSS: CMML-specific prognostic scoring system, BM: Bone marrow.

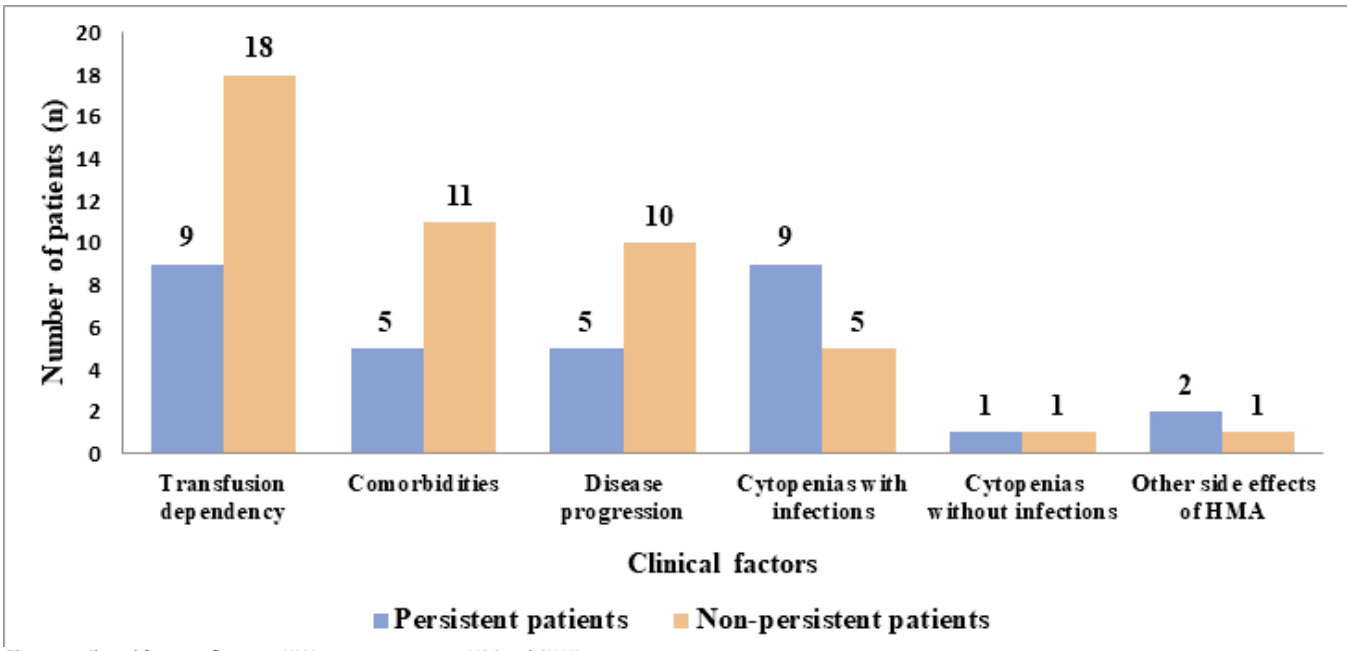

Figure-1: Clinical factors influencing HMA persistence among MDS and CMML patients.
HMA: Hypomethylating agents, MDS: Myelodysplastic syndromes, CMML: Chronic myelomonocytic leukaemia.

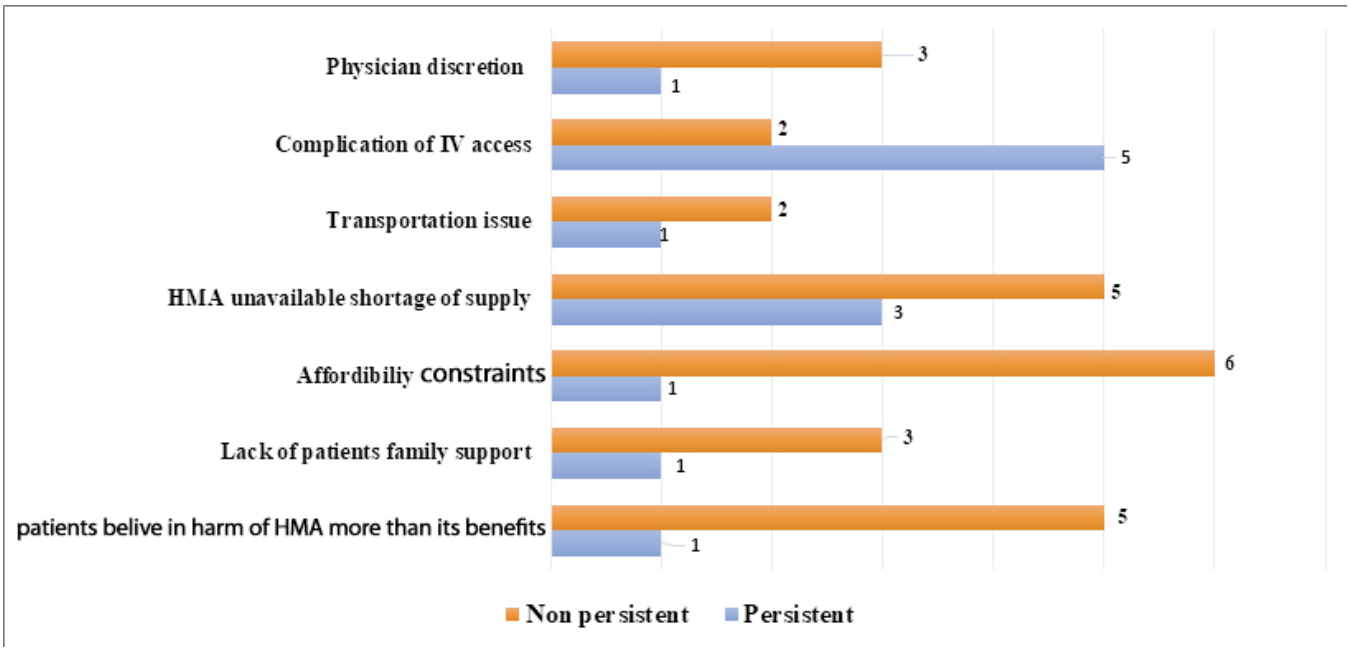

Figure-2: Non-clinical factors influencing HMA persistence among MDS and CMML patients.
HMA: Hypomethylating agents, MDS: Myelodysplastic syndromes, CMML: Chronic myelomonocytic leukaemia, IV: Intravenous.

by patient's perception of the disease, family structure and unavailability of drugs (Figure 2).

In terms of final outcome, 7(17.9%) patients died during the study, 5(12.8%) were continuing with treatment, 13(33.3%) transformed to AML and 14(35.9%) patients were lost to follow-up.

Discussion

High-risk MDN and CMML have dismal patient outcomes despite early diagnostic evaluation and advancements in treatment in the Western world.[2] In Pakistan, a third world country, outcomes of these disorders have not been reported yet, but one can speculate poor outcomes considering the scarcity of resources, patient's skewed

perception of disease, and therapy-related complications. Thus, treatment utilisation, complications and outcome remain under-researched and under-reported in Pakistani cohort. One of the reasons could be rarity of the disorders, as no crude figure indicating the true incidence of MDS and CMML in Pakistan. A study quoted 2.4% cases of MDS per 208 patients investigated for pancytopenia in Pakistan.[33] No such figures are available for CMML. The incidence of MDS in Asian population has been reported to be 1.6 cases per 100,000 population[25] and for CMML, 0.19 per 100,000 cases.[34]

In the current study, one of the first done in Pakistan, MDS and CMML patients who were started on monthly HMA therapy, but who either discontinued treatment, or encountered significant gap between cycles. It was observed that median number of administered HMA cycles (~3 cycles) was surprisingly low. Cabrero, et al. reported that at least 12 cycles of HMA are required to prolong overall survival (OS) and progression-free survival (PFS) in MDS.[35] No fixed number of cycles with an impact on overall survival has been delineated for CMML, but it is believed that satisfactory response cannot be expected with the administration of <4 HMA cycles.[3] Overall, the current study population was either underutilising HMAs or had significant gap between cycles due to patient-related causes, drug-related adverse events or logistical factors. The current patients were divided into persistent and non-persistent groups on the basis of gap of at least 3 months in between cycles to compare how they differed in demographics, and evaluated reasons for poor persistence.

The clinical factors assessed included comorbid illness, infections, transfusion dependence, disease progression and adverse effects of HMA, like cytopenia and nausea/vomiting. Of the 39 patients, 17(43.5%) experienced cytopenia, and in 15(38.4%) patients it was complicated by superimposed infections, which led to cycle delay and even death due to sepsis in three cases. Mukherjee, et al. also reported HMA discontinuation, highlighting that 96% of their MDS patients had cytopenia(s), including anaemia (92.8%), neutropenia (53%) and thrombocytopenia (52.7%).[19] Cytopenias during HMA therapy are well documented that are overcome by growth factor administration to shorten the duration of neutropenia.[7,18] A trial following on-time HMA administration to MDS patients reported overall response rate (ORR) of 63% versus 35% for the trial using cycle delays, indicating that delays in HMA cycles have a major impact on disease outcome.[36] Fungal infection was the common one observed in the current study. Nachtkamp, et al. reported the cause of death in 2,877 MDS patients, with infections being the direct cause in 27% cases.[37] An observational study in Spain observed outcomes of 263 MDS patients and 26 CMML patients on HMA cycles that developed infections during the course of therapy. Infections of the respiratory system were the most common, but fungal pneumonia was rare (3.51%). The median number of HMA cycles was lower in the infection group, and adherence to HMA therapy was also affected with increased morbidity.[38] The current study found that the patients experienced significant gap between HMA cycles (non-persistence) due to infections, and it can be considered a major clinical factor determining persistence to HMA, and efforts should be focused on preventing infections during the neutropenic phase of the therapy.

As MDS and CMML patients are usually of senescent age, the coexistence of comorbid illness is a frequent occurrence, and exacerbation of these illnesses might occur during HMA therapy. New evidence also suggests that there might be a bidirectional association between clonal haematopoiesis of MDS/CMML and non-malignant inflammatory processes.[39] Voso, et al. investigated 13 patients with high-risk MDS and CMML who had discontinued HMA treatment.[40] One of the significant reasons for premature cessation of azacitidine therapy was development or exacerbation of comorbid conditions, including cardiac complications and Chronic Obstructive Pulmonary Disease(COPD). Four patients (30.7%) in the current study discontinued treatment due to side-effects, including infections such as pneumonia, which were similar with the findings of Voso M.T et al.[40] Comorbid conditions found in the current cohort were observed more in the non-persistent group, although the difference was not statistically significant. A study by Zeiden, et al. concluded that increased comorbidity and poor disability status before the start of HMA therapy resulted in lower odds of persistent HMA, although with borderline significance.[41] MDS patients who were more profoundly dependent on RBC or platelet transfusion were less likely to receive persistent HMA therapy as well.[41] In the current study, transfusion dependence (69.2%) was a major concurring clinical burden on the patients, especially those in the non-persistent group (69%), but did not influence persistence to therapy. Other clinical cause of poor persistence was disease progression. Around 57.6 % patients had disease progression while on HMA therapy, and 38.5% led to either treatment discontinuation as per patient preference, or switch to more intensive chemotherapy.

Evaluation of non-clinical factors in the current study provided several crucial determinants of persistence. One of the main non-clinical causes was patient's preference

to discontinue treatment due to incorrect or inadequate understanding of disease biology and outcomes. This disparity in understanding disease and its treatment was majorly observed in uneducated non-persistent patient group. About 15.3% patients believed that HMA therapy had done more harm than benefit, and they opted to stop treatment. This patient narrative cannot be solely attributed to illiteracy as a few Western studies have also highlighted that MDS patients have poor understanding of their disease because of which they choose to discontinue therapy despite physician efforts.[42,43] No such data is available to confidently comment on CMML population, but similar challenges are to be expected in this cohort as well.[18] Affordability constraints (17.9%) was also a common non-clinical cause of poor persistence in the current study. The economic burden of MDS, CMML and HMA therapy has been discussed in several studies.[18, 20,44,45] Therefore, the financial burden on Pakistani patient population cannot be overstated. The relative cost of one vial of 50mg decitabine in Pakistan is around PKR35,000 (~$124.5USD) and as it is given in the dose of 20mg/m^2 over a three-hour intravenous (IV) infusion requiring admission to day-care facility and an additional cost of PKR10,000 (~$36USD), rounding off to total cost of PKR100,000 (~$360USD) per cycle. Thus, it is quite unaffordable for patients belonging to middle and low social classes who live hand-to-mouth on daily wages. The current study found that 23% patients discontinued HMA because they could not afford the prescribed therapy, and almost all of these patients were in the non-persistent group. Other non-clinical causes included lack of family support, transportation difficulties and delay in the arrangement of drugs. The likely cause of delay in the arrangement of drugs at the NIDB was due to pharmaceutical supply chain disruptions, which sometimes may take weeks to resolve and have become a common logistical cause of poor persistence encountered several times every year.[46]

Another logistical cause of poor persistence seen in the current patients was IV access issues (19.2%). Considering that the IV route is the only route of administration of decitabine, which is the frequently used HMA at NIDB, IV access problems, including phlebitis, difficult cannulation and injection-site haematomas, frequently hinder uneventful HMA administration. Patients reported IV access problems as an inevitable part of treatment, and openly expressed preference for oral therapy which has been observed in the West as well.[10,21] Zeidan, et al. studied 89 MDS patients on IV HMA, and around 74.2% said there was treatment-related interference with their social activities, and 66.3% experienced pain due to IV administration. Among the 49.6% of employed patients, 61.4% felt unproductive during treatment, and, hence, 69.5% MDS patients specified that they would prefer oral MDS treatment to IV/subcutaneous(SC) therapies.[47] Patients coming from interprovincial rural areas often had to travel to main city for haematological treatment due to unavailability of specialist centres in their regions. About 7.6% patients from the current cohort had primary residence out of the city, and they reported transportation problems as one of reasons of poor adherence to HMA therapy. When questioned to deliberate further, the patients reported that personal and family problems, complicated by transportation issues, were responsible for their poor persistence, like family members unwilling to compromise work and accompany the patient to hospital for the administration of IV HMA in a day-care setting. Similar patient problems in receiving azacitidine therapy for MDS and CMML were also reported by Tendas, et al.[18]

Lastly, the non-clinical factor having an impact on patient's treatment regime was physician discretion. Supportive care was a better option in improving patient's QOL, keeping in view patient's preference, affordability and performance status. Physician discretion regarding HMA therapy has also been reported by Steensma, et al. who showed that 69% of physicians prescribing HMA for MDS and CMML recommended stopping treatment before the completion of a planned treatment course, most frequently because of adverse events and because the burden of therapy outweighed the benefit.[24] The patients (81%) in the latter study believed that it was the recommendations of their physician that had the greatest influence on patients' treatment decisions.[24] This was, however, not the case in the current study in which physician discretion was rarely the reason of poor persistence.

The current study has limitations as the sample size was not statistically calculated with respect to power and effect size because all eligible cases were included. Prospective studies are needed to validate the current findings.

Conclusion

The factors contributing to poor persistence with HMA therapy among MDS and CCML patients could be clinical and non-clinical. Physicians must identify and address these factors when initiating HMA therapy to ensure better outcomes.

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