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Myelodysplastic syndromes in Pakistani population-analysis of 52 cases and their outcome on best available treatment options

Abstract

The Myelodysplastic syndromes (MDS) are clonally evolved bone marrow disorders leading to the bone marrow failure, peripheral cytopenia and a propensity for progression to acute myeloid leukemia (AML). To observe the trend and outcome of MDS in Pakistani population, a retrospective data analysis was carried out in National Institute of Blood Diseases & Bone Marrow Transplantation, from January 2010 to December 2014. Fifty-two MDS or MDS/MPN cases were analyzed out of which 39(75%) were males. Median age at the time of diagnosis was 60years. Secondary/t-MDS was observed in 2(3.8%) cases while others were de-novo MDS. Low intensity treatment was offered to 16(30.7%) cases out of which 5(31.25%) cases responded to treatment. Full HLA matched related donor allogenic HSCT was unsuccessfully attempted in 2(3.8 %) cases. At the time of analysis only 19cases were alive after a median follow up 10months (range 2months to 48months). Median progression free survival was 1.9months for very high risk, 6Months for high risk, 12.8months for intermediate risk and 39 Months for very low and low risk while median overall survival was 3 months for very high risk, 8.5 months for high risk and 18.7 months for intermediate risk. All patients were alive in very low and low risk category when study was concluded.

Keywords: myelodysplastic syndrome, prognostic scoring, treatment outcome

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Abbreviations: MDS, myelodysplastic syndromes; AML, acute myeloid leukemia; IPSS, international prognostic scoring system; SD, statistical mean; ESAs, erythropoietin stimulating agents; HI, hematological improvement

Introduction

Discussed formally as "odo-leukemia", or at the verge of leukemia by, Chevallier and colleagues in 1942, myelodysplastic syndromes are clonal hematopoietic disorders varying from relatively indolent clonally derived anemia, to resistant clonal multi lineage cytopenia or to oligoblastic myelogenous leukemia all having variable propensity to progress towards acute myeloid leukemia. They are mostly evolved de novo but are sometimes secondary to prior exposure of chemotherapeutic agents or an underlying immune dysfunction.[1] MDS is a relatively uncommon disorder, American studies describe epidemiology of MDS 3-5 per 100,000 annually.[2] data from the Düsseldorf MDS-[1]registry shows the crude incidence in Europe as 4.15/100,000/year.[3] From Japan age-adjusted incidences of MDS in 2008, standardized by the world standard population, were 1.6 and 0.8 cases per 100,000 for men and women, respectively, while incidences standardized by the 1985 Japanese population were 2.5 and 1.2 cases per 100,000 for men and women, respectively.[4] From Pakistan only crude figures are available in terms of frequencies. In a largest available study in Pakistan MDS is found in 2.4% out of 208 cases of pancytopenia.[5] No national registry for evaluation of disease burden is established in Pakistan yet nor any clinical study on disease outcome has been carried out in the past.

With the advancement in the field of research and therapeutics and better understanding of this disease at molecular level separate treatment options are available currently to deal with low and high risk categories in MDS. This has improved the outcome of MDS in last 30 years. The survival and rate of leukemic progression of 4147 patients from the Duesseldorf MDS registry diagnosed during the last 30 years and found an improvement of survival in those patients diagnosed after 2002 (30 vs. 23months, $p<0.0001$). In detail, the improvement of the prognosis was restricted to high-risk MDS patients diagnosed between 2002 and 2014 in comparison to the patient group diagnosed between 1982 and 2001 (19 vs 13months, $p<0.001$), whereas the prognosis of low-risk MDS patients did not change significantly.[6]

To evaluate the disease prognosis and outcome on best available treatment options in Pakistan a retrospective study was conducted from year 2010 and onwards in one of its largest hematology Centre. This is the first detailed south Asian study in which, data of 52patients suffering from myelodysplastic syndrome is compared with the developed world figures to highlight the differences of disease outcome in struggling countries.[7]

Methods

This retrospective survey was carried out in the department of clinical hematology at National institute of blood disorders and bone marrow transplantation Karachi, a tertiary referral Centre for hematological disorders. All consecutive patients with the diagnosis of MDS or MDS/MPN over a 5year period from January 2010 to December 2014 were included. Eligibility criteria was age >15years and availability of detailed report of a bone marrow aspirate and trephine biopsy from hospital's registry. Patients were diagnosed on the basis of morphology, using WHO 2008 diagnostic criteria for myelodysplastic syndromes; defined as dysplasia in one or more of myeloid lineages associated with variable degree of cytopenia(s), ineffective hematopoiesis and presence of bone marrow or peripheral

blood blasts less than 20% in the absence of recurrent cytogenetic abnormalities associated with AML.[8] Diagnosis was not made while patients were receiving any growth factors.

Prognosis was evaluated using revised international prognostic scoring system (IPSS-R)[9] and treatment response was assessed using modified International Working Group response criteria for hematologic improvement in MDS (Table 1)[10] as it is currently a better predictive model for prognosis evaluation among all others and also incorporated lately in NCCN guidelines for myelodysplastic syndromes.

Table 1 Baseline characteristics of 52 patients

Characteristics	Value
Median age in years	60(16-85)
Gender ratio(males/females)	39(75%)/13
Hemoglobin range(at the time of first visit)	3.4-13.2g/dl
Average red cell concentrates transfusion per month	2.09(range 0-6 transfusions/month)
Platelets range(at the time of at the time of first visit)	2-490x10^9/l
Average adult therapeutic dose platelets(ATD) transfusion per month	1.26(range 0–6 times/month)
Severe neutropenia at the time of diagnosis	12(23.07%)
Underlying comorbid illness	15(28.8%)
History of prior chemotherapy	2(3.8%)

Statistics

Descriptive statistics included mean (SD) or median (minimum-maximum) as appropriate for continuous variables and frequency (percentage) for categorical variables. The Kaplan-meier analysis was used to obtain estimated survival rates in months for very high, high, intermediate, low and very low risk IPSS-R categories. Low and very low risk categories were merged together due to availability of only a single very low risk case. The study was performed in accordance with the ethical standards of the Helsinki Declaration and it has been approved by the institutional review board of National institute of blood diseases and bone marrow transplantation.

Results

The main characteristics of 52patients, 39 men (75%) and 13 women, fulfilling the inclusion criteria have been collected and analyzed shown in Table 1. Main comorbid illnesses are also documented commonest being diabetes mellitus 9(17.3%) (Table 2). Neither the prevalence nor the incidence of MDS could be estimated given the retrospective design of the study and lesser number of patients. Median age of the patients was 60years at the time of diagnosis. RCMD was the commonest category seen 14(26.9%) among WHO 2008 classified MDS categories. t-MDS was seen in 2(3.8%) cases one had t-RCMD and another had t- RAEB-II (Table 3). In prognostic classification via IPSS-R system, intermediate risk group was most frequently seen, 22(42.3%) (Table 4).

Table 2 Documented comorbid illness comments being diabetes mellitus

Comorbid conditions	N(%)
Diabetes Mellitus	9(17.3%)
Hypertension	6(11.5%)
Chronic kidney disease	5(9.6%)
Chronic liver disease	3(5.8%)
Ischemic heart disease	4(7.7%)
Stroke	1(1.9%)
Chronic obstructive pulmonary disease	2(3.8%)

Table 3 WHO 2008 classified MDS categories

WHO MDS categories	Value(%)
RCUD	9(17.3%)
RA-RS	0(0.0%)
RCMD	14(26.9%)
RAEB-1	9(17.3%)
RAEB-2	8(15.3%)
MDS-U	2(3.8%)
MDS with isolated del 5q	1(1.9%)
Hypoplastic MDS	5(9.6%)
MDS/MPN	2(3.8%)
t-MDS	2(3.8%)

Table 4 Prognostic classification via IPSS-R system

IPSSR- Risk	Score	Value(%)
Very low	≤1.5	1(1.92%)
Low	>1.5≤3.0	14(26.9%)
Intermediate	>3.0≤4.5	22(42.3%)
High	>4.5≤6.0	6(11.5%)
Very high	>6.0	8(15.3%)

Among cytogenetic analysis no cytogenetic abnormality was encountered in 45 out of 52(86.5%) cases. Only 7 cases showed cytogenetic abnormalities. Chromosome 5 involvement was observed most frequently in 4cases (57.1%). Isolated deletion 5q was seen only in a single female patient who presented as refractory anemia. Numerical gain of chromosome 11 a rare cytogenetic finding in MDS is also observed in one case.[11] Other cytogenetic findings are mentioned in Table 5.

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Table 5 Cytogenetic findings

Abnormal cytogenetics n=7	IPSS-R cytogenetics grading	Morphological category
Isolated del 5q	Good	RA(RCUD)
Trisomy 8	Intermediate	RAEB-2
20q-, 5q-, +8, +11	Very Poor	RCMD-RS
47xxy	Intermediate	RCMD
Monosomy 5,7,8	Poor	Hypoplastic MDS
47xxx, t3:12del7q +5	Very Poor	MDS/MPN
Complex karyotype	Very poor	RAEB-1

Management (Figure 1)

Supportive care: All 52patients received supportive care with red cell concentrates transfusion, while platelets transfusion was required due to symptomatic bleeding episodes in 18 out of 52patients (34.6%). Antibiotics and hospitalization for infections were needed in 28(53.5%) patients, out of this; double gram negative cover was provided to 18 out of 28(64.2%) patients due to underlying neutropenia. Iron chelation was carried out in none of the transfusion dependent cases.

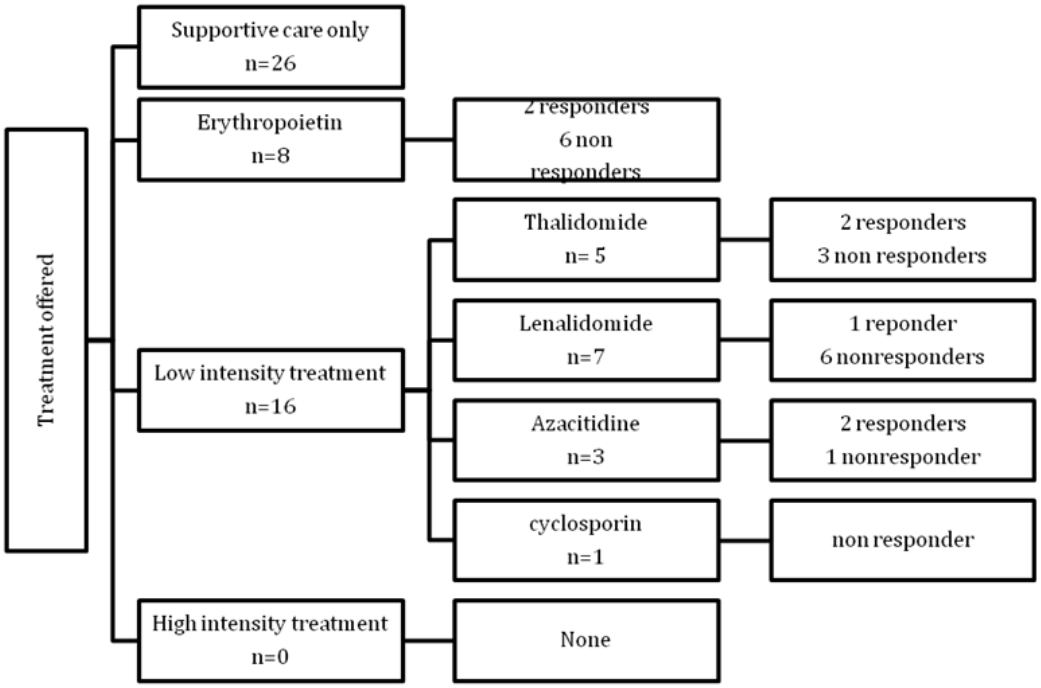

Figure 1 Management of myelodysplastic syndromes.

Vitamin B12 and folic acid

At least a fortnightly trial of B 12 and folic acid is given to all patients at the time of first follow up in OPD after Clinical evaluation and review of complete blood counts and peripheral smear. Serum B 12 and red blood cell or serum folate levels are also advised and treatment discontinued when results turn out to be normal in next visit; if patients get their levels done or no improvement in counts observed in next follow up after 2weeks. Only 16patients carried out their B12 and folic acid levels testing out of which 4(25%) turned out to be B12 deficient while only 1 patient (6.25%) was folate deficient. Hematological improvement (HI) lasting 8 weeks at least, was observed in none of the cases.

Erythropoietin

Erythropoietin-alpha was offered to 8cases (15.33%) at the dose of 40'000 units per week in three divided doses out of which 2(25%) cases showed erythroid response (HI-E). Both had refractory anemia. Out of these cases one is transfusion independent now and another sustained Hb >9g/dl for 24months period.

Thalidomide and lenalidomide

Thalidomide was prescribed to 5 (9.6%) patients out of whom only 2 intermediate risk cases (40%) showed sustained HI. One case with RCMD showed complete hematological improvement (HI) up to 24months while another case with RA still sustains HI-E since onset of treatment. Lenalidomide was given to 7(13.4%) patients out of whom only 1patient (14.2%) responded who had RCMD. The response lasted only for 9months. Another case worth discussing here is isolated deletion 5q syndrome who upon initiation of lenalidomide did not give any response, despite proper compliance. She is still transfusion dependent since 48months and has not progressed further in an advanced MDS subtype.

Azacitidine

Azacitidine was accepted as a treatment option by 3 high risk MDS (5.76%) cases out of which 2cases (66 %) showed HI. Short lived HI-E was observed for 12weeks in a patient of RAEB-2 while complete HI in all 3 cell lines was seen in a case of RAEB-1 who progressed into RAEB-2, 15months post treatment.

Allogenic Hematopoietic Stem cell Transplant.

Allogenic HCT was planned in two high risks young MDS cases (3.8%), both expired during conditioning; because necrotizing enterocolitis in one case and sudden anaphylaxis in other; when test dose of amphotericin B was administered for suspected fungal infection.

Cyclosporin

Cyclosporin failed to give any response in a case of hypoplastic MDS (1.92%), who survived for 15months after diagnosis.

Follow up, outcome and mortality

The median follow up was10months (range 2months to 48months) from the time of diagnosis of MDS. 9cases lost to follow us out of which 4left after progressing into an advanced MDS subtype, 24 were dead due to MDS related complications while 19 were alive at the time of data analysis (). Median progression free survival of all followed up cases is 1.5months for very high risk, 6months for high risk, 13months for intermediate risk, and 39months for very low and low risk category while overall survival was 2.3months in very high risk, 8.3months in high risk and 19 Months in intermediate risk category. All very low and low risk cases are still alive so overall survival is not obtained in this risk group (Table 7) (Figure 2). Disease specific treatment was chosen by only 26(50%) patients due to availability of resources out of which 1(3.8%) was very low risk, 9(34.6%) were low risk, 11(42.3%) were intermediate risk and 5(19.2%) were high risk category patients. Very high risk cases were managed on supportive care only. Sustained hematological improvement for more than 8 weeks was obtained only in 3(33.3 %) low risk, 2 intermediate risk (18.1%) and 2(40%) high risk cases.

Table 6 Data analysis of MDS related complications in abnormal cytogenetics

Morphological category	Lost to follow up N=09	Alive N=19	Dead N=24
RCUD n= 10	1 case (lost after 24months)	9	None
RCMD n=15	4 cases (2 lost after 24months, one after 18months another after diagnosis)	8	3
RAEB-1 n=9	2 cases (lost after diagnosis)	1	6
RAEB-2 n=9	None	None	9
Hypoplastic MDS n=5	1 (lost after diagnosis)	None	4
MDS/MPN n=2	1 (lost after 2 months)	None	1
MDS-U N=2	None	1	1

Table 7 Data analysis of survival of patients in risk conditions

IPSS-R category	Median progression free survival	Median overall survival
Very high risk	1.9months	3months
High risk	6Months	8.5Months
Intermediate risk	12.8Months	18.7Months
Very low and low risk	39Months	All alive

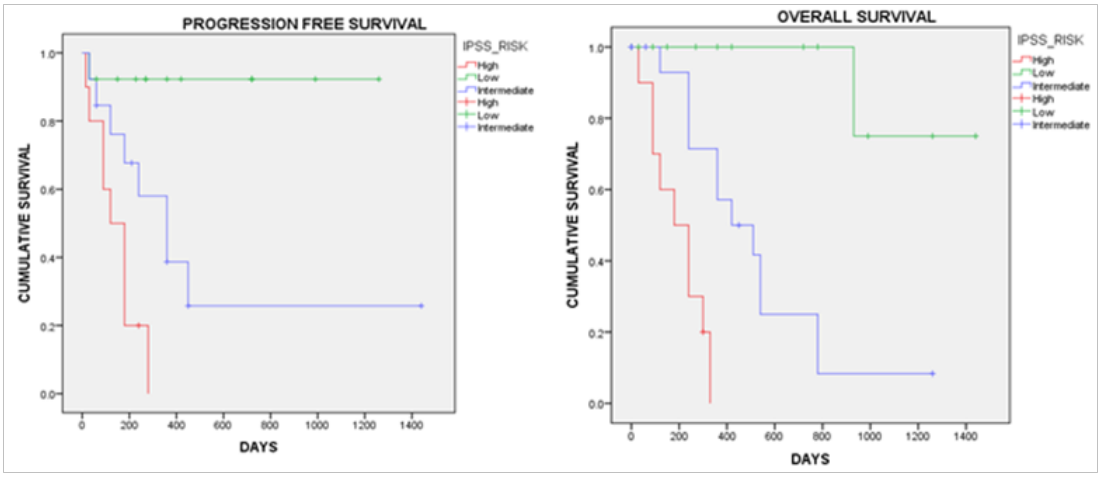

Figure 2 Progression free and overall survival curves of very low & low (green), intermediate (blue), very high and high IPSS-R risk groups (red).Significant difference seen in the cumulative survival of low risk group (p value 0.00).

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Discussion

With recent therapeutic advancements and provision of best supportive care better outcome of MDS is seen in published data from developed countries.[6] The majority of de novo MDS patients are diagnosed with lower or intermediate risk disease, and although prognosis in this ample subgroup of patients is highly heterogeneous, their most frequent problem is, at least in two-thirds of the cases, confined to anemia. Therefore, first-line therapy is frequently used only to increase hemoglobin levels. Erythropoietin stimulating agents (ESAs) have been found to increase hemoglobin levels and abolish transfusion dependence in 19%-68% of MDS cases.[12] Lenalidomide is highly responsive in terms of transfusion independence in MDS with isolated 5q deletion.[13] In ESA-refractory MDS patients without 5q alteration, the reported response tolenalidomide is 26% (transfusion independence).[14] While thalidomide on the other hand showed 56% response in a study of 34 MDS patients by Strupp et al.[15] The outlook does not worsen as long as anemia remains the sole problem and even >50% disease free survival in treatment refractory MDS is achievable in carefully selected low risk patients.[16,17]

For high risk patients the outcome after allogeneic sibling donor stem cell transplantation has improved a bit in last few years due to reduced non relapsed mortality but a 5-year relapse rate is still significantly high- 44% for RAEB and 52% for RAEB-t.[18] Also the use of azacitidine and decitabine in the treatment of higher risk MDS has improved survival up to 50% in patients who used to have very poor survival.[19,20] This reflects in the Spanish data presented in annual ASH meeting in 2012 where median overall survival rates are 113.7months in very low risk, 60.3months in low risk, 30.5months in intermediate risk and 21.2months in high risk IPSS-R cases (Table 8).[21]

Table 8 Median overall survival rates of patients in IPSS-R category

MDS IPSS-R risk category	Estimated median survival in the absence of therapy(in years)	Median overall survival obtained in Spain (in months) n=2410(GESMD study)	Median overall survival obtained in Pakistan (in months) n=52
Very Low	8.8(104months)	113.7	All alive when study was concluded.
Low	5.3(63months)	60.3	
Intermediate	3(36months)	30.5	18.7
High	1.6(18months)	21.2	8.5
Very high	0.8(8months)	Not evaluated, 1 case only	3

Albeit the above mentioned data is promising in terms of survival in myelodysplasia, data from developing world does not reflect the similar picture due to lack of established health insurance systems and government assistance. In an Indian data published in 2009 only 7patients received disease specific treatment out of 30 cases. The reason in opting for the palliative treatment was economical in most of the cases while in old patients there was reluctance for hospital admission and intravenous chemotherapy while 60patients lost their follow up since the initiation of study. The survival in myelodysplasia is mentioned in span of days and WHO 2008 MDS categories were taken for survival estimation. Statistics were 119.2days (3.9months) for RA, 302.7days for RAEB-1 (10 months), 233.7days for RAEB-2 (7.7 months) and 165days for RA with multi lineage dysplasia (5.5 months).[4] While from Iran median MDS survival as a whole, without any disease or risk categorization is only 14.6months.[22]

More or less same picture appears in this study when matched with our neighbor countries which is likely due to non-availability of histone deacetylase inhibitors in Pakistan and nearly out of reach allogenic hematopoietic stem cell transplant facility due to lack of expertise and sky rocketing cost of transplant in private sector. Eventually all the high and very high risk cases do not even survive for more than a year. Survival in intermediate and low risk category is also less satisfying although treatment was initiated in 21 out 38 (55. 2%) cases in this study. Treatment response was obtained only in 18.1% of intermediate risk and 33.3% low risk MDS cases. Erythropoietin, lenalidomide, thalidomide and cyclosporine were all ineffective in providing sustained hematological improvement. The reasons for this low response are likely due to treatment interruptions due to cost issues, poor-compliance and less effective best supportive care. There might be an underlying genetic basis for this different disease behavior in our population as gene expression profiling and molecular behavior of MDS in our population is unknown. Data from other centers in Pakistan is also needed to be brought forward to refute the possibility of intra-observer variation in this study.

Conclusion

We conclude, without development of cost effective measures outlook of MDS is staying same in developing countries as it was in pre 2000 era in developed world, unless this problem is overcome by establishment of the MDS registry in Pakistan. This will help in directing attention of therapeutic industries for new molecule development and preparation of MDS specific drugs locally. Estimation of disease burden by further epidemiological studies in Pakistan is also essential in order to convince governing bodies to finance clinical and scientific researches and prepare effective health policies in this not uncommon disease entity

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Conflict of interest

The author declares no conflict of interest.

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