



Extra-Haematological Comorbidities, Transfusion Dependency and Polypharmacy in Older Adults with Low Risk Myelodysplastic Syndromes



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Introduction

Myelodysplastic syndromes (MDS) are heterogeneous clonal disorders ranging from indolent conditions with a near-normal life expectancy to forms approaching acute myeloid leukemia (AML). Comorbid conditions have rarely been systematically studied among patients with myelodysplastic syndromes. Older age per se has a negative impact on survival of MDS patients, in particular of those with lower risk [7,8]. However, age indirectly affects also the survival of higher-risk patients by limiting their eligibility to intensive treatments. In addition, aging is associated with an increasingly high risk of developing comorbidity, and a high prevalence of co-morbid diseases has indeed been reported in MDS patients. Poly pharmacy and the impact of multi morbidities / comorbidities in patients with low risk MDS patients is poorly explored topic, thereby in this study we focused on medications, multi morbidities and comorbidities of 155 low risk MDS patients followed in our Haematological University Hospital.

One or more comorbidities were present at diagnosis in 24 younger patients with MDS syndromes (31 %), whereas 56 older patients with MDS (75%) presented 1 or more comorbidities ($P < 0.001$). The most frequent comorbidity was cardiac comorbidity 18% in younger patients and 25% in older patients. Congestive heart failure was the most frequent observed. Our study have shown a statistical correlation between transfusion dependency and polipatology ($P = 0.0014$). These data were also confirmed in a sub analysis of the younger group of patients. Our study have shown that comorbidity is very common among patients with myelodysplastic syndromes, potentially impacting the clinical course and out-come of MDS patients.

Myelodysplastic syndromes (MDS) are heterogeneous clonal disorders ranging from indolent conditions with a near-normal life expectancy to forms approaching acute myeloid leukemia (AML). The incidence of MD Sin the general population is 5/100,000, but

it increases to 22-45/100,000 among subjects aged >70 years and continues to increases with advancing age, thus making it the most frequent hematological disease in the elderly [1]. Comorbid conditions have rarely been systematically studied among patients with myelodysplastic syndromes. In the 20-30 years, the life expectancy of persons with low risk MDS and their health related quality of life have improved, principally due the introduction of hypo methylating agents, erythroid stimulating agents and chelating agents widely used in the treatment MDS [2-6]. Older age per se has a negative impact on survival of MDS patients, in particular of those with lower risk [7,8]. However, age indirectly affects also the survival of higher-risk patients by limiting their eligibility to intensive treatments.

In addition, aging is associated with an increasingly high risk of developing comorbidity, and a high prevalence of co-morbid diseases has indeed been reported in MDS patients. Comorbidity is defined by the presence of one or more diseases co- occurring in the same person as a consequence of a primary disease, while multi morbidity is the co- existence of two or more long-term conditions with no obvious relationship with the primary disease. Comorbidities and multi morbidity are associated with intake of multiple drugs [9-11]. Management of older adults with MDS and AML needs to be individualized, accounting for both the heterogeneity of disease biology and patient characteristics, which can influence life expectancy and treatment tolerance [12].

For those reasons the decisional algorithm for treating MDS elderly patients reasonably should include diagnosing the subtype of MDS (WHO classification) and assessing their prognosis on the basis of risk, as well as a comprehensive geriatric assessment (CGA) that allows an estimate of life expectancy and treatment tolerance, and the identification of reversible conditions that may interfere with treatment choice. By integrating chronological age with life expectancy, and the MDS classification with a geriatric

assessment (CGA), it should be possible to achieve a personalised treatment.

Poly pharmacy and the impact of multi morbidities/comorbidities in patients with low risk MDS patients is poorly explored topic, thereby in this study we focused on medications, multi morbidities and comorbidities of 155 low risk MDS patients followed in our Haematological University Hospital. The patient population was divided in two groups according to age and included 78 patients diagnosed with low risk MDS syndromes aged <65 years, and 75 MDS patients aged >65 years. All patients were regularly followed at Fondazione Ospedale Maggiore Policlinico IRCCS, Milan, Italy and University Hospital Luigi Sacco, Milan, Italy.

These investigations were approved by local Ethics committee, all patients gave written informed consent, and the procedures followed were in accordance with The Helsinki Declaration. Information's on comorbidities were extracted from detailed review of the patient's medical charts and laboratory values at diagnosis and during the course of disease. Characteristics of younger and older patients were compared using univariate analysis with the chi-squared test for categorical variables, whereas the t test was used for continuous variables. All analysis was carried out with SPSS. Thirty-eight (49%) of younger MDS low risk patients presented multilineage dysplasia as compared with fifty-two patients (57%) in the group of elderly patients ($p=0.01$).

One or more comorbidities were present at diagnosis in 24 younger patients with MDS syndromes (31%), whereas 56 older patients with MDS (75%) presented 1 or more comorbidities ($P<0.001$). The most frequent comorbidity was cardiac comorbidity 18% in younger patients and 25% in older patients. Among cardiac comorbidity congestive heart failure was the most frequent observed comorbidity among MDS patients regardless to the age group. The association between heart failure and extra hematological mortality is a well-known condition.

Several studies have found that MDS patients who have congestive heart failure or chronic obstructive pulmonary disease had significantly shorter survival than patients without those conditions. The tight association between heart failure and myelodysplasia probably recognize iron overload as pathogenetic mechanism of cardiac damage. Cardiac iron overload shortens the life expectancy of thalassemia patients, whereas its effect is unclear MDS patients. It is well known that iron overload has been associated with an increased risk of progression to leukemia and with shorter survival in non-chelated low-risk patients with MDS. Iron-mediated organ damage has been shown in multiply transfused, low-risk MDS patients with several reports highlighting that mortality rate is greater in heavily iron-overloaded MDS patients developing hepatic and cardiac dysfunction.

Regarding transfusion dependency our study have shown a statistical correlation between transfusion dependency and

polipatology ($P=0.0014$) indicating that polipatological MDS patients have and increased transfusion requiring as compared to non polipatology MDS patients. In particular poli transfusion is strictly associated with whatever heart disease ($P<0.001$), and in particular to congestive heart failure ($P<0.001$). The sub analysis of patients younger than 65 years have confirmed that transfusion requirement is higher in multilineage dysplasia, and also in this subgroup of patients politransfusion is strictly associated with polipatology, and in particular with cardiac disease.

We also study the impact of erythroid stimulating agents (ESAs) or bio similar ESAs on transfusion dependency. 102 MDS patients (66.67%) treated with ESAs achieved an erythroid response (ER), 95 patients (62%) became transfusion independent and remained free from transfusion requirement for at least 3 months, while 12 patients had reduction in transfusion requirement of at least four RBC transfusions/8 weeks compared with the pre treatment transfusion requirement. 44 patients were non-responders (29%), of whom four patients were low risk and three intermediate-I risk. 44 transfusion independent patients were low risk, and 44 were intermediate-1 risk.

Further, Hb values after treatment were significantly higher than those before treatment, within subsamples of patients classified as responders (median Hb pre treatment value=8.60g/dl; median post treatment value=11.15g/dl) and non-responders (median hemoglobin pre treatment value=7.95g/dl; median post treatment value=8.20g/dl) ($p<0.03$). Our data shown that ESAs are effective in reducing transfusion requirement, Our study show a statistical correlation between cardiac heart failure, transfusion dependency and levels of ferritin ($p=0.002$), suggesting strict relation between iron overload and cardiac failure. These data were also confirmed in a sub analysis of the younger group of patients. Our study have shown that comorbidity is very common among patients with myelodysplastic syndromes, potentially impacting the clinical course and out-come of MDS patients. WPSS risk assessment may be of clinical relevance in the management of myelodysplasia.

In patients with low or very low WPSS risk, who are not suitable for disease modifying therapies, the risk assessment according to WPSS score is essential for optimizing supportive therapy. In these patients, whose life expectancy is not different among younger and older MDS patients, the control of anemia, especially in presence of cardiac comorbidity is the main goal to prevent negative interaction between anaemia and heart disease. Regarding the type of used drug among MDS patients they generally use antihypertensive drugs, diuretics, antacids, iron products. Statistical analysis has shown a significant correlation between polypharmacy and transfusion dependency.

Polypharmacy warrants further study as a modifiable marker of vulnerability among older adults with MDS, suggesting that poly treated patients are particularly prone to the negative effects of anaemia. This has been attributed to several factors including

the high prevalence of multi morbidity (i.e. the presence of two or more chronic conditions) in older populations and the large number of evidence-based guidelines which advocate the use of more than one drug in the management of long-term conditions, Ensuring that older people receive the most appropriate combinations of medications is an ongoing challenge faced by healthcare professionals (HCPs).

Polypharmacy has been identified as the principal determinant of potentially inappropriate prescribing for older populations [4,5] and linked to negative clinical consequences, including adverse drug events (ADEs), drug interactions and medication non-adherence. The overall health status (mainly cardiovascular) greatly affects the life expectancy and quality of life of MDS patients, and so it is necessary to identify “frail” elderly patients whose many comorbidities and poor functional status may expose them to additional toxicity in comparison with their younger counterparts. The usual way of identifying frailty in clinical practice is to make a multidimensional comprehensive geriatric assessment (CGA). This two-step approach is still only a hypothesis that needs to be validated in specific prospective studies due to the evidence that frailty should be considered in prognostic models and as potential target for therapeutic intervention in optimizing clinical outcomes in older MDS patients.

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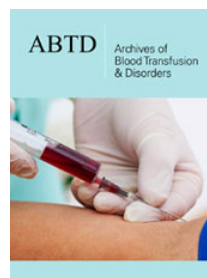
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