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Hematologic response predictor factors in adults with myelodysplastic syndromes (SMD) treated with cyclosporin A (CSA)

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Abstract

Background: *Myelodysplastic syndromes (MDS) are clonal diseases of hematopoietic cells. The International Prognostic Scoring System (IPSS) is the risk scale most employed in MDS. Cyclosporin A (CsA) has been used in the treatment of cytopenias in MDS.* **Objective:** *To evaluate hematologic response and identify response predictive factors in adults with MDS treated with CsA.* **Material and methods:** *Patients with MDS diagnosed according World Health Organization (WHO) classification were recruited from January 1997 to June 2012. All patients were classified with IPSS, IPSS revised (IPSS-R), WHO Prognostic Scoring System (WPSS), and WPSS revised (WPSS-R) risk scales. Cyclosporin A was administered orally at a dose of 5 mg/kg/day. Hematologic response was evaluated following the International Working Group for MDS (2006 version) criteria.* **Results:** *Inclusion criteria were met by 32 patients. Median age was 56.5 years, with a median follow-up of 3.1 years. Hematologic response was 56.2% and erythrocyte independence transfusion was found in 42.9% of patients. Age, hemoglobin level, and WPSS at diagnosis were independent predictive factors for CsA response. Survival was longer in responder than in nonresponder CsA patients (p = 0.06).* **Conclusions:** *Cyclosporin A induced hematologic response in > 50% of patients with MDS aged < 57 years, with Hb < 8 g/dl and low WPSS at diagnosis.* (Gac Med Mex. 2015;151:322-9)
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Introduction

Myelodysplastic syndromes (MDS) are clonal diseases arising from hematopoietic stem cells, characterized by inefficacious hematopoiesis, variable degrees of cytopenia and an increased risk of transformation into acute myeloid leukemia (AML)[1]. The incidence of MDS increases with aging[2].

There are several risk scales, but up to this moment, the most widely accepted and considered the standard in patients with primary MDS is the IPSS[3]. Its most recent update, IPSS-R, stratifies more broadly the degree of cytopenias and the proportion of blasts, and incorporates new cytogenetic abnormalities[4]. Another prognostic scale is WPSS, the importance of which lies in that it is the only one that considers transfusion-dependence, in addition to including the WHO classification for MDS and the karyotype according to the IPSS[5]. In the updated version, WPSS-R, transfusional requirement has been substituted by Hb values[6].

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Several mechanisms involved have been identified in the pathophysiology of MDS[7,8]. Immune imbalance promotes hematopoietic stem cells apoptosis[9,10]. Apparently, the expansion of cytotoxic T-cells is the main inhibitor of hematopoiesis[11]. T-cell normalization after immunosuppressive therapy (IST) suggests a causal relationship between immune alterations and the development of cytopenias[12].

The main clinical challenge in patients with MDS is morbidity caused by cytopenias[13]. Anemia is the cytopenia with the highest morbidity and mortality rates[6], and has also been shown to be an additional adverse prognostic factor of survival in the IPSS scale[14]. According to the National Comprehensive Cancer Network (NCCN) clinical guidelines for the management of MDS, patients with low-risk MSD are those who benefit the most from IST[15].

The only IST approved by the U.S. Food and Drug Administration (FDA) for the treatment of MDS is anti-thymocyte gamma-globulin (ATG)[1]. The IST (ATG or cyclosporine A [CsA]) offering the best rate of hematologic response has not yet been identified, and published factors predictive of response have not been reproducible[12]. In Mexico, availability of CsA is constant and its price is significantly lower than that of ATG.

CsA inhibits cytotoxic T-lymphocytes and its clinical use in MDS started in 1991[16-18]. Rates of hematologic response range from 51 to 82%[19-22], with a median time to response of 7-10 weeks[19,23], with packed red blood cells (PRBC) transfusion independence achieved in 47-100% of cases[19,21]. Response to CsA appears to confer a favorable impact on survival in MDS[24].

There is variability in predictive factors of response; the most consistent are: normal cytogenetics, haplotype expression (DRB1*1501)[20], younger age, chromosome 8 trisomy, low and intermediate-1 IPSS[25], presence of paroxysmal nocturnal hemoglobinuria cells and disease duration < 4 months[26]. Bone marrow (BM) hypocellularity has been considered to be another response predictive factor[16,19,27], but this has not been reproduced in other studies[10,20,22-24].

In MDS, therapeutic effectiveness is measured by the capacity to reduce transfusional requirements and to delay transformation into AML. Owing to the iron elimination physiological limitation, patients with anemia and RBPC chronic requirement develop iron overload[28], which has a deletereous impact on survival[29].

The purpose of this study is to assess hematologic response and survival in patients with MDS treated with CsA, and to identify predictive factors associated with hematologic response.

Material and methods

Retrospective, non-randomized, descriptive study with patients recruited between January 1997 and June 2012. The protocol was approved by the Ethics Committee of our institution. Patients ≥ 17 years of age, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, with cytogenetics at diagnosis and who met the criteria for primary MDS established by the WHO[30] were included. Patients with liver and kidney failure, any active malignancy or uncontrolled arterial hypertension were excluded, as well as pregnant women. Patients developing kidney or liver failure while on treatment or those who decided to leave the study were censored.

Patients classified according to the French-American-British (FAB) group criteria were reclassified according to the WHO criteria for MDS[30]. All patients were assessed using the IPSS[3], IPSS-R[4], WPSS[5] and WPSS-R[6] risk scales at diagnosis. Serum ferritin was also quantified at diagnosis.

All patients received an initial dose of CsA of 5 mg/kg/day, divided in two takes 1 h before the meals. A complete blood cytometry with reticulocytes, serum creatinine and CsA were requested every visit. The CsA dose was titrated aiming to maintain serum concentration at 150-300 ng/ml. In the absence of adverse events, minimal duration of treatment was 6 months.

To assess the response to CsA, the International Working Group in Myelodysplasia (IWG-MDS)[31] hematological improvement criteria were used. Tranfusion dependence was defined as the need of at least one PRBC unit every 4 weeks in a 4-month period[5]. The patients received PRBC with Hb ≤ 8 g/dl or in presence of anemic syndrome[32]. Based on serum ferritin values, iron overload was regarded as a ≥ 200 ng/ml concentration in females and ≥ 300 ng/ml in males, without any inflammatory state being present and with a transferrin saturation index ≥ 45% for females and ≥ 55% for males[33].

Patients < 40 years, with ≥ 1 PRBC unit transfusional weekly requirement and with failure to CsA therapy were considered for hematopoietic stem cell allotransplantation (Allo-HSCT)[30,34].

Quantitative variables were compared with the Mann-Whitney U-test or Fisher's exact test, and qualitative variables, with the chi-square test. Binary logistic regression was used for the multivariate analysis. Survival was calculated from the day of diagnosis until the last day of follow-up or death by any cause using the Kaplan-Meier test. Age cutoff as a predictive factor of

Table 1. Transfusion dependence and clinical and laboratory characteristics at diagnosis

Age, years	
– median (range)	56.5 (17-81)
Gender	
– n (female/male)	17/15
Neutrophils x 10^3/µl	
– median (range)	1.19 (0.2-2.9)
Hb, g/dl	
– median (range)	8.8 (4.7-17.8)
Platelets x 10^3/µl	
– median (range)	53 (7-308
BM cellularity	
– Hypocellular	11/32 (34.4%)
– Normocellular	1/32 (3%)
– Hypercellular	15/32 (46.8%)
– Non-evaluable	5/32 (15.7%)
Transfusional dependence	25/32 (75.8%)
RBC	14/25 (56%)
Platelets	8/25 (32%)
RBC and platelets	3/25 (12%)

response to CsA was obtained by means of receiver operating characteristic (ROC) curve analysis. The SPSS 15.0 software was used.

Results

Thirty-two patients met the inclusion criteria. Median age was 56.5 years; 37.5% were > 60 years and the male:female ratio was 0.8:1. With regard to serious cytopenias, 12 patients (37.5%) had Hb ≤ 8 g/dl; 2 (6.3%), total neutrophils (TN) ≤ 0.5 x 10^3/l, and 6 (18.8%), platelet counts < 20 x 10^3/µl. Hypocellular MDS was present in 34.4% of patients and 75.8% of them were transfusion dependent, mainly of PRBC (Table 1). Nineteen subjects (69.4%) had normal cytogenetics; only one patient showed an isolated chromosome 5q deletion. Twenty-nine subjects (91.6%) had MDS of the refractory cytopenia with multilineage dysplasia (RCMD)-type (Table 2).

Eighteen patients (56.2%) showed response to CsA. Only by stratification of the Hb values by IPSS-R and low WPSS a statistically significant difference ($p < 0.05$) was reached between CsA responders and non-responders (Table 2). The remaning analyzed variables, such as age, TN and platelet count, karyotype, percentage of blasts and BM cellularity, and classification according to WHO, IPSS, IPSS-R and WPSS-R, did not reach statistically significant differences. In the multivariate analysis, independent response-predictive variables that reached statistical significance were: age ≤ 57 years, Hb ≤ 8 g/dl and low score in the WPSS scale (Table 3).

Twenty-nine patients (90.6%) received CsA as monotherapy. One patient received CsA with erythropoietin (EPO) and filgrastim for 4 weeks, but he experienced gastrointestinal intolerance that did not improve. The second patient received CsA with prednisone and experienced a creatinine elevation to 2 mg/dl 4 weeks after therapy was started. None of both these patients showed response to CsA. The third patient received CsA with mesterolone and achieved a rapid platelet response, but developed hypertransaminasemia after 4 months. All three patients with combined treatment had to discontinue their regimen due to adverse events.

Of the 18 patients who responded to the treatment with CsA, 8 (44.4%) showed erythroid response, 5 (27.8%), erythroid and platelet response, 3 (16.7%), platelet and neutrophil response, 1 (5.5%), platelet response and 1 (5.5%), neutrophil response. Transfusional independence was attained in 6 out of 8 PRBC-dependent patients (42.9%) and in 1 of 8 platelet-dependent patients (12.5%). The rest of patients experienced a reduction in the frequency of their transfusional requirements. Median time to response was 7 weeks, being most evident in the erythroid line. Minimum treatment duration was 6 months, and maximum, 4 years.

Four patients (12.5%) who failed to respond to CsA underwent Allo-HSCT due to high transfusional requirements associated with serious thrombocytopenia with hemorrhage. Median exposition time to CsA prior to the Allo-HSCT was 8.5 months, ranging from 4 to 14 months. Median age of these patients was 27.5 years. All of them had low-risk MDS of the RCMD-type and hypocellular BM. Only one patient developed grade II host vs. graft disease in the liver, without further complications. Currently, all patients are still alive and in complete remission.

Ferritin was quantified at diagnosis in 26 patients and iron overload was found in 61.5% of cases (7 males and 9 females). Ferritin value at diagnosis did not have a statistically significant impact on the response rate to IST.

One patient had an abnormality in liver function tests and another had an elevation of serum creatinine > 2 mg/dl, which did not improve with CsA interruption and, therefore, the drug was permanently discontinued. Four patients had gastrointestinal alterations

Table 2. Variables associated with response to the treatment with CsA

Variables	Total (n = 32)	Responders (n = 18)	Non-responders (n = 14)	p
Age				
– ≤ 60 years	20 (62.5%)	9/18 (50%)	11/14 (78.5%)	0.09
– > 60 years	12 (37.5%)	9/18 (50%)	3/14 (21.5%)	
Neutrophils x 10^3/µl				
– IPSS-R				
– ≥ 800	27 (84.3%)	16/18 (88.8%)	11/14 (78.5%)	0.37
– < 800	5 (15.7%)	2/18 (11.2%)	3/14 (21.5%)	
– IPSS				
– ≥ 1,800	7 (21.9%)	5/18 (27.7%)	2/14 (14.2%)	0.31
– < 1,800	25 (78.1%)	13/18 (72.2%)	12/14 (85.7%)	
Hb, g/dl				
– IPSS-R				
• ≥ 10	10 (31.2%)	5/18 (27.7%)	5/14 (43%)	0.04
• 8 - < 10	10 (31.2%)	3/18 (16.6%)	7/14 (43%)	
• < 8	12 (37.5%)	10/18 (55.7%)	2/14 (14%)	
– IPSS				
• ≥ 10	10 (31.2%)	5/18 (27.7%)	5/14 (43%)	0.45
• < 10	22 (68.7%)	13/18 (72.2%)	9/14 (64.2%)	
– WPSS-R				
• ≥ 8 (F) or ≥ 9 (M)	17 (53.1%)	7/18 (38.9%)	10/14 (71.4%)	0.11
• < 9 (M)	7 (21.9%)	5/18 (27.7%)	2/14 (14.3%)	
• < 8 (F)	8 (25%)	6/18 (33.3%)	2/14 (14.3%)	
Platelets x 10^3/µl				
– IPSS-R				
• ≥ 100	8 (25%)	6/18 (33.3%)	2/14 (14.3%)	0.20
• 50 - < 100	9 (28%)	6/18 (33.3%)	3/14 (21.5%)	
• < 50	15 (46%)	6/18 (33.3%)	9/14 (64.2%)	
– IPSS				
• ≥ 100	8 (25%)	6/18 (33.3%)	2/14 (14.3%)	0.20
• < 100	24 (75%)	12/18 (66.6%)	12/14 (85.7%)	
Karyotype				
– IPSS-R				
– Low	20 (62.5%)	13/18 (72%)	7/14 (50%)	0.07
– Intermediate	8 (25%)	4/18 (22%)	4/14 (28.5%)	
– Poor	1 (3%)	1/18 (5.5%)	–	
– Very poor	3 (9.3%)	–	3/14 (21.5%)	
IPSS				
– Low	20 (62.5%)	13/18 (72.2%)	7/14 (50%)	0.43
– Intermediate	7 (21.9%)	3/18 (16.6%)	4/14 (28.6%)	
– Poor	5 (15.6%)	2/18 (11.1%)	3/14 (21.4%)	
BM blasts (%)				
– IPSS-R				
• ≤ 2	31 (96.9%)	18/18 (100%)	13/14 (92.8%)	
• > 2 to < 5	–	–	–	0.43
• ≥ 5	1 (3.1%)	–	1/14 (7.1%)	
– IPSS				
• < 5	31 (96.9%)	18/18 (100%)	13/14 (92.8%)	
• 5-10	1 (3.1%)	–	1/14 (7.1%)	0.43
• 11-20	–	–	–	
BM cellularity				
– Hypocellular	11 (34%)	6/18 (33%)	5/14 (35.7%)	0.59
– Non-hypocellular	21 (66%)	12/18 (67%)	9/14 (64.3%)	

(Continue)

Table 2. Variables associated with response to the treatment with CsA *(continued)*

Variables	Total (n = 32)	Responders (n = 18)	Non-responders (n = 14)	p
WHO				
– 5q-	1 (3.1%)	1/18 (5.5%)	–	0.07
– RAEB-1	2 (6.3%)	–	2/14 (14.3%)	
– RCMD	29 (91.6%)	17/18 (94.4%)	12/14 (85.7%)	
IPSS				
– Low	5 (16%)	4/18 (22%)	1/14 (7%)	0.10
– Intermediate-1	23 (72%)	13/18 (72%)	10/14 (71.4%)	
– Intermediate-2	14 (44%)	1/18 (6%)	30/14 (21.5%)	
– High	–	–	–	
IPSS-R				
– Very low	2 (6.3%)	2/18 (11.11%)	–	0.06
– Low	15 (46.8%)	9/18 (50%)	6/14 (42.8%)	
– Intermediate	11 (34.3%)	6/18 (33.4%)	5/14 (35.7%)	
– High	1 (3.3%)	1/18 (5.5%)	–	
– Very high	3 (9.3%)	–	3/14 (21.4%)	
WPSS				
– Very low	1 (3.12%)	1/18 (5.5%)	–	0.01
– Low	9 (28.12%)	9/18 (50%)	–	
– Intermediate	12 (37.5%)	5/18 (28%)	7/14 (50%)	
– High	7 (21.87%)	1/18 (5.5%)	6/14 (42.8%)	
– Very high	3 (9.3%)	2/18 (11%)	1/14 (7.1%)	
WPSS-R				
– Very low	–	–	–	0.69
– Low	11 (34.4%)	6/18 (33.3%)	5/14 (35.7%)	
– Intermediate	12 (37.5%)	8/18 (44.4%)	4/14 (28.6%)	
– High	9 (28.1%)	4/18 (22.2%)	5/14 (35.7%)	
– Very high	–	–	–	

F: females; M: males; 5q-: isolated chromosome 5 deletion syndrome.

Table 3. Multivariate analysis of variables associated with response to CsA in patients with MDS

Variable	C. β	P (Wald)	OR	95% CI
Age (≤ 57 years)	3.38	0.015	29.5	1.9-457
Hb (≤ 8 g/dl)	1.93	0.022	6.9	1.3-36
Intermediate and high WPSS	–1.75	0.017	0.173	0.04-0.7

OR: odds ratio; CI: confidence interval.

with CsA that improved with temporary interruption of the drug, and one patient refused reinitiation of the drug. Six patients discontinued CsA, 3 due to economic issues and 3 (9.4%) due to previously-described adverse events.

Median follow-up in all 32 patients was 38 months, ranging from 2 to 185 months. Nine patients (28%) were lost to follow-up. Survival was 62.5%, with a median duration of 83 months and a range of 2 to 135 months. None of the analyzed variables (age, Hb, TN and platelet counts, karyotype, precentage of blasts and BM cellularity, and classification according to the WHO, IPSS, IPSS-R and WPSS-R) had a statistical impact on survival. Survival in subjects with some type of response to CsA was longer than in those not responding to CsA, with medians of 107 (range: 88-126) and 73 months (22-124), respectively, but this difference did not reach statistical significance (Fig. 1).

The mortality rate was 9.5% (n = 3); causes of death included cerebral hemorrhage (n = 2) and septic

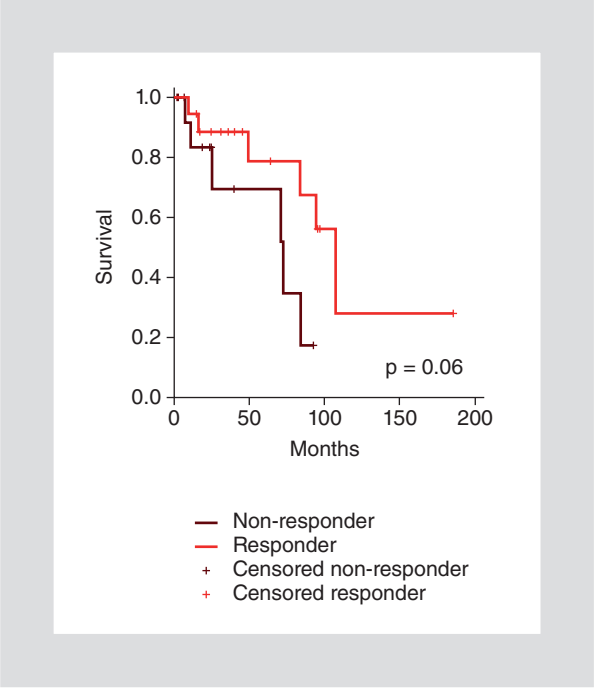

Figure 1. *Survival according to CsA-mediated hematologic response.*

shock (n = 1). One patient with refractory anemia with excess of blasts 1 (RAEB-1) progressed to AML (3%) and died due to cerebral hemorrhage associated with refractoriness to platelet transfusion. Other patient with RCMD progressed to RAEB-1, but was lost to follow-up.

Discussion

Improvement of cytopenias is the most important challenge in the treatment of patients with MDS. One of the mechanisms involved in pathogenesis are immune alterations[9-11,16,22,25]. The subgroup of MDS patients that benefits the most from IST has been shown to be those with younger age and low risk[15,35].

The main risk factor for the development of MDS is age. Age < 60 years is a favorable predictive factor of survival[3-5,30]. In our population, 62.5% were younger than 60 years and the age cutoff with favorable impact on the rate of response to CsA was 57 years. This is consistent with data published on other series, where the rate of response to IST is higher in patients < 60 years[25,36,37]. In our population, younger than those reported in other series[1,3,4,6,35-38], age > 57 years or > 60 years did not impact on survival. Maybe younger age is associated with higher amounts of hematopoietic stem cells and, therefore, with better IST-associated recovery[36].

In our series, there were more males than females, unlike figures found in most studies of MDS[1,3,4,6,13,19,20,38]. The frequency of cytopenias was similar to that reported in the literature[3,4,30]: the most common were anemia and thrombocytopenia, and the less frequent, serious neutropenia. In the present study, a 3-fold higher frequency of hypoplastic MDS was found, which suggests higher prevalence of MDS in younger people[39]. There was also a higher frequency of MDS of the RCMD type, as other authors have reported[5,30].

Independent variables predictive of response to CsA in the multivariate analysis were: younger age, stratification of Hb values by IPSS-R and low WPSS. The cytopenia with the highest morbidity continued to be anemia, which explains that the main transfusional dependence was on PRBC, similar to observations in previous studies[4,6,14]. One study reported that for each 1 g/dl decrease in Hb, there was a 1.9-fold higher probability of responding to CsA[40]. Although IPSS has been shown to be a highly reproducible scale, its most important limitation is that it doesn't distinguish the magnitude of cytopenias, which over time has shown to be a marker of clinical evolution. Therefore, the IPSS does not allow for the prognosis of patients with mild cytopenias to be predicted. This explains why the Hb value, better stratified by the IPSS-R, happens to be the variable associated with the response to CsA, rather than the Hb value by IPSS.

The WPSS prognostic scale has been shown to be useful especially in those subjects with low-risk MDS, and it is the only scale that considers transfusional dependence as in independent indicator of poor prognosis[5]. Several authors consider that a history of transfusion use could involve a subjective decision and, therefore, they substituted this variable with a numeric Hb value according to sex. This change was included in the WPSS-R version[6]. They found that a Hb value < 9 g/dl in males and < 8 g/dl in females was able to identify the same risk groups than the WPSS, but with higher statistical impact on survival, since these are risk factors for cardiovascular mortality. Although in Hb by sex it was equivalent to transfusional requirements, this was not reproduced and, therefore, we concluded in our series that Hb value by sex did not confer a response predictive value, but the number of PRBC units did.

Studies focused on analyzing factors predictive of response have shown variability in their results, due to heterogeneity and numbers of included patients[41]. There is the concept that BM hypocellularity is the most important predictor of response to IST[25,36,40]. In our

study, this variable was also not associated with better response to IST. In recent years, genetical markers have provided valuable prognostic information in MDS, even for the response to IST. The presence of the haplotype (HLA-DR15) has been shown to be highly predictive of response to the treatment with ATG or ATG in combination with CsA[42]. Other, more recent analysis, found pre-treatment HLA-DR15 expression, younger age and short duration of transfusional requirements to be independent predictors of response to IST. The combination of these 3 variables was sufficient to define the probability of response to IST[36]. This highly accurate predictive value leads to wonder if genetic differences mark the immune response, rather than the immunosuppressing drug, although this wouldn't explain the need for immunosuppression to be started early in order to achieve a successful response over the course of anemia. It should be noted that no patient in our study was tested for HLA-DR15. Other genetical alteration that has been associated with response to ITS is chromosome 8 trisomy[25], but such alteration was not found in our population.

In the present study, we analyzed variables not considered in previous studies to assess the response to CsA, such as MDS classification according to the WHO and the IPSS-R and WPSS-R scales. We found that, in spite of modifications made, either in the magnitude of cytopenias or identification of new cytogenetic alterations, there were no changes in the rate of response to CsA.

According to the IPSS, 88% of our population had low-risk MDS. When patients were reclassified from IPSS to IPSS-R, 35% (n = 11) of the low-risk patients were moved up to intermediate risk, 75% (n = 4) of those at high risk were moved to very high risk (n = 3), and no subject at very high risk was moved down to intermediate risk. This improved group stratification by IPSS-R is not repeated when reclassifying by WPSS-R, since very high and very low groups are eliminated, and most patients are concentrated in only three groups, unlike distribution observed in the original study[6].

Time to response, response rate, transfusional independence and predominance of erythroid response with CsA were similar to those reported by othe authors[16,20,21,27,40]. Our response rate in the platelet and neutrophil lines was lower than that reported[19]. Administration of combined regimens with cytokines and other immunosuppressants doesn't seem to improve the response rate compared with CsA alone, as we found in our study[40]. In our work, the few patients on combined therapy had to discontinue this treatment due to adverse events, and they also failed to achieve response. Treatment with CsA was well tolerated, since no patients experienced serious adverse events.

Transfusion dependence can be considered an independent indicator of disease seriousness[5]. In our work, iron overload at diagnosis did not affect the rate of response to IST or survival. CsA early start, with the subsequent reduction of transfusional requirements, might explain this favorable evolution.

No significant difference in survival was found in our study between the response groups. It appears that IST is not the best treatment option in patients with MDS, since an impact on overall survival has neither been seen in other studies. However, in some patients with MDS, the use of CsA may be useful as bridging therapy prior to allo-HSCT. The study by Passweg et al.[38] compared the ATG/CsA combination with the best supportive therapy, and there was a statistically significant difference in response rate (31 vs. 9%), but there was no impact on overall survival (49 vs. 63%). Broliden et al.[35] assessed the ATG/CsA combination in the management of low-risk MDS patients without finding a difference in survival between responders (median survival not reached) and non-responders (median survival of 30 months).

There is only one study that has demonstrated a survival benefit in CsA-responders[24]. The number of patients included, the inclusion and exclusion criteria and the rate of response to CsA were similar to those in our work. Of note, its median age was even lower than ours (46 vs. 56.5 years) and 87% of the subjects had Hb < 8 g/dl. In this study, only one patient out of 20 responders died, whereas 7 out of 12 non-responders did, with no losses to follow-up. In our population, there were 3 deaths, confined to the group of non-responders, with 9 patients lost to follow-up and, therefore, we had a lower mortality rate (20 vs. 58%), with longer follow-up time (38 vs. 14 months), with our results probably reflecting more accurately the impact of the response to IST on long-term survival.

In conclusion, our population with MDS is comprised mainly by low-risk young patients, which suggests the probability that maybe risk factors other than age are playing an important role in the pathophysiology of this group of diseases. Being younger (< 57 years), Hb < 8 g/dl and low WPSS are the factors that in our series predict higher probability of response to ITS. The development of a prognostic scale with these three parameters, obtained since the initial assessment of MDS patients, might just help to early identify potential CsA-responders.

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