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ORIGINAL ARTICLE

Low IPSS score and bone marrow hypocellularity in MDS patients predict hematological responses to antithymocyte globulin

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Immunosuppressive therapy has been shown to induce sustained hematological responses in a subset of patients with myelodysplastic syndromes (MDS). In particular, antithymocyte globulin (ATG), a polyclonal immunoglobulin induces hematological responses in up to 60% of MDS patients. We report herein on the results of a retrospective multicenter study on the use of ATG in the treatment of 96 patients with MDS. Patients were evaluated for duration of response to ATG, as well as survival after administration of ATG. The median age of the cohort was 54.7 years (range: 19–75 years), with a median follow-up of 33.8 months (range: 0.8–133 months). A total of 40 patients (42%) achieved a hematological response, of which 30 patients (75%) had a durable hematological response lasting a median duration of 31.5 months (range: 6–92 months). On multivariate analysis, both low International Prognostic Scoring System (IPSS) and bone marrow (BM) hypocellularity were independent predictive factors for improved response to ATG (IPSS Int-2/high: odds ratio (OR) 0.08, $P=0.018$ and BM normo/hypercellularity: OR 0.49, $P=0.012$). In addition, IPSS was the sole predictor of overall survival, with Int-2/high risk patients having a significantly poorer survival outcome (OR 0.08, $P<0.01$). In conclusion, this study identifies BM hypocellularity and a low IPSS as important factors predicting response to ATG.

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Keywords: antithymocyte globulin; myelodysplastic syndromes; immunosuppressive therapy

Introduction

The myelodysplastic syndromes (MDS) are a heterogenous group of clonal disorders characterized by dysplasia, ineffective hematopoiesis and cytopenias, with progressive evolution to acute leukemia in 25% of cases.[1] There is increasing evidence to suggest that immunological dysregulation plays an important role contributing to ineffective hematopoiesis and progressive cytopenias. There is a recognized association between autoimmune phenomenon, such as connective tissue disorders and systemic vasculitic disorders with the presence of MDS.[2–5] Clinical and laboratory findings have suggested an autoimmune mediated component to the pancytopenia and bone marrow (BM) failure seen in MDS[6–9] with observations of increased oligoclonal expansion of T cells and possible cytotoxic T-cell-mediated suppression of Hematopoietic progenitors.[10–12]

Immunosuppressive therapy has been shown to induce sustained hematological responses in a subset of patients with MDS. In particular, antithymocyte globulin (ATG), a polyclonal immunoglobulin, induces hematological responses in up to 60% of MDS patients.[7,13–17] ATG is known to react with a number of cell types that include T cells and natural killer cells, as well as molecules modulating the immune response, such as integrins and certain chemokine receptors.[18] While its precise mechanism of action remains unclear, it is believed to involve the amelioration of lymphocyte-mediated suppression of the BM environment.[11] Herein, we report on the results of a retrospective multicenter study into the use of ATG in the treatment of MDS. A total of 96 patients were treated with ATG and we review the impact of pretreatment variables on the hematological response to ATG.

Materials and methods

Patient demographics

A total of 96 patients from centers in UK ($n=65$), Germany ($n=13$) and Italy ($n=18$) were treated with ATG (Lymphoglobuline, SangStat). All patients had an established diagnosis of MDS, with the subtype of MDS as defined by the French–American–British (FAB) criteria.[19] Data were collected from the various centers using regular data forms, which were reviewed and complied by ZL. The cohort includes 30 patients previously reported in a UK-based pilot study on the use of ATG for patients with 'low-risk' MDS[7] with extended follow-up, as well as 66 patients treated off study as the best available treatment for their disease. Blood and BM morphology in all patients were reviewed critically, and BM hypocellularity was defined by $<20\%$ cellularity. Cytogenetics studies were performed at initial presentation, and cytogenetic results were accepted only in patients with at least 20 analyzable metaphases. Paroxysmal noctural hemoglobinuria (PNH) clones were detected by the analysis of glycophosphatidylinositol-anchored membrane proteins on granulocytes performed by flow cytometry, using monoclonal antibody specific to CD55, CD59 and CD66b. In addition, the following hematological criteria were met: hemoglobin concentration (Hb) <10 g/dl or red cell transfusion dependence of >2 U every 4 weeks for at least 2 months, or thrombocytopenia with platelets $<100\times10^9$/l and with significant hemorrhage, or neutropenia with an absolute neutrophil count $<1.5\times10^9$/l and recurrent infections. Informed consent was obtained from all patients and local Hospital Research

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Ethics Committees approval was granted for all patients treated within a clinical trial.

The median age of the cohort was 54.7 years (range: 19–75 years), with a median follow-up of 33.8 months (range: 0.8–133 months). Using the FAB classification for MDS, 74 patients (77%) had refractory anemia (RA), 15 patients had refractory anemia with excess blasts (RAEB) (16%), seven patients had refractory anemia with ring sideroblasts (RARS) (7%). Based on the International Prognostic Scoring System (IPSS),[20] 77 patients (81%) were low risk/intermediate-1, and 14 patients (14%) were in the intermediate-2/high risk categories. Five patients could not be fully assigned an IPSS owing to unavailable cytogenetics data. Seventy-nine patients were transfusion dependent (82%) and 44 patients (46%) were platelet transfusion dependent. Forty-three patients (45%) had a normocellular or hypercellular BM pretreatment, while 53 patients (55%) had a hypocellular marrow. Cytogenetic data were available on 91 patients (95%), and based on the IPSS cytogenetics classification, 65 patients (68%) were good risk, 16 (17%) intermediate risk and 10 (10%) poor risk. Human leukocyte antigen (HLA)-DR15 status was tested in 34 patients (35%), and was positive in 14 cases. Further details of the patient characteristics are listed in Table 1.

Table 1 Characteristics of 96 patients receiving ATG

Variable	*Number (%)*
Median age, years	56
(Range)	(19–79)
Median follow-up, months	33.8
(Range)	(1.5–133)
FAB	
RA	74 (77%)
RARS	7 (7%)
RAEB	15 (16%)
IPSS	
Low	14 (15%)
Int-1	63 (66%)
Int-2	8 (8%)
High	6 (6%)
Unavailable	5 (5%)
Bone marrow	
Hypocellular	53 (55%)
Hypercellular/normocellular	43 (45%)
Cytogenetics	
Good risk	65 (68%)
Intermediate risk	16 (17%)
Poor risk	10 (10%)
Unavailable	5 (5%)
HLA-DR15	
Yes	14 (41%)
No	20 (59%)
Unavailable	62
PNH clone	
Yes	1 (4%)
No	22 (96%)
Unavailable	73
Median cell counts pre-therapy	
Hemoglobin ($\times 10^9$/l)	8.4
(Range)	(4.5–15.5)
Neutrophil ($\times 10^9$/l)	1.85
(Range)	(0.0–6.7)
Platelet ($\times 10^9$/l)	76
(Range)	(3–604)
Transfusion dependence	
Yes	79 (82%)
No	17 (18%)
Platelet dependence	
Yes	44 (46%)
No	52 (54%)
Prior therapy	
EPO	13
G-CSF	5
Cyclosporine	6
Intensive chemotherapy	3
Corticosteroids	4
Others[a]	3

Abbreviations: ATG, antithymocyte globulin; ATRA, all-*trans* retinoic acid; EPO, erythropoietin; FAB, French–American–British; G-CSF, granulocyte colony-stimulating factor; HLA, human leukocyte antigen; IPSS, International Prognostic Scoring System; PNH, paroxysmal noctural hemoglobinuria; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ring sideroblasts.
[a]Others, 1 ATRA, 1 valproic acid, 1 thalidomide.

ATG protocol

A single treatment course of lymphoglobuline (Sangstat) was administered (1.5 vials/10 kg/day for 5 days; 1 vial contains 100 mg protein). A test dose of one-tenth of a vial was given before giving the full dose. Before each daily dose of lymphoglobuline, hydrocortisone 100 mg and chlorpheniramine 10 mg was given as hypersensitivity prophylaxis. Antibiotic, antifungal and septrin (co-trimoxazole) prophylaxis was given to all patients together with oral prednisolone for the prevention of serum sickness in accordance with individual institutional protocols. In addition, nine patients received cyclosporin as part of their immunosuppressive therapy following ATG.

Response criteria and statistical analysis

All patients were assessed for hematological response to ATG at 6 months following treatment. The treatment response was evaluated based on defined criteria from the International Working Group on MDS.[20] Patients were evaluated for duration of response to ATG, as well as survival after administration of ATG. Overall survival (OS) was measured from day 0 to death from any cause or last known follow-up. OS was estimated using the Kaplan–Meier method and cumulative incidence curves were used to estimate time to treatment failure in patients responding to ATG with death being treated as a competing event in the analysis. Variables analyzed included age (>55 vs <55 years), IPSS (low/Int-1 vs Int-2/high), BM cellularity (normo/hypercellularity vs hypocellularity), HLA-DR15 status, cytogenetics (as defined in the IPSS), blood transfusion dependence and platelet dependence. The presence of a PNH clone was not included in multivariate analysis owing to the limited number of patients tested. Cox proportional hazard regression was used to assess the significance of variables on response to ATG therapy as well as OS. Data were censored at 30 June 2006 or at time of last documented patient follow-up.

Results

The median time from diagnosis to ATG was 8.3 months (range: 0–342 months). A total of 40 patients (42%) had a hematological

response as defined by Cheson *et al*.[20] Thirty-one patients were transfusion dependant and 18 were platelet dependent before ATG therapy. Unilineage responses were seen in 15 patients, with responses in two or more lineages in 25 patients. Thirty patients had a Hb response (24 major and six minor), 30 had a platelet response (17 major and 13 minor) and 10 patients had a response in the neutrophil lineage (eight major and two minor). Twenty-three patients were transfusion independent following therapy. Of the 40 responders, 30 patients (75%) had a durable hematological response lasting a median duration of 31.5 months at time of reporting (range: 6–92 months). Ten patients had a transient response to ATG lasting for a median of 22 months (range: 2–46 months). Of the 10 patients with a transient response to initial ATG therapy, three patients subsequently received a second course of ATG, with two patients achieving a hematological response. Two other patients had evidence of hematological improvement following further therapy with valproic acid and valproic acid with all-*trans* retinoic acid. Five other patients died from disease progression or infectious complications. (Characteristics of responders to ATG are detailed in Table 2).

At last follow-up, nine of the 40 responders had died. Four patients (with initial diagnosis of three RAEB and 1 RA-Int-1) developed and subsequently died from disease progression (three acute myeloid leukemia and one RAEB). Two patients with therapy related MDS died from relapse of their primary malignancy (one bronchial carcinoma and one Hodgkin's lymphoma). An additional three patients died of complications from cytopenia and neutropenic sepsis.

Two out of seven patients with RARS and four out of 15 patients with RAEB had an initial response to ATG. None of the patients with pre-existing chromosomal abnormalities displayed evidence of cytogenetic remission following ATG therapy. All four patients with trisomy 8 pre-therapy had no evidence of response, but three out of seven patients with isolated 5q-syndrome had a hematological response.

Of the 56 patients who failed ATG, nine patients with a median age of 48 years (range: 34–59) proceeded to receive an allogeneic reduced intensity conditioning hematopoietic stem cell transplantation (HSCT). Seven patients received a second course of ATG with three patients attaining a transient hematological response. A further four patients received a combination of growth factor support (erythropoietin or granulocyte colony-stimulating factor) together with ciclosporine. Five patients received other therapies: one thalidomide (responder), one 5-azacitidine (partial response), one lenalidomide (responder), two sodium valproate (one responder).

Factors predicting response to ATG

On univariate analysis, IPSS low/Int-1 stage and BM hypocellularity were both identified as independent factors predicting a favorable response to treatment (Table 3). In addition, using stepwise cox regression multivariate analysis, both variables retained significance as predictive factors for response (IPSS Int-2/high: odds ratio (OR 0.08 95% confidence interval (CI): 0.01–0.65, $P=0.018$ and BM normo/hypercellularity: OR 0.49 95% CI: 0.28–0.86, $P=0.012$). Neither HLA-DR15 status (data only available on 34 patients), age or transfusion dependence influenced responsiveness to ATG therapy.

Factors influencing OS

The overall 3-year survival of the cohort was $69.9\pm5.4\%$. On analysis, there was a trend for a better outcome in responders to ATG when compared with non-responders (85.2 ± 6.2 vs $58.2\pm7.7\%$, $P=0.08$, see Figure 1). On univariate analysis, responsiveness to ATG, IPSS, cytogenetics, and transfusion dependence were all independent predictors of OS (Table 4). However, on multivariate analysis, IPSS emerged as sole predictor of OS, with Int-2/high risk patients having a significantly poorer survival outcome (OR 6.94 95% CI: 2.85–16.95, $P<0.01$).

Discussion

Treatment options for low-risk MDS are limited with supportive care remaining the mainstay of therapy for the majority of patients, but it is clear that a subgroup of MDS patients can achieve a durable hematological response following immunosuppressive therapy. In our initial pilot study of 30 low-risk MDS patients within the UK, we had observed a response in 10 out of 20 evaluable patients, and other studies using ATG have reported response rates of up to 60%.[6,7,13,17,21,22] In this study, 40 patients (42%) had evidence of hematological response, with 30 patients (31%) demonstrating a durable hematological response. On multivariate analysis, the two factors identified to predict response to ATG treatment were low/Int-1 IPSS, and BM hypocellularity.

It is clear from various studies that patients with low-risk MDS have a higher response to ATG. Of note, two patients with RARS also demonstrated a hematological response, one of which has been described previously.[7] The observation that patients with RARS may respond to ATG has since been also described by others.[14,15] While hematological responses were observed in four patients with RAEB, three of these only had a transient response with the patients subsequently progressing to more advanced disease. When compared with the other 11 patients in the study with RAEB who did not respond to ATG, there was no significant difference in OS ($P=0.47$).

Broliden *et al*.[16] recently reported on brief cytogenetic remissions in two patients treated with ATG and cyclosporine. In addition, Sloand *et al*.[23] have described the increased responsiveness of patients with trisomy 8 to ATG, and correlated this with the observation that trisomy 8 cells within the BM are preferentially suppressed by cytotoxic T lymphocytes. However, none of the patients in our cohort had a cytogenetic resolution of disease, and none of the four patients with trisomy 8 (one RAEB, one RARS, two RA (Int-1)) were among the responders.

There is great heterogeneity in MDS, and patients with hypocellular MDS have been observed to share an overlap of characteristics with aplastic anemia. There is skewing of CD4:CD8 ratios, restricted T-cell receptor Vβ usage together with high plasma levels of tumor necrosis factor-α and interferon-γ indicating a T-cell-mediated myelosuppression.[10,12,24,25] ATG has been used successfully in the alleviation of cytopenias in severe aplastic anemia,[25] and while earlier reports from Molldrem *et al*. and Killick *et al*. had identified BM hypocellularity as an important factor predicting with ATG response, several recent reports have failed to confirm this association.[14–16,22] Our study indicates that patients with hypocellular MDS have the highest response to ATG, although responses are observed in some patients with normo/hypercellular BMs. Of note, when compared with previous studies, a higher proportion of patients (55%) in this study had a hypocellular BM, which suggests a physician bias towards the use of ATG therapy in this cohort of patients.

Sauntharajah *et al*.[15,22] have previously identified the presence of HLA-DR15 as a primary factor linked with treatment

Table 2 Patient details of responders to ATG

UPN	*Age (years)*	*FAB type at diagnosis*	*Cytogenetics at diagnosis*	*HLA-DR15 status*	*Transfusion dependence (blood/platelet)*	*IPSS*	*BM cellularity at diagnosis*	*Response*	*Response duration (months)*
3	19	RA	46XX, iso 7q	NA	Y/N	Int-1	Hypo	HI-E major	75.0
4	22	RA	46XX	No	N/N	Int-1	Hypo	HI-E major	92.0
7	41	RA	46XX	No	Y/N	Int-1	Hypo	HI-E/HI-P minor	39.0
8	32	RA	46XY	No	N/N	Int-1	Hypo	HI-N minor/HI-P minor	60.0
9	36	RA	46XX	No	Y/N	Int-1	Hypo	HI-E major, HI-N major, HI-P minor	30.0
12	59	RA	46XX	No	N/N	low	Normo/hyper	HI-N major	49.0
13	47	RA	46XY	No	Y/N	Int-1	Normo/Hyper	HI-E major, HI-P major	51.0
14	63	RA	46XX	Yes	Y/Y	Int-1	Hypo	HI-E major, HI-P major	55.0
17	20	RA	46XY	Yes	N/N	Int-1	Hypo	HI-E major, HI-P major	28.0
18	49	RA	46XX	No	Y/N	Int-1	Normo/Hyper	HI-E major, HI-N major HI-P minor	12.0
19	68	RAEB	46XX	No	Y/Y	Int-2	Hypo	HI-E major	5.0
20	50	RA	46XX	Yes	Y/N	Int-1	Hypo	HI-E minor, HI-P minor	23.0
24	37	RA	46XX	NA	Y/Y	Int-1	Hypo	HI-E major HI-P minor	42
25	69	RA	46XX	NA	Y/Y	Int-1	Hypo	HI-E major HI-P major	81
27	45	RA	46XY	NA	Y/Y	Int-1	Normo/Hyper	HI-E major HI-P major	69
29	50	RAEB	NA	NA	Y/Y	NA	Normo/Hyper	HI-P minor	10
31	42	RA	46XY, t(6;12)	NA	N/N	Int-1	Hypo	HI-E major HI-P major HI-N major	58
37	55	RA	46XX, del(5)(q13q22)	NA	Y/N	Int-1	Normo/Hyper	HI-E minor, HI-P minor	19
38	61	RA	46XY, t(1;13)	NA	Y/Y	Int-1	Hypo	HI-E minor, HI-N major	33
39	46	RAEB	46XY	NA	Y/Y	Int-1	Normo/hyper	HI-E major, HI-P major	57
42	50	RA	46XY	No	Y/N	Int-1	Hypo	HI-E major, HI-N major	9
45	69	RA	46XX	Yes	Y/Y	Int-1	Normo/Hyper	HI-E major, HI-N major	26
51	69	RA	46XY	ND	Y/Y	Int-1	Hypo	HI-E minor	19
55	72	RAEB	46XX	ND	Y/N	Int-1	Hypo	HI-E minor, HI-P major	46
58	66	RARS	46XY	ND	Y/Y	Int-1	Normo/Hyper	HI-P,E major	12
59	63	RA	46XX, t(2;11)(p21;p23), del(5)(q22;q33)	ND	Y/N	Int-1	Normo/Hyper	HI E major	22
62	46	RA	46XX, del(5)(q13q22)	ND	Y/N	Int-1	Hypo	HI-P, E major/HI-N minor	6
63	51	RA	46XY	ND	Y/N	Low	Normo/Hyper	HI-E major	5
65	65	RA	46XY, t(1;7)	ND	Y/Y	Int-1	Hypo	HI-P, N major	2
78	50	RA	46XX	Yes	Y/Y	Low	Hypo	HE major, HP major	24.0
81	55	RA	NA	ND	Y/Y	NA	Hypo	HE major, HP major	33.0
82	56	RA	NA	ND	N/N	NA	Hypo	HE major, HP major	27.0
84	59	RA	46XX	No	Y/N	Int-1	Hypo	HP minor	6.0
86	44	RA	46XY	Yes	Y/Y	Int-1	Hypo	HE major, HP minor	66.0
88	69	RARS	46XY	ND	Y/N	Int-1	Hyper	HP minor	41.0
89	57	RA	46XX	Yes	N/N	Int-1	Hypo	HP minor	5.0
91	65	RA	46XY[10]/45X,−Y[13]	ND	N/Y	Int-1	Normo/Hyper	HP major	38.0
93	69	RA	46XY	ND	Y/N	Low	Hypo	HE major	31.0
95	62	RA	46XY[16]/45X –Y[4]	ND	Y/Y	Int-1	Normo/Hyper	HP major	22.0
96	61	RA	45XX, del(5)(q13q22)	Yes	N/Y	Low	Hypo	HP major	72.0

Abbreviations: ATG, antithymocyte globulin; BM, bone marrow; FAB, French–American–British; Hypo, Hypocellular; IPSS, International Prognostic Scoring System; Int-1 (IPSS intermediate-1); NA, not available; ND, not performed; Normo/Hyper, normocellular or hypercellular; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ring sideroblasts.

Table 3 Univariate and multivariate analysis of factors predicting response to ATG

	OR (95% CI)	*Significance (P-value)*
Univariate analysis variables		
Disease stage	0.46 (0.13-1.55)	0.21
IPSS	0.09 (0.01-0.68)	0.02
BM cellularity	0.51 (0.29-0.87)	0.01
Age	0.64 (0.28-1.47)	0.30
HLA-DR15 status	0.75 (0.19-2.96)	0.68
Cytogenetics[a]	0.78 (0.31-1.97)	0.59
Transfusion dependence	1.74 (0.61-4.99)	0.30
Platelet dependence	1.06 (0.47-2.40)	0.89
Multivariate analysis variables[b]		
IPSS		0.02
Low/Int-1[c]	—	
Int-2/High	0.08 (0.01-0.65)	
BM cellularity		0.01
Hypocellular[c]	—	
Normo/Hypercellular	0.49 (0.28-0.86)	

Abbreviations: ATG, antithymocyte globulin; BM, bone marrow; CI, confidence interval; HLA, human leukocyte antigen; IPSS, International Prognostic Scoring System; Int-1 (IPSS intermediate-1); Normo/Hyper, normocellular or hypercellular; OR, odds ratio.
[a]Analyzed as good risk versus intermediate/poor risk.
[b]On multivariate analysis, both Int2/high IPSS score and normo/hypercellular bone marrow are associated with a significantly lower response rate to treatment with ATG.
[c]Indicates reference category.

Table 4 Univariate and multivariate analysis of factors influencing overall survival

	OR (95% CI)	*Significance (P-value)*
Univariate analysis variables		
Response to ATG	2.03 (0.91–4.51)	0.08
IPSS	0.19 (0.08–0.42)	<0.01
BM cellularity	1.80 (0.67–4.91)	0.42
Age	0.56 (0.27–1.18)	0.13
Cytogenetics[a]	0.45 (0.19–1.02)	0.06
Transfusion dependence	7.03 (0.95–51.75)	0.06
Platelet dependence	1.95 (0.90–4.22)	0.10
Multivariate analysis variables[b]		
IPSS		
Low/Int-1[c]	—	<0.01
Int-2/High	6.94 (2.85–16.95)	
Response to ATG		0.92
Yes	—	
No	1.05 (0.34–3.03)	

Abbreviations: ATG, antithymocyte globulin; BM, bone marrow; CI, confidence interval; IPSS, International Prognostic Scoring System; Int-1 (IPSS intermediate-1); OR, odds ratio.
[a]Analyzed as good risk versus intermediate/poor risk.
[c]Indicates reference category.
[b]On multivariate analysis, Int2/high IPSS score is associated with a significantly lower overall survival.

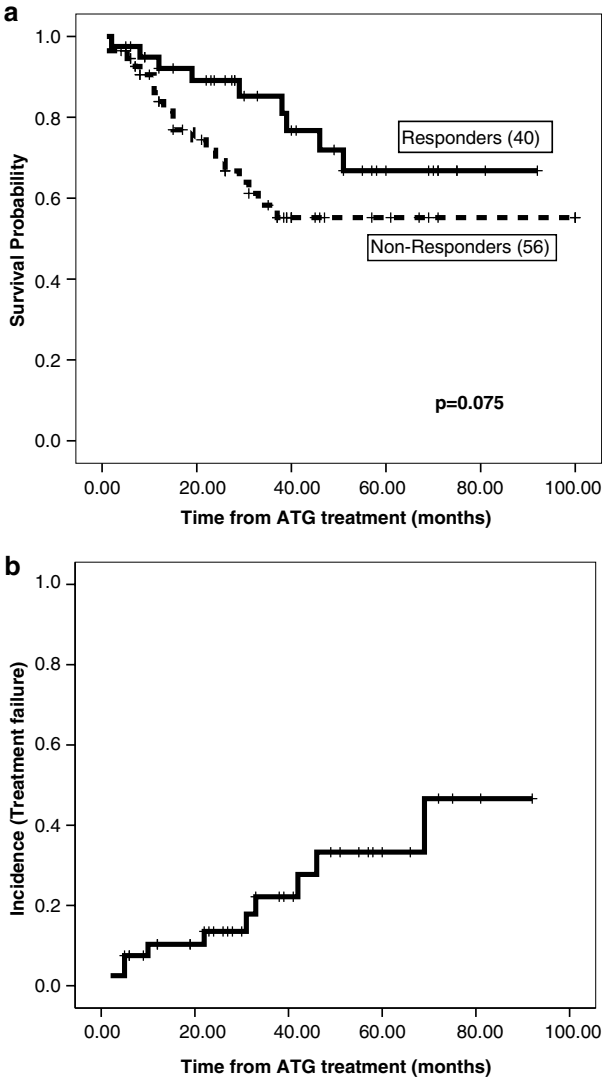

Figure 1 (**a**) Overall survival for responders vs non-responders to ATG therapy. (**b**) Cummulative incidence of treatment failure among patients responding to ATG.

responsiveness to ATG. The frequency of HLA-DR15 has been shown to be higher in both RA as well as aplastic anemia, although only patients with RA have been noted to have a higher response rate to ATG.[26,27] While only 34 patients were tested for HLA-DR15 in this study, a high proportion (10 patients, 29%) was found to be positive for HLA-DR15, similar to the reported incidence of 30–36% among MDS patients in other studies. However, within a limited analysis of this subset of patients, HLA-DR15 positivity was not a predictive factor for ATG response ($P=0.68$).

In addition to ATG, other immunosuppressive and immunomodulatory agents including enternacept and ciclosporine have been used with varying success in the management of low-risk MDS. Of those only achieving a transient response or not responding to ATG, hematological response was seen in several patients to a variety of alternative immunosuppressive agents. The development of methods to assess immunological responses following ATG therapy may assist in identifying patients who may benefit from maintenance therapy, or require treatment with an alternative IST. Conversely, patients who are less likely to respond to IST should be considered for more intensive therapies where suitable. Nine non-responders (median age of 48 years) in the study eventually proceeded to allogeneic HSCT, and it should be emphasized that at present, allogeneic HSCT remains the only curative treatment for MDS.

In conclusion, this study confirms BM hypocellularity and a low IPSS as important factors predicting response to ATG. The findings from our study, taken together with other similar studies suggest that there are likely to be several co-dominant immunological factors contributing to the pathophysiobiology of low-risk MDS. Further studies on the immunological factors influencing the pathogenesis of low-risk MDS are necessary to identify patients who will respond best to immunosuppressive therapy, as well as establishing the most appropriate IST for each individual.

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