CLINICOPATHOLOGICAL FEATURES OF NIGERIANS WITH MYELODYSPLASTIC SYNDROMES

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Aim: Myelodysplastic syndromes are a group of haematologic disorders characterized by varying degrees of cytopenias and a propensity to leukaemic transformation. The aim of this study is to determine the prevalence, clinical and laboratory characteristics and the outcome of management in Nigerians with this disorder.

Methods: Ten patients who have full clinical and laboratory information were retrospectively studied. Data extracted included demographic parameters, clinical features at presentation, haematological parameters, including bone marrow cytology (and cytogenetic findings, where available), management instituted and outcome of such therapy.

Results: Ten patients with de novo MDS were managed and followed-up for a median period of 3 months. The majority (90.0%) were aged 50 years or above with a median age of 65 years. All presented with symptoms of cytopenias such as anaemia (100%), neutropenia (50.0%), and thrombocytopenia (10.0%). Patients had mainly supportive management such as blood product supports. One patient, however, in addition received growth factor and cytotoxic chemotherapy, while one received cytotoxic drugs alone. These were however not adequate due to financial constraints. Eight deaths were recorded (88.9%), either cytopenia related (five) or renal failure (three). Cause of death in one was not known as he died at home. The mean survival was 50.5 ± 96.1 weeks (range=2.1–308.4 weeks)

Conclusion: It could be concluded that though clinical and laboratory features of Nigerians with MDS are similar to what is obtained from other parts of the world, non-availability of both specific and supportive drugs, and poor socio-economic status of most patients contributed significantly to the poor outcome recorded in this report.

Key words: Myelodysplastic syndromes, Presenting features, Nigerian

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INTRODUCTION

The myelodysplastic syndromes (MDS) are a group of acquired invariably fatal clonal haematopoietic stem cells disorders characterised by ineffective haematopoiesis, peripheral cytopenias (1) and potential to evolve into acute leukaemia. There is increased apoptosis in early and mature haematopoietic cells. The bone marrow may be normocellular or hypercellular, in the presence of peripheral monocytopenia (usually anaemia) or pancytopenia (anaemia with neutropenia and/or thrombocytopenia). The major clinical problems manifested by these patients are related to the cytopenias, most especially anaemia, most often transfusion-dependent. However, apart from the ineffective erythropoiesis, factors such as autoimmune haemolysis (2) and production of pro-inflammatory cytokines by macrophages causing immune destruction of cells, and intramedullary cell destruction (3) have also been suggested.

Based on percentage marrow blasts and ringed sideroblasts, Bennet, et al (4) classified MDS into 5 morphologic subgroups, the relatively indolent refractory anaemia (RA, blasts < 5%) and refractory anaemia with ringed sideroblasts (RARS, blasts < 5%), the aggressive refractory anaemia with excess blasts (RAEB, blasts 5-20%)) and the more highly aggressive refractory anaemia with excess blasts in transition (RAEB-T, blasts 20-30%), as well as the incurable chronic

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Table 1.Clinical and laboratory features of patient with MDS at diagnosis

	*MDS	*RA	RARS	*RAEB	RAEB-t	CMML
Patients	10	5	1	2	1	1
Mean age (yr)	62.50	63.5	72.0	61.50	52.0	60.0
Mean PCV (%)	15.0	13.2	18	14	21	17
Mean neutrophils, $X10^9/L$	2151.9	1650.8	1156	2456.6	1606	5600
Mean platelets, $X10^9/L$	92000	114600	78000	15500	30000	217000
BM blasts (%)	0-54	0	0	0-11	54	5-50
Pre-leukaemic duration (weeks)	1-8	-		-	1	8
Survival (weeks)	50.5	73.0	151.2	12.4	13.0	date

** Mean value for the subtype*

RA=Refractory anaemia, RARS= Refractory anaemia with ringed sideroblasts, RAEB= Refractory anaemia with excess of blasts, RAEB-t=Refractory anaemia with excess of blasts in transformation, CMML=Chronic myelomonocytic

myelomonocytic leukaemia (CMML, blasts 1-20%). Refractory anaemia with ringed sideroblasts (RARS) has sideroblasts in excess of 15%, compared to other variants with ringed sideroblasts of less than 15%. Median survival range from 50 months in RA and RARS, 18 months in CMML, 13 in RAEB and only 6 months in RAEB-t (4). The latest WHO classification has put RAEB-t under acute myeloblastic leukaemia and reclassified CMML as a variant of chronic myelocytic leukaemia (5).

Using proportions of marrow blasts, type of cytogenetic aberration and the degree of cytopenia, MDS has been stratified into 4 risk groups (the International prognostic Scoring System-IPSS), the low risk group with IPSS score of 0, the Intermediate-1 group with a score of 0.5-1.0, the second Intermediate-2 with 1.5-2.0 score and the more aggressive poor risk with an score of greater than 2.5 (6). Good-risk patients survived for 5.7 years, compared to 3.5 years for the Intermediate-1, while the Intermediate-2 and poor risk groups had the worst prognosis, surviving for only 1.2 and 0.4 years, respectively.

Until very recently, therapy of MDS was mainly supportive aimed at controlling the associated anaemia and infections. Growth factor (erythropoietin with or without G-CSF), low-dose Cytarabine have been used with variable results; even, corticosteroids have been tried in the very rare cases immune-related MDS (7). Allogeneic stem cell transplantation is the ultimate in the fit, younger patients (< 40 years) with suitable donor.

Azacitidine, a DNA methyltransferase inhibitor has recently been introduced with good results, even in individuals with the more advanced RAEB and RAEB-t. Similarly, antiangiogenesis such as thalidomide and lenalidomide have been used, with variable responses (8). This report retrospectively analysed some clinical, haematological and immunological features of Nigerians with MDS managed in our hospital over a period of 14 years (1991-2005)

Table 2. Clinical Features of Nigerians with MDS at Presentation

Symptomatic anaemia	10 (100%)
Features of infection	5 (50.0%)
Bleeding manifestation	1 (10.0%)
Skin deposit	1 (10.0%)

MATERIAL AND METHODS

The data of patients with the diagnosis of MDS managed between January 1991 and December 2005 were retrieved from the Departmental register and analysed.

The following demographic data were extracted from their case files: age, gender, blood counts including reticulocytes count at the time of diagnosis, erythrocyte sedimentation rate (ESR), clinical features and physical findings at presentation, blood transfusion requirements, bone marrow (BM) aspiration cytology results (including Perl's stained marrow to check for ringed sideroblasts), cytogenetic study findings, result of Coomb's test, the final diagnosis, management instituted, length of time of follow-up, eventual outcome, and the cause (s) of death. However, events such as infection as a result of neutropaenia, haemorrhage from thrombocytopenia, pancytopaenia from BM failure and acute leukaemia transformation were all considered as MDS-related causes of death. The Leishman-stained marrow and peripheral blood (PB) films of each patient were re-evaluated for the purpose of classification using the French-American-British (FAB) system. Diagnosis was confirmed based on the presence of

Table 3. Number of Peripheral Blood Cytopenias in Nigerians with MDS

Number of lineage	%
Trilineage	70
Bilineage	15
Single	15

clinical features of cytopenias (anaemia, infections/fever or bleeding diathesis) and the finding of cytomorphologic features of dyshaematopoiesis in the peripheral blood film and the marrow. All patients were classified into the various subtypes of MDS based on the FAB system (4).

SPSS for Windows version 11 (SPP Inc 1989-2001) was used for computing all statistical calculations, including Kaplan-Meier survival studies.

RESULTS

Patients' Clinical Characteristics

Within the study period of 14 years, a total of 688 haematological malignancies were managed, out which 13 (1.9%) were classified as MDS. However, only 10 patients whose complete data could be found were analysed, given a prevalence of 1.5 %. All were de-novo (primary) MDS. They were made up of 7 males (70.0%) and 3 females (30.0%) with a male to female ratio of about 2 to 1 (Table 1). Their mean age at presentation was 62.50 years with a range of 42 – 80 years. Nine (90.0%) of the patients were 50 years and above at the time of presentation. All of them presented with features of cytopenias (Table 2), including severe weakness (100%), fever (36.4%) and one patient each presented with gum bleeding and skin deposit (9.1%). Hepatomegaly was found in 5 (50.0%) while one patient also had splenomegaly. One patient (classified as CMML) had massive cellulitis; one was in congestive cardiac failure (classified as RAEB-t) while another had pedal oedema.

Haematological Parameters

All patients presented with severe anaemia, with a mean PCV of 15.0% (range = 9 – 21%), while 72.7% of them had platelet count of < 90,000/mm^3 with a range of 10,000 to 217,000/mm^3. The median white cell count at presentation was 4550/mm^3 (range = 900 – 28000/mm^3) and the erythrocyte sedimentation rate ranged between 12mm and 140mm in the first hour (Westergren), with a median of 124mm in the first hour.

The peripheral blood film examination showed dyshaematopoiesis in the three cell lines in 63.6%, two cell lines and one cell line in 18.2% of patients, respectively. The BM slides could be retrieved in 9 cases; 5 were found to be hypercellular while the rest 4 were found to be normocellular.

Dyshaematopoiesis was observed in all the cell lines in 7, bilineage in 1, and single lineage also in 1 (Table 3). Based on the PB and BM findings, 5 (50.0%) were classified Refractory Anaemia (RA), one (10.0%) has Refractory Anaemia with Ringed Sideroblasts (RARS), two (20%) patients presented with Refractory Anaemia with Excess of Blast; and one each presented with Refractory Anaemia with Excess of Blast in transformation (RAEB-t) and Chronic Myelomonocytic Leukaemia (CMML). Only one patient (CMML) showed positive Coombs' test and also had normal karyotypes.

Management and Outcome

All patients had blood transfusion support during the course of their disease. This ranged from 1 to 25 units with a median of 4 units. Those with evidence of sepsis and neutropenic fever also had antibiotic support. Those with the diagnosis of RAEB, RAEB-t and CMML had, in addition, cytotoxic chemotherapy (low dose Ara-C and/or Hydroxyurea). In addition, one patient who could afford Erythropoietin had the growth factor. Two patients with renal failure had haemodialysis support (Table 4).
The period of follow-up of patients ranged from 3 weeks to 288.0 weeks, with a mean of 12 weeks. Kaplan-Meier survival studies showed that all cases survived for between 2.1 to 308.4 weeks with a mean of 50.5 ± 96.1 weeks. Only one patient is still being followed up in the Clinic as the time of compiling this report, one was lost to follow up, five (50.0%) died of MDS-related causes and three (30.0%) died of renal failure (Table 5).

Table 4. Management

Blood and blood products	10 (100%)
Haematinic	10 (100%)
Erythropoietin	1 (10.0%)
Haemodialysis	2 (20.0%)
Antibiotics	5 (50.0%)
Hydroxyurea	1 (10.0%)
Ara-C	3 (30.0%)

Table 5. Cause of Death in Nigerians with MDS

MDS-related*	5 (50.0%)
Renal failure	3 (30.0%)
Unknown	1 (10.0%)

**cytopenias-related death*

DISCUSSION

The clinico-pathological features of Nigerians with myelodysplastic syndromes (MDS) were analysed in this study (Table 1). The prevalence of 1.5% of obtained from this study suggests that it is not a common malignancy in this environment when compared with others earlier reported from this same institution (9,10). The majority of our patients (90.0%) were aged 50 years or above, with none below 40 years. This distribution is in keeping with published works in other parts of the world (1,11,12).

With the exception of skin deposit found in one patient, all the other manifestations were cytopenia-related, including anaemia, bleeding and infection (Table 2). Symptomatic anaemia necessitating blood transfusion was encountered in all the patients with a mean of 6.7 (range 1- 25) units of blood given. The study however showed that the severity of the anaemia has no correlation with the number of cell lines (Table 3) involved in the dyshaematopoiesis. The use of haemopoietic growth factors (recombinant human erythropoietin [rhEpo] and granulocyte colony stimulating factors [G-CSF]) have been found to useful in the management of anaemia in MDS as it may induce long-lasting improvement of haemoglobin levels and does not increase the risk for leukaemic transformation (13). However, because of the cost, only 1 of our patients who could afford some doses of rhEpo had the growth factor, which was however not found to be effective. Studies have however shown that best results are obtained when rhEpo is combined with G-CSF(14). Although only one patient presented with marked leucopenia, and three with significant neutropenia (Tables 1 and 2), more than 50% of them presented with features of infection at presentation. Studies of patients with MDS have suggested several factors including abnormalities of cytokine elaboration(15), reduction in oxygen intermediates production and phagocytosis in both polymorphs and monocytes(16) and low amount of important granules such as myeloperoxidase, elastase, lysozymes and super oxide anion (17), as being responsible for their increased susceptibility to infection. However, infection was not found to increase mortality in our patients as reported in some cohort (18).

Cancer management in Nigeria is faced with some problems (19), ranging from inadequate laboratory facilities, non-availability of some essential drugs (cytotoxic) and supportive drugs (growth factors), scarcity of free voluntary blood donors to provide the necessary blood support, poverty of majority of our patients to fund their treatment, and the believe in the community on the aetiopathogenesis of cancers which made majority of these patient to seek traditional mode of therapy once they are aware of the diagnosis. In view of this, it is not surprising the low survival of 50.5 weeks in this cohort of patients, though better than what was obtained for another malignancy, Multiple myeloma (11 weeks), in the same environment by the same authors (9). Although only one patient was lost to follow-up, mortality was unacceptably high as 90% deaths were recorded and majority of which were cytopenia related (Table 6). This high mortality could be related to already highlighted inadequate definitive and supportive facilities in our environment. By and large, using the FAB classification, our study have also shown the longer periods of survival in RARS and RA subtypes as opposed to other subtypes (1,12,20).

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