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Clinical Presentation and Outcomes of Patients with Myelodysplastic Syndrome

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Abstract

Objective: To analyze the clinical presentation, treatment outcomes, and survival patterns of MDS patients in Pakistan, addressing critical gaps in LMIC-specific data.

Methodology: This single-centre cohort study was conducted at the Armed Forces Bone Marrow Transplant Centre between January 2019 and December 2023, included 128 patients diagnosed with MDS per WHO 2016 criteria. Treatment strategies were categorized as palliative (growth factors, immunosuppressants) or definitive (hypomethylating agents [HMA], venetoclax, stem cell transplantation [HSCT]). Patients were followed-up and analysed for disease and survival outcomes.

Results: The cohort demonstrated a male predominance (3:1 ratio) with a mean age of 52.5 ±17.01 years. Anemia (85.9%), infections (27.3%), and bleeding (20.3%) were common presentations. Risk stratification revealed 44.5% lower-risk (very low/low IPSS-R) and 55.5% higher-risk (intermediate/high/very high IPSS-R) disease. Definitive therapy achieved 11% complete remission (CR) rates while palliative regimen showed 10.9%low transfusion dependence or transfusion independence after 1st line treatment. HSCT recipients (13.3%) had neutrophil engraftment at 13 days (IQR:12–14) and platelet engraftment at 21.4 days. The overall survival (OS) rate was 42.5% with median survival days of440 while disease free survival (DFS) rate was 22.7% with mean DFS days of 456.OS differed significantly by risk: 75% for very low-risk vs. 0% for very high-risk patients (p=0.01).Myeloablative conditioning (MAC) improved OS to 56% versus 7.7% in non-transplant high-risk patients.

Conclusion: This study highlights distinct MDS characteristics in LMICs, including younger age at diagnosis and stark outcome disparities linked to risk stratification and treatment access. While HSCT demonstrated survival benefits in intermediate-risk patients, limited CR rates with HMA-venetoclax underscore the need for optimized regimens. The findings emphasize urgent requirements for LMIC-tailored diagnostic protocols, expanded transplant infrastructure, and risk-adapted therapeutic strategies to address challenges in management of MDS.

Keywords: Myelodysplastic syndrome (MDS), Hypomethylating agent -venetoclax(HMA-Ven), Hemopoietic stem cells transplant (HSCT)

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Introduction

Myelodysplastic syndrome (MDS) is a clonal hematopoietic disorder that is characterized by dysplasia along with anaemia, thrombocytopenia or neutropenia and a risk of progression to acute myeloid leukaemia (AML). In the United States, the yearly incidence of MDS is approximately 4 per 100 000 people, notably higher among older population.[1,2] Incidence rising tenfold by the age of eighty (80) years.[3] Prognostic systems, such as the revised International Prognostic Scoring System (IPSS-R), offer rationally accurate estimates of survival at the population level. The goals of treatment in individuals having lower-risk MDS includes improving quality of life and minimizing red blood cells (RBCs)and platelet transfusions. Therapeutic goals in patients having higher-risk MDS (HR-MDS), include decreasing the risk of transformation to AML and increasing survival. Haematopoietic cell transplantation (HCT) has the potential to cure MDS, but less than 10% of affected people undergo this treatment.[1,4,5]

Improvements in the understanding of MDS has resulted in newer management strategies for these patients. As a result, the treatment landscape for MDS patients is changing. All these advancements are expected to improve the survival rate of patients suffering from MDS.[8]

There is limited data on presentation and outcomes of MDS patients in low middle-income countries (LMICs).

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The Aim of our study is to assess the clinical presentation and treatment outcomes in patients with MDS in a low middle-income country.

Methodology

This is a single-centre retrospective cohort study with analytical design, which was approved by the hospital ethics committee (IRB-017/AFBMTC/Approval/2022). Data collection was done from the hospital records on pre designed study forms. The study was conducted at the Armed Forces Bone Marrow Transplant Centre, a tertiary care facility located in Rawalpindi, Pakistan and included all consecutive patients having age >15 years diagnosed with MDS as per revised WHO 2016 criteria from January 2019 till December 2023. [9] The data of 128 patients was collected, followed-up and analyzed for disease and survival outcomes. Patients lost to follow up in the first 12 weeks of diagnosis or with insufficient extractable data were excluded from the study.

The initial demographic and clinical information collected included age, gender, clinical presentation and laboratory parameters. Bone marrow (BM) morphology and cytogenetics were used to establish the diagnosis of MDS. Subclassification was done using revised World health organization (WHO) 2016 classification of hematopoietic and lymphoid tumours. Patients were risk stratified using international prognostic scoring system (IPSS) and revised-IPSS (R-IPSS) scoring as per available data. Initial treatment was stratified depending upon the aim of treatment (palliative, definitive), supportive treatments given were blood products and antibiotics. For palliative intent treatments included growth factors, immunosuppressants, lenalidomide, low dose cytarabine. For the purpose of study, definitive treatment was hypomethylating agents (HMA), venetoclax, intermediate/high dose cytarabine and stem cell transplantation (SCT). Response to treatment was documented as per recommendations of the international working group (IWG) 2018 for low risk and IWG 2023 for high risk MDS.

For non-transplant patients OS was defined as duration from date of diagnosis till death/last follow up and DFS as duration after being transfusion independent or complete remission till any event(death/relapse) or last follow up, while for transplant patients OS was calculated as duration from date of transplant till death/last follow up and DFS as duration from date of transplant till death, relapse or last follow up. Data analysis was done through SPSS version 27.0. In descriptive analysis, percentage and frequency was calculated for categorical variables and mean ± standard deviation or median with interquartile range (IQR) for the continuous variables. Survival statistics were calculated using Kaplan Meier analysis. Univariate and multivariate regression was used to document significant factors affecting survival.

Results

The study included 128 patients, mean age was 52.5 ± 17.01 (16-90) years with male to female ratio of 3:1(Table I). Fanconi screening was available for 33 patients and was negative for all the patients. Transfusion history at the time of diagnosis revealed mean transfusion of 4.23 ± 4.84 (0-35) red cell concentrates (RCCs). The goal of treatment was stratified as palliative versus definitive. Palliative treatment was received by 81(63.3%) patients while definitive treatment by 47 (36.7%). The mean age of patients receiving definitive treatment was 45.85 ±14.45 (95% CI: 41.66-50.05) and mean age of patients treated with palliative intent was 56.60 ±17.23 (95% CI: 52.76-60.44) (p_{Anova}=0.0001). The chemotherapy administered included HMA + venetoclax for 35(27.3%), low dose cytarabine (LDAC) for 7 (5.5%), LDAC +venetoclax for 2(1.6%), venetoclax alone for 1(0.8%), Daunorubicin+Cytarabine (D3A7), (D3A4), intermediate dose cytarabine (IDAC) and high dose cytarabine (HIDAC) for 1 (0.8%), HMA only for 1(0.8%), Idarubicin, cytarabine for 1 (0.8%) patient. The first- line treatments administered with curative intent were included azacytidine + venetoclax for 19(14.8%), decitabine + venetoclax to 14(10.9%), azacytidine alone, Idarubicin with D3A7 and venetoclax each was administered to 1(0.8%) patient while 7 (5.5%) patients underwent upfront transplant. The response to definitive treatment was CR in 14(11%), hematologic improvement in erythroid and neutrophils(HIE-HIN) in 1(0.8%) while no response in 28(22%) patients .The palliative treatment included erythropoietin (EPO) for 39(30.5%) patients ,ciclosporin(CSA) for 9(7%), lenalidomide for 5(3.9%), EPO+CSA for another 5 (3.9%) , LDAC for 4(3.1%) patients, supportive treatment for 19(14.8%).The combination of CSA, EPO, eltrombopag was received by 2(1.6%) while CSA with eltrombopag and hydroxyurea each was received by 1(0.8%).The

response documented for patients receiving palliative 1st line treatment included HIE NTD(non-transfusion dependent) for 9(7%), HIE LTD(low transfusion dependent) in 5(3.9%), CR and CRL(CR with low count recovery) in 1(0.8%) patient each. No response was documented in 47(36.7%) patients while 2(1.6%) patients progressed to AML.

Table I: Clinical presentation of study.

		N(%)
Sub-Type	MDS-MLD	36(28.1)
	MDS-EB1	14(10.9)
	MDS-EB2	35(27.3)
	MDS-Unclassifiable	33(25.8)
	MDS-del5q	2(1.6)
	MDS-SLD	5(3.9)
	MDS-RS	3(2.3)
R-IPSS Score	Very low risk	4(3.1)
	Low risk	53(41.4)
	Intermediate risk	44(34.4)
	High risk	21(16.4)
	Very high risk	6(4.7)
Anemia	Yes	110(85.9)
	No	18(14.1)
Infection	Yes	35(27.3)
	No	93(72.7)
Bleeding	Yes	26(20.3)
	No	102(79.7)
FISH Del5q	Not detected	19(14.8)
	detected	3(2.3)
	NA	106(82.8)
Fish Del 17p	Not detected	26(20.3)
	detected	1(0.8)
	NA	101(78.9)
Cytogenetics	Very Good	1(0.8)
	Good	60(46.9)
	Intermediate	7(5.5)
	Poor	2(1.6)
	Very-Poor	2(1.6)
Myeloid Gene Panel	Negative	19(14.8)
	SF3B1	1(0.8)
	NA	108(84.4)

Patients that underwent HSCT were 17(13.3%) in which 11 (8.5%) patients received cytoreductive therapy before transplant, 13(10.2%) patients were not in remission while 4(3.1%) in first CR (CR1). The stem cell source for 13 patients was bone marrow harvest (BMH) while BMH+PBSC (peripheral blood stem cells) for the remaining four patients. Conditioning type was myeloablative conditioning (MAC) in 16(12.5%) while reduced intensity conditioning (RIC) in 1(0.8%) of the study population. Out of 17 donors for SCT, 15 (88.2%) were male while 2 (11.8%) were females. The median CD 34 dose achieved was 2.76 x10^6 (IQR: 2.36-3.79). All of the HCT patients received methotrexate and cyclosporine as graft vs host disease (GVHD) prophylaxis. The median duration for neutrophils engraftment was 13 (IQR:12-14) days and mean days for platelet engraftment were 21.4 ± 3.82 (16-28). Post transplant complications were febrile neutropenia in 16 (12.5%), mucositis in 13(10.2%) while azotemia and gut toxicity each in 3 (2.3%) patients. aGVHD was observed in 4 (3.1%) patients while cGVHD in 7 (5.5%) patients.

Out of 113, the overall survival rate was 42.5% with median survival days of440 (CI 95%:161.7-718.2) (Figure 1).

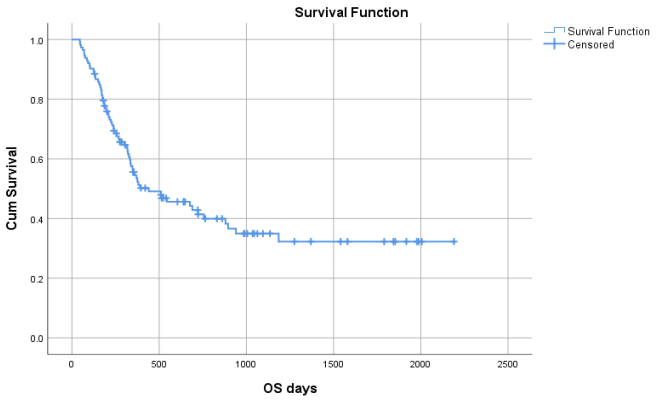

Figure 1. Overall Survival.

The OS rate for very low risk patients was 75% with median survival days of 690,for low risk 48% with median survival days of 676,for intermediate risk was 50% with median survival days of 756,for high risk was `16.7% with median survival days of 198 and was zero% for very high risk patients with median survival days of 337(95% CI:289-384)(P=0.01).OS for patients receiving treatment with palliative intent was 25% with mean survival days of 520 while for definitive treatment was 21.3% with mean survival days of 408(P=0.5).Survival for patients receiving HMA-Ven was 36.4%,zero % for patients receiving venetoclax, LDAC while 49.3% for patients who did not receive any chemotherapy (P=0.02) .OS rate was 56% for patients received MAC conditioning with mean survival days of 1227(95% CI:803-1651)(P=0.01). In intermediate risk patients, the OS was 57% for transplant while 48.4% for non-transplant, similarly for high risk patients, MSD had OS of 25% while 7.7% in non-transplant patients while for very high-risk patient's OS was zero % both for transplant and non-transplant patients. Out of 119, The disease-free survival (DFS) rate

Table II: Association of risk-based treatment and intent of treatment with OS.

		Total N	Death	Alive		CI 95%	
R-IPSS Score	Treatment Intent			%	Median OS days	Lower	Upper
Very low risk	Palliative treatment	4	1	3(75)	690	.	.
	Overall	4	1	3(75)	690	.	.
Low risk	Definitive treatment	7	3	4(57.1)	510	25.93	994.06
	Palliative treatment	41	22	19(46.3)	676	239.12	1112.87
	Overall	48	25	23(47.9)	676	.	.
Intermediate risk	Definitive treatment	20	10	10(50)	545	0	1182.96
	Palliative treatment	18	9	9(50)	756	68.96	1443.03
	Overall	38	19	19(50)	880	212.38	1547.61
High risk	Definitive treatment	12	9	3(25)	170	131.59	208.40
	Palliative treatment	6	6	0(0)	198	0	524.38
	Overall	18	15	3(16.7)	327	38.44	615.56
Very high risk	Definitive treatment	5	5	0(0)	337	289.76	384.23
	Overall	5	5	0(0)	337	289.76	384.23
Overall	Overall	113	65	48(42.5)	440	161.73	718.26

Note: log rank test was applied

was 22.7% with mean DFS days of 456 (CI 95%: 309-603) (Figure 2). The DFS rate for patients having response to 1st line treatment of NTD was 80% while for CR was 50% (P=< 0.001). Similarly, patients which received MAC had DFS of 50% and for RIC was zero% with median DFS days of 74.0(P=0.01) and for patients having cGHVD was 57% with mean DFS days of 1277(95% CI:658-1896) (P=0.02). The association of risk-based treatment strategies and intent of treatment with OS is shown in Table II

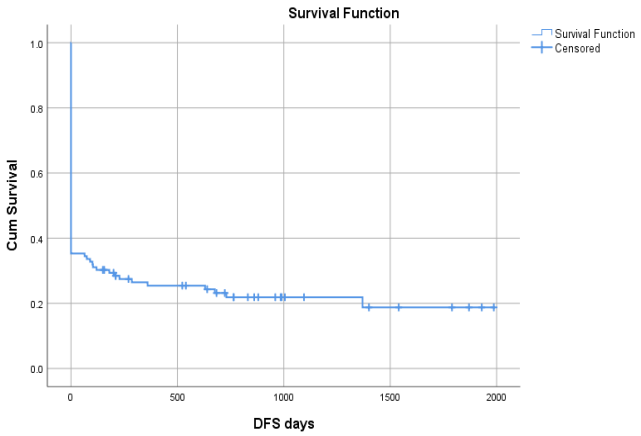

Figure 2: Disease Free Survival.

Discussion

This study focused on the clinical presentation and outcomes of different treatment modalities in MDS patients. The patients were followed up to till 30th June 2024 in terms of their overall survival and disease-free status and for those that underwent transplant, the transplant related complications that included peri transplant and GHVD was also taken into consideration. The mean age of the patients was 55.5 years, with the males accounting 75% while 25% were females. In study by Garcia, J.S., et al median age of the patients was 71 years, that included 75% males and 25% females.[10] Similarly, Stahl M et al reported the median age of his research population was 65 years that were constituted by 63% male and 37% female population. [11] In the same way Komrokji RS et al. reported median age of study population as 68 years that consisted of 62% males.[12]

Anaemia was found in 85.9% patients at the time of diagnosis in our study population. The study by Dias R et al. identified MDS as the cause of anaemia in 32% patients. [13] Similarly, Haring, Y., et al recorded anaemia in 85% of patients.[14] Infections were documented in 27.3% of patients at the time of diagnosis. In the same way Kasprzak A et al. documented infections in 42% patients, while Bazinet, A et al recorded infections in 47% population.[15,16] The study recorded bleeding in 20.3% patients while Mo, A., et al recorded bleeding in 11.2% patients of MDS.[17] Similarly, Strapatsas J et al. stated that 14% of his patients showed signs and symptoms of bleeding at the time of diagnosis, contrary to that Peña, AL et al. recorded bleeding in 50% of the population recruited for the research.[18,19]

Treatment options for low risk MDS include Erythropoietin (EPO), Thrombopoietin receptor agonists (TPO-RA), Lenalidomide, Luspatercept, immunosuppressive agents and hypomethylating agent (HMA) therapy while HR-MDS patients should be

considered for allogeneic hematopoietic stem cell transplantation (HSCT). [5,6]

Patients receiving palliative treatment as first line were 51.6% that included CSA, EPO, hydroxyurea, lenalidomide and eltrombopag. and the response documented were non transfusion dependency in 7%, low transfusion dependency in 3.9%, CR in 0.8%, CR with low county recovery in 0.8%, no response in 36.7% while 1.6% patients progressed to acute myeloid leukemia (AML). In study by Gascón P et al the patients that received erythropoietin or darbepoetin, the response rate was 39% in patients with del(5q), while 52% in patients with non-del (5q). [20] Similarly Fenaux P et al recorded that the 31.8% patients achieved erythroid response up to 24 weeks with epoetin alfa. [21]

Curative treatment as first line were received by 33.6% that included Decitabine+venetoclax, Aza+ven, Aza only, Idarubicin with D3A7, venetoclax and upfront transplant in 5.5% patients and CR rate was 11%. In the same way Zeidan AM et al documented CR rate of 6.8% in response to Azacytidine+ venetoclax. [22] In contrast, Du YC Li and J Yan documented CR rate of 67.6% in high risk MDS. [23] While Ball BJ et al. revealed 14% CR rate after treatment with Aza+ venetoclax or decitabine + venetoclax.[24]

HSCT was done for seventeen patients in which median days for neutrophils and platelets engraftment were 13 and 21 days respectively. In the same way Zhang Y et al.[25] documented median days of engraftment for platelets and neutrophils as 13 and 15 days respectively. Gao L et al. determined engraftment of neutrophils and platelets as 12 and 15 days respectively. [26] Acute GVHD (aGHVD) was observed in 3.1% patients. Contrary to that, Asensi Cantó P et al found aGVHD in 32% of his patients while Gao, L, et al observed grade II-IV aGHVD in 35% of patients after MSD transplant.[26,27] Chronic GVHD (cGHVD) was observed in 5.5% patients while Gao L et al.[26] reported cGHVD in 78% patients with MSD HSCT. Similarly, Konuma, T et al. documented incidence of limited cGVHD in 19% each of high and low risk patients while extensive cGHVD in 28% low risk and 32% high risk patients. [28]

MDS patients having TP-53 mutations have lower survival compared with wild-type patients.[7] We recorded an overall survival rate of 37.5% and the disease-free survival DFS rate of 21.1% in our population including non-transplant and transplant patients. Maurya N, et al followed 152 patients of MDS and found an OS rate of 75%. [29] Mądry K et al found a 5-year OS rate of 47.3% in the population that included low risk MDS patients.[30] Usuki K, et al observed 5-year OS rate of higher-risk MDS patients after treatment with azacitidine was 12.1% and 33.9% for lower-risk patients.[31] In the study by Wang, Q et al the 3-years (DFS) rate was 52.5% for MDS-EB2 and MDS-AML after peripheral blood SCT. [32] In study by Sasaki, K., et al patients with low risk MDS were treated with Azacytdine and decitabine and the response was transfusion independence of 32% with azacytidine while 41% with decitabine.[33]

The study had certain limitations as the population was from a specific area that included almost all types of MDS and all risk groups while most of the studies considered a specific subgroup of MDS. Moreover, the treatment modalities were diverse that included patients receiving transplant and non-transplant. In addition, the patients were followed for a minimum of 6-54 months and there was a lot of variation in duration of follow up in each patient. So further studies with a larger number of patients is suggested to enhance the reliability and relevance of the results

Conclusion

This study highlights distinct MDS characteristics in LMICs, including younger age at diagnosis and stark outcome disparities linked to risk stratification and treatment access. While HSCT demonstrated survival benefits in intermediate-risk patients, limited CR rates with HMA-venetoclax underscore the need for optimized regimens. The findings emphasize urgent requirements for LMIC-tailored diagnostic protocols, expanded transplant infrastructure, and risk-adapted therapeutic strategies to address challenges in management of MDS.

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