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Transfusion dependence development and disease evolution in patients with MDS and del(5q) and without transfusion needs at diagnosis

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ABSTRACT

Patients with isolated del(5q) and MDS are considered to have good prognosis as compared to other MDS subtypes. Most patients suffered of anemia and 50% of them required transfusions at diagnosis. It is known that for patients with MDS and del(5q) in transfusion dependence(TD), Lenalidomide is the first choice treatment. However, there are no data regarding natural evolution of anemia in patients diagnosed in MDS and del(5q) without TD, factors that may impact on the development of TD or disease outcome. In the present study we have performed a retrospective multicenter analysis on 83 patients with low-int 1 MDS and del(5q) without TD. During the study 61 patients became TD at a median of 1.7 years and only the Hb level 9 g/dL was associated with poorer TFS ($p = 0.007$) in the multivariate analysis. Among these 61 TD patients, 49 received treatment (19 Lenalidomide). Median follow up was 48 months, estimated OS at 2 and 5 year was 92% and 50% respectively. In the multivariate analysis for OS, platelets <100,000 mm^{-3} and Lenalidomide treatment retained the statistical significant impact. LFS at 2 and 5 years was 86% and 73% respectively, and median time to sAML was 8.16 years (CI 95%: 6.05–10.27). In the multivariate analysis only thrombocytopenia retained statistical significance. In summary, this retrospective study show that level of Hb is an important parameter in order to determine the time until TD, it should be also stressed the importance of an early treatment in order to prevent TD development and shorter survival.

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1. Introduction

Myelodysplastic syndromes (MDSs) are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by cytological dysplasia, ineffective hematopoiesis leading to peripheral blood cytopenias and high incidence of progression to Acute Myeloid Leukemia (AML) [1]. Several factors including the number and deepness of cytopenias, percentage of bone marrow (BM) blast cells, cytogenetic abnormalities combined in a classic International Prognostic System (IPSS), [2] recently revised (IPPS-R), distinguishes between various MDS subgroups with significantly different risk of progression to AML and overall survival [3]. The 5q− Syndrome was first described by Van den Berghe et al. in 1974 [4]; the well-known clinical features of the 5q− syndrome described in the first report were macrocytosis, anemia, a normal or high platelet count, and hypolobulated megakaryocytes in the bone marrow. Patients with 5q− syndrome and with MDS with this cytogenetic signature isolated del(5q) are considered to have good prognosis compared with other MDS subtypes, with lower probability to develop a secondary Acute Myeloid Leukemia (sAML) and an expected survival longer than 30 months [5–9]. Five q deletion is the only cytogenetically defined MDS category recognized by the World Health Organization (WHO) in 2001 and 2008 and is defined as a MDS characterized by the presence of an isolated deletion on the long arm of chromosome 5 and less than 5% blast cells in BM [8]. However, it has been referred that patients with isolated del(5q) have a shorter life expectancy when compared with healthy age and gender matched cohorts [9,10]. Regarding MDS and del(5q), Patnaik et al. [6] reported that age, transfusion needs at diagnosis and dysgranulopoiesis were independent predictors of shortened survival. Similar results have been recently reported by the German group regarding the importance of transfusion dependency (TD) on survival at diagnosis among these low risk MDS patients. However, as far as we know, the clinical or biological factors that could favor the development of TD in these patients have not been previously reported, as well as the disease evolution of this subgroup of patients without transfusion needs at diagnosis. Recent published analysis showed that 60% of patients whit this low risk MDS and del(5q) are diagnosed when TD has not been developed [11]. In the present study we have performed a retrospective multicenter analysis on patients with low-int 1 MDS and 5q deletion without transfusion dependency in order to answer these questions.

2. Subject and methods

2.1. Subjects

Data from eighty-four low risk MDS patients (according to IPSS and IPSS-R criteria) diagnosed between 1980 and 2012 were retrospectively analyzed. All of them were included in the Registry of the Spanish Group of Myelodysplastic Syndromes (GESMD) as patients with MDS and del(5q) and without TD at diagnosis.

2.2. Statistical methods

Data were summarized using median, range, and percentage. The event of TD was defined as the development of TD according to the IWG criteria (2006) [12] and/or the beginning of a treatment, which could potentially modify disease course (as Lenalidomide or erythroid stimulating agents). Patients' follow up was updated on March 30, 2013, and all follow up data were censored at that point. Transfusion Free Survival was measured from diagnosis to event of TD (or to last follow up if there was no TD). Overall survival was considered from diagnosis to last follow up or death from any cause and evolution to AML was measured from diagnosis to the date of AML (presence of more than 19% of blasts in bone marrow or peripheral blood). Transfusion Free Survival, overall survival and AML free survival were analyzed using the Kaplan–Meier method. The Log-rank test was used to compare variables and their impact on survival for univariante analysis. Multivariable analysis was performed using Cox's [13] proportional hazards regression model. Incidence of progression to AML was analyzed with cumulative incidence competing risk method [14]. For comparison of Kaplan–Meier curves the long rank test was used, *p*-values less than 0.05 denoting statistical significance [15]. Statistical analysis was performed using SPSS 15.0 and NCSS V.8, 2010 for cumulative incidence analyzed.

Table 1
Hematological and cytogenetic characteristics of the study population.

Characteristics	*N* = 84	(%)
Age (years): median (range)	79 (43–97)	
Gender: *M*/*F*	19/65	23/77
FAB classification		
RA/RAS/RAEB	43/36/5	51/43/6
WHO 2001 classification		
RA, RAS, RCMD, RCMD-RS/5q− Syndrome/RAEB-1	13/66/5	15/79/6
Cytogenetics		
Del(5q) single	74	90
Del(5q)+ one additional aberration	8	10
Not known	2	
IPSS		
Low/intermediate I	63/18	78/22
Not known	3	
IPPS-R		
Very low/low/intermediate	37/41/3	46/50/4
Not known	3	
Type of MDS		
Primary ("de novo")/secondary	82/2	98/2
	Median	Range
Cytopenias		
Hemoglobin (g/dL)	10.4	7.4/13.9
Platelets ($\times 10^3/\mu L$)	259	58/1.000
ANC ($\times 10^3/\mu L$)	2.09	4.0/9.3

Abbreviations: *M*, male; *F*, female; RA, refractory anemia; RAS, refractory anemia with ring sideroblasts; RAEB, refractory anemia with excess blasts; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia and ring sideroblasts; ANC, absolute neutrophil count.

3. Results

The most important clinical and hematologic features of the 84 patients are summarized in Table 1. Ninety five percent of them had less than 5% blasts in bone marrow, with a mean of 2% of blast (range 0–9%). The great majority (90%) of patients had a single 5q deletion and according to IPSS-R, 99% were in low and very low risk. All patients at diagnosis were RBC transfusion free.

During the study 61 (73%) became transfusion dependent at a median of 1.7 years from diagnosis (CI 95%: 1.2–2.8 years) (Fig. 1A). Several factors with potential impact on TD were studied by univariante analysis (Table 2) but only the Hb level below 9 g/dL was associated with poorer Transfusion Free Survival (TFS) ($p = 0.008$) (Fig. 1B) and this impact was retained when multivariate analysis was done [HR: 3490 (CI 1274–9560) (Table 3)].

Among the 61 TD patients 49 received treatments other than RBC transfusions: 19 Lenalidomide, 24 ESA and 6 other treatments. Fifteen patients were treated previous to TD development (7 with Lenalidomide and 8 with ESA). No differences in clinical characteristics were observed between both subgroups of patients.

Median follow up of the series was 48 months, 46% of patients are still alive at the time of the last follow up, 43% have died and 31% have developed sAML. Estimated OS at 2 and 5 year was 92% and 50% (Fig. 2A), respectively. Regarding univariate analysis (Table 2),