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ORIGINAL REPORT

Immunosuppressive Therapy for Patients With Myelodysplastic Syndrome: A Prospective Randomized Multicenter Phase III Trial Comparing Antithymocyte Globulin Plus Cyclosporine With Best Supportive Care—SAKK 33/99

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ABSTRACT

Purpose
Immunosuppressive treatment is reported to improve cytopenia in some patients with myelodysplastic syndrome (MDS). Combined antithymocyte globulin (ATG) and cyclosporine (CSA) is most effective in patients with immune-mediated marrow failure.

Patients and Methods
This trial was designed to assess the impact of immunosuppression on hematopoiesis, transfusion requirements, transformation, and survival in patients with MDS randomly assigned to 15 mg/kg of horse ATG for 5 days and oral CSA for 180 days (ATG+CSA) or best supportive care (BSC), stratified by treatment center and International Prognostic Scoring System (IPSS) risk score. Primary end point was best hematologic response at 6 months. Eligible patients had an Eastern Cooperative Oncology Group performance status of ≤ 2 and transfusion dependency of less than 2 years in duration.

Results
Between 2000 and 2006, 45 patients received ATG+CSA (median age, 62 years; range, 23 to 75 years; 56% men) and 43 patients received BSC (median age, 65 years; range, 24 to 76 years; 81% men). IPSS score was low, intermediate-1, intermediate-2, high, and not evaluable in eight, 24, seven, one, and five patients on ATG+CSA, respectively, and eight, 25, five, zero, and five patients on BSC, respectively. Refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess of blasts (RAEB) -I, RAEB-II, and hypoplastic disease were present in 21, six, nine, zero, and nine patients on ATG+CSA, respectively, and 18, eight, 11, two, and four patients on BSC, respectively. By month 6, 13 of 45 patients on ATG+CSA had a hematologic response compared with four of 43 patients on BSC ($P = .0156$). Two-year transformation-free survival (TFS) rates were 46% (95% CI, 28% to 62%) and 55% (95% CI, 34% to 70%) for ATG+CSA and BSC patients, respectively ($P = .730$), whereas overall survival (OS) estimates were 49% (95% CI, 31% to 66%) and 63% (95% CI, 42% to 78%), respectively ($P = .828$).

Conclusion
This open-label randomized phase III trial demonstrates that ATG+CSA treatment seems to be associated with hematologic response in a subset of patients without apparent impact on TFS and OS.

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INTRODUCTION

The myelodysplastic syndromes (MDS) comprise a heterogeneous group of diseases; their hallmark is dysplastic hematopoiesis, cytopenia, and transformation to leukemia.[1] Frequently, patients are older adults with comorbidities. Approximately half of patients die of leukemic transformation, and the remainder of patients die from cytopenia including bleeding, infection, and hemochromatosis. The International Prognostic Scoring System (IPSS) predicts survival based on number of lineages involved, blast count, and karyotype.[2] Stem-cell transplantation is the only curative approach but is not feasible for most patients.[3,4] In some patients, hematopoietic growth factors, azacitidine, decitabine, and lenalidomide may improve cytopenias and may prolong survival.[5,6] Effective treatment must improve transfusion dependency and slow leukemic transformation. It has recently been shown that transfusional

iron overload is associated with decreased survival, highlighting the importance of achieving transfusion independence.[7]

Associations between autoimmune phenomena, such as connective tissue disorders and vasculitis, and MDS are well recognized. Immunologic abnormalities may play a role in promoting apoptosis of hematopoietic progenitors, leading to ineffective hematopoiesis and cytopenia. Increased oligoclonal T-cell expansion and suppression of hematopoietic progenitors by cytotoxic T cells have been observed.[8-18]

Immunosuppressive therapy, similar to treatment of aplastic anemia, has been shown to induce hematologic response in a subset of patients with MDS.[19-33] The National Institutes of Health has developed a scoring system to predict response based on age, duration of transfusion dependence, and presence of HLA-DR15.[34]

Antithymocyte globulin (ATG), a polyclonal immunoglobulin, is known to react with a number of cell types, including T cells and natural killer cells, as well as molecules modulating the immune response, such as integrins and certain chemokine receptors. Although the mechanism of action remains unclear, ATG is believed to block the lymphocyte-mediated suppression of dysplastic hematopoiesis.

Here, we report results of a randomized phase III clinical trial comparing the combination of ATG + cyclosporine (CSA), which is well established in the immunosuppressive treatment of aplastic anemia, with best supportive care (BSC) in patients with low- and intermediate-risk MDS.

PATIENTS AND METHODS

Patient Selection

This trial was conducted across 17 centers. Patients were randomly assigned to receive either ATG+CSA or BSC, stratified by IPSS risk score and center. Inclusion criteria were documented MDS, refractory anemia with or without sideroblasts, refractory anemia with excess of blasts (RAEB) -I, and hypoplastic MDS, defining a group of low- to intermediate-risk MDS with less than 10% blast cells in bone marrow. Patients with higher blast counts were eligible if no other treatment was available. Patients were transfusion dependent for less than 24 months in duration, defined as packed RBC transfusion more than 2 units per month for a period of $\geq$ 2 months or untransfused hemoglobin level $\leq$ 8 g/dL, platelet transfusion more than 1 unit per 2 weeks for a period of more than 1 month, or untransfused platelet count $\leq 20 \times 10^9$/L or neutrophils less than 0.5×10^9/L. Patient age was greater than 18 years, and Eastern Cooperative Oncology Group performance status was $\leq$ 2. Patients with chronic myelomonocytic leukemia, refractory anemia with excessive blasts in transformation, and secondary MDS were excluded, as were patients with infection.

The primary end point was best hematologic response rate (RR) at 6 months (complete remission [CR] + partial remission [PR]). CR was defined as normalization of peripheral-blood counts (unsustained hemoglobin > 100 g/L, unsustained platelets > 100 g/L, and neutrophils > 1.5 g/L), and PR was defined as transfusion independence for more than 60 days. The trial protocol was activated before the publication of the International Working Group response criteria[35]; hence, hematologic improvement (improved blood counts but without transfusion independence) was not used as an outcome measure.

The protocol was approved by local ethics review boards, and patients gave informed consent. The trial was registered at the National Institutes of Health (trial identifier: NCT00004208).

Treatment

As per random assignment, patients received horse ATG (Lymphoglobuline; Genzyme, Cambridge, MA) at a dose of 15 mg/kg for 5 days in combination with oral CSA for 180 days. BSC allowed for transfusional support, iron chelation, antibiotics to treat infections, and growth factors to treat neutropenia or anemia, if the serum erythropoietin level was considered to be low (erythropoietin < 100 U/L). Patients were allowed to cross over from the BSC arm to the ATG+CSA arm at the time of disease progression or after 6 months in the case of nonresponse (cross-over arm).

Statistical Design and Analysis

This multicenter phase III trial used a group sequential two-stage design, with the primary end point being best hematologic RR at 6 months after trial random assignment. A 5% RR was assumed for the BSC arm, and a 30% RR was assumed for the ATG+CSA arm. Under this design, incorporating the O'Brian-Fleming spending function, with a two-sided 5% significance level and 80% power, 42 patients were required for each treatment arm, allowing for one interim analysis.

Adverse events, recorded using the Common Terminology Criteria for Adverse Events (version 3), were summarized by event type and grade over the total number of therapy cycles administered, as well as within patients (worst recorded adverse event grade per event type per patient).

Time-to-event analyses included overall survival (OS), defined as the time from trial registration until death as a result of any cause; leukemia-free survival (LFS), defined as the time from trial registration until either leukemic transformation or death, with patients censored at the time of a stem-cell transplantation; and transformation-free survival (TFS), defined as survival without transformation to leukemia or a higher degree of MDS (eg, refractory anemia to RAEB). Patients were censored at the last known date they were alive or at treatment arm cross over, where appropriate. All time-to-event analyses were carried out using the intent-to-treat principle, maintaining the power of this trial to detect a difference in response at 6 months. The trial was not powered to detect survival differences. Other secondary end points included duration of response, medical resource use (defined as the number of transfusions and hospitalizations days), and prognostic factors for response using logistic regression.

RESULTS

Patients

Forty-five patient were randomly assigned to the ATG+CSA arm and 43 patients were assigned to the BSC arm between November 2001 and October 2006; median patient age was 62 years (range, 23 to 75 years) and 65 years (range, 24 to 76 years), respectively (Table 1; Fig 1). Patients were included for transfusion dependence on RBCs or platelets; one patient only was included for severe neutropenia. Significantly fewer men were in the ATG+CSA arm compared with the BSC arm (56% *v* 81% men, respectively; $P = .01$). There were no significant differences between randomly assigned trial arms and MDS type (Table 1). Median follow-up time was 2.3 years (range, 0 to 6.5 years). Five patients randomly assigned to ATG+CSA were not treated for various reasons including patient and physician withdrawal (n = 3), allergy to wasp stings (n = 1), and early progression before treatment administration (n = 1), whereas one patient in the BSC arm was erroneously treated with ATG+CSA. The average daily dose of CSA was 290 mg administered for an average of 157 days (range, 2 to 307 days). CSA administration was interrupted in 12 of 50 patients for various reasons (infection, abnormal liver or kidney function tests, neurologic adverse effects, and disease progression). Fourteen patients in the BSC arm crossed over to ATG+CSA treatment, seven of whom fulfilled the cross-over response criteria at 6 months after BSC treatment. Of the remaining seven patients, five crossed over because of progression to cytopenia without transformation to leukemia, and two crossed over because of alloimmunization and refractoriness to transfusion support.

Table 1. Patient Baseline Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	Treatment Arm: ATG+CSA (n = 45) No. of Patients	%	BSC (n = 43) No. of Patients	%	*P*
Age, years					.45
Median	62		65		
Range	23-75		24-76		
Male	25	56	35	81	.01
IPSS score					.97
Low	8	18	8	19	
Intermediate-1	24	53	25	58	
Intermediate-2	7	16	5	12	
High	1	2	0	0	
Not evaluable (missing cytogenetics)	5	11	5	12	
MDS type					.38
RA	21	47	18	42	
RAS	6	13	8	19	
RAEB-I	9	20	11	26	
RAEB-II	0	0	2	5	
Hypoplastic	9	20	4	9	

Abbreviations: ATG, antithymocyte globulin; CSA, cyclosporine; BSC, best supportive care; IPSS, International Prognostic Scoring System; RA, refractory anemia; RAS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess blasts.

Response

At 6 months, 13 (29%) of 45 patients achieved a hematologic response (CR+PR) in the ATG+CSA arm, whereas four (9%) of 43 patients achieved a hematologic response in the BSC arm ($P = .0156$, adjusted for the interim analysis; Table 2). One of the responders in the ATG+CSA arm had not received therapy. The four responders in the BSC arm are explained by one patient being patient transfusion independent at 6 months but with increasing blast counts, a patient with fluctuating transfusion requirements, a patient erroneously receiving ATG+CSA despite random assignment to the BSC arm (analysis by intent to treat), and a patient with response to erythropoietin after random assignment to the BSC arm who was not previously treated with growth factors. Two additional patients in the ATG+CSA arm and two in the BSC arm responded at 6 months after trial random assignment; two patients responded after cross over. According to the International Working Group criteria published after trial initiation, three, two, and nine responses in the ATG+CSA arm and zero, two, and two responses in the BSC arm qualified as CR, PR, and hematologic improvement, respectively. Median response duration in the ATG+CSA arm was 16.4 months

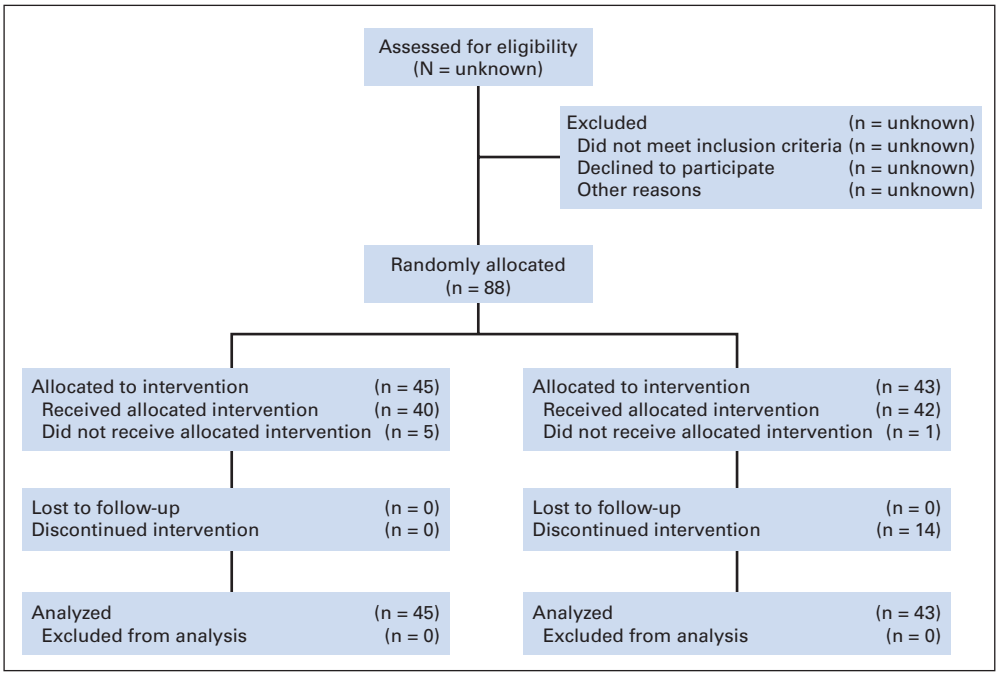

Fig 1. CONSORT diagram.

Table 2. Response and Time-to-Event Analyses

Measure	Treatment Arm		P
	ATG+CSA (n = 45)	BSC (n = 43)	
No treatment, No. of patients*	5	—	
Crossed over to ATG+CSA, No. of patients	—	14	
Hematologic response (CR+PR) by 3 months			
No. of patients	9	4	
%	20	9	
Hematologic response (CR+PR) by 6 months†			.016
No. of patients	13	4	
%	29	9	
Hematologic response (CR+PR+HI) by 6 months (IWG criteria)†‡			.009
No. of patients	14	4	
%	31	9	
Median response duration, months	16.4 (3 relapses)	NA	
Transformation-free survival probability at 2 years, %	0.46	0.55	.730
95% CI	0.28 to 0.62	0.34 to 0.70	
Leukemia-free survival probability at 2 years, %	0.51	0.62	.910
95% CI	0.31 to 0.67	0.41 to 0.78	
Overall survival probability at 2 years, %	0.49	0.63	.828
95% CI	0.31 to 0.66	0.42 to 0.78	

Abbreviations: ATG, antithymocyte globulin; CSA, cyclosporine; BSC, best supportive care; CR, complete remission; PR, partial remission; HI, hematologic improvement; IWG, International Working Group; NA, not applicable.
*Reasons for no treatment included patient ineligible, progression, patient refusal, and complications.
†Adjusted for the interim analysis.
‡Our study was carried out before the definition of the IWG criteria; therefore, analysis of response by IWG criteria is to be considered a post hoc analysis.

(range, 6.9 to 34.1 months) for the three patients with a recorded relapse (Fig 2). No relapse was observed in either the BSC patients or the patients who crossed over and had a response. Response at 6 months was significantly associated with marrow cellularity (favoring hypoplastic marrow), blast counts on the aspirate (favoring low blast counts), MDS subtype (favoring hypoplastic MDS), and treatment arm. There were associations of borderline significance with disease duration (favoring short duration), transfusion dependency, and age (favoring young age) as shown in Table 3. When modeled in a multivariable setting using logistic regression, treatment arm and marrow cellularity were significantly associated with response at 6 months (Table 3).

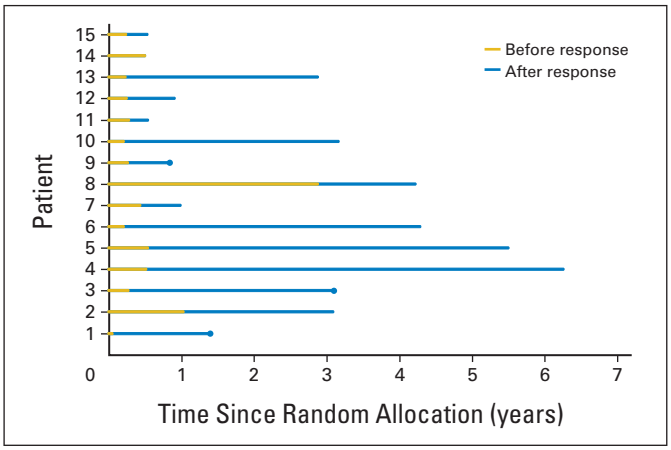

Fig 2. Response duration in patients in the treatment group (antithymocyte globulin plus cyclosporine). Patients 1, 3, and 9 all experienced relapse at the times shown (1.4, 2.8, and 0.6 years after remission, respectively). All other patients are currently alive without relapse.

Time-to-Event Analysis

TFS probability estimates at 2 years were 46% (95% CI, 28% to 62%) for the ATG+CSA arm and 55% (95% CI, 34% to 70%) for the BSC arm when censoring at the time of cross over ($P = .730$). When allowing for further splitting by cross over, the TFS probability estimate at 2 years became 50% (95% CI, 30% to 67%) for BSC patients without cross over and 12% (95% CI, 1% to 39%) for BSC patients with cross over. Two-year LFS probabilities were 51% (95% CI, 31% to 67%) and 62% (95% CI, 41% to 78%) for the ATG+CSA and BSC arms, respectively, when allowing for cross-over censoring in the BSC arm ($P = .910$), or 58% (95% CI, 37% to 75%) for BSC patients without cross over and 48% (95% CI, 18% to 74%) for patients with cross over. In total, 40 deaths occurred; 17 of 45 patients in the ATG+CSA arm died, and 14 of 45 patients in the BSC arm died (nine of 14 patients died after cross over). Causes of death were infection (n = 13), leukemia (n = 11), organ failure (n = 5), MDS cytopenia (n = 1), hemorrhage (n = 4), toxicity (n = 2), pneumonia (n = 1), and respiratory insufficiency (n = 1); cause of death was unknown in two patients. Two-year OS probability estimates were 49% (95% CI, 31% to 66%) for patients in the ATG+CSA arm and 63% (95% CI, 42% to 78%) in the cross-over censored BSC arm ($P = .828$), or 59% (95% CI, 38% to 75%) for BSC patients without cross over and 41% (95% CI, 14% to 67%) for patients with cross over. Median OS time was 1.9, 2.8, and 1.9 years in the ATG+CSA, BSC, and cross-over arms, respectively (Fig 3). When treatment was modeled as a time-dependent covariate, allowing for cross-over patients, no significant

Table 3. Factors Associated With Response at 6 Months for All Patients in a Univariate Analysis

Factor	Model *P*	
	Univariate Analysis	Multivariate Analysis
Treatment arm: BSC *v* ATG+CSA	.029	.040
Age	.064	
IPSS score: low (3/14 patients, 21%) *v* intermediate/high (11/59 patients, 19%)	.769	
Blast count, marrow biopsy	.132	
Blast count, marrow aspirate	.039	
Marrow cellularity biopsy: low (7/20 patients, 35%) *v* normal/high (6/51 patients, 12%)	.091	
Marrow cellularity aspirate: low (11/24 patients, 46%) *v* normal/high (5/42 patients, 12%)	.004	.009
Duration of disease at random assignment	.059	
Duration of transfusion dependency	.064	
Cytogenetics: normal (8/45 patients, 18%) *v* other (6/29 patients, 21%)	.628	
MDS type: RA (3/37 patients, 16%), RAS (3/12 patients, 25%), hypoplastic (6/12 patients, 50%), and RAEB (2/20 patients, 10%)	.049	

Abbreviations: BSC, best supportive care; ATG, antithymocyte globulin; CSA, cyclosporine; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; RA, refractory anemia; RAS, refractory anemia with ringed sideroblasts; RAEB, refractory anemia with excess blasts.

Table 4. WHO Grade 3 or 4 Toxicities

Event	Grade 3 or 4 Toxicity (No. of patients)	
	ATG+CSA	BSC
Transaminases	2	1
Hyperbilirubinemia	1	1
Anemia	21	24
Leukopenia	15	17
Neutropenia	17	20
Thrombocytopenia	24	21
Febrile transfusion reaction	5	0

Abbreviations: ATG, antithymocyte globulin; CSA, cyclosporine; BSC, best supportive care.

difference in death rate was observed (hazard ratio, 0.935; 95% CI, 0.608 to 1.439; $P = .7613$).

Adverse Events

In additional to the 40 deaths, 20 serious adverse events (SAEs) were reported (16 in the ATG+CSA arm and four in the BSC arm; $P = .005$). Reported SAEs were heterogeneous and included the most common types of infectious and inflammatory complications. The SAEs more specifically seen in the ATG+CSA arm were major hemorrhage (n = 2), cardiac events (n = 2), serum sickness/fever (n = 2), thrombosis (n = 2), severe infection (n = 4), and various others (n = 4). The SAEs in the BSC arm included severe infection (n = 2) and others (n = 2). In addition, three SAEs were reported after cross over (severe infection in two patients and thrombosis in one patient). In addition to the reported SAEs, Table 4 lists all grade 3 and 4 toxicities reported.

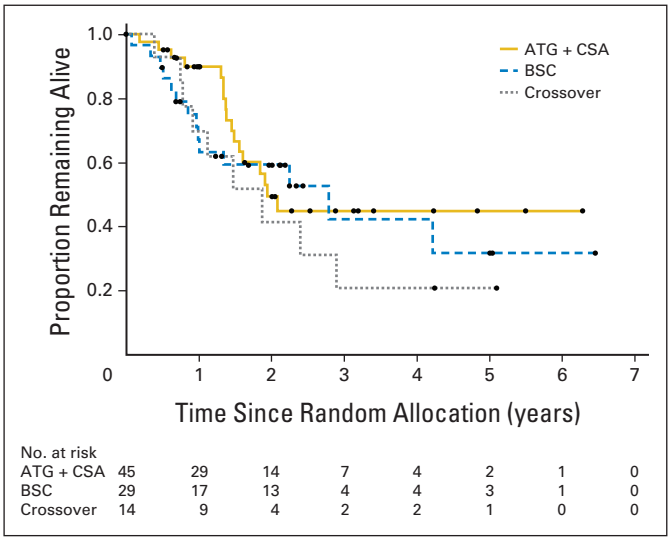

Fig 3. Overall survival in the antithymocyte globulin plus cyclosporine (ATG+CSA), best supportive care (BSC), and cross-over arms.

Medical Resource Use

Medical resource use between trial arms was evaluated in a limited manner counting transfusion requirements and days in hospital. Median number of days in hospital per patient was 25 days (range, 4 to 148 days; n = 32) and 18 days (range, 1 to 229 days; n = 17) for the ATG+CSA and BSC treatment arms, respectively, before cross over while on trial therapy administration. The number of antibiotic days was 15 days (range, 3 to 152 days; n = 19) and 23 days (range, 1 to 130 days; n = 10) for the ATG+CSA and BSC arms, respectively. For the ATG+CSA and BSC arms, the median number of RBC transfusion units was 28 units (range, 0 to 148 units; n = 42) and 16.5 units (range, 0 to 205 units; n = 40), respectively; the median number of platelet transfusion units was 3.5 units (range, 0 to 85 units; n = 42) and 0 units (range, 0 to 97 units; n = 40), respectively; and the median number of growth factor days were 14 days (range, 3 to 100 days; n = 5) and 41 days (range, 1 to 62 days; n = 3), respectively. Of the three patients in the BSC arm receiving growth factors, one patient became an erythropoietin responder, as mentioned earlier when discussing responses in the BSC arm. Of the five patients in the ATG+CSA arm who received growth factors, two patients had received growth factors before response to trial treatment, but response was considered not to be associated with growth factor use.

DISCUSSION

This clinical trial comparing immunosuppressive treatment with ATG+CSA versus BSC shows response in a substantial proportion of patients (29%). This RR is considerable and is in line with prior publications of phase II trials reporting variable RRs. The majority of the responses achieved are still ongoing. Because, to our knowledge, this is the first randomized trial reported comparing ATG+CSA with

BSC, it is of interest that 9% of patients in the control arm were also responders. Analyses of these control responders showed that one of the four patients had inadvertently received ATG+CSA, and one patient responded to erythropoietin, reducing the number of patients meeting response criteria as a result of fluctuation of the blood counts to two patients (5%).

No significant differences existed among the arms in TFS, LFS, and OS. Previous phase II trials and patient series have shown better long-term outcome in responders compared with nonresponders. This trial was not powered to detect changes in the rate of these events; however, the ultimate goal of this treatment strategy will be to demonstrate superior survival in treated versus untreated patients. A previously published study by the National Institutes of Health compared survival of patients treated with ATG or with ATG+CSA with historical control patients taken from the International MDS Risk Analysis Workshop (IMRAW) cohort.[32] This was the cohort of untreated patients originally used to establish the IPSS score who were recruited at a different time period and probably received inferior supportive care. Similarly, the Groupe Francophone de Myélodysplasie study had used the IMRAW cohort data to compare patients treated with granulocyte colony-stimulating factor and erythropoietin and showed a survival benefit.[36] The question remains whether such differences can be reproduced using concurrent controls. The trial presented here failed to show evidence in favor of improved survival.

Previous studies identified patient age, disease duration, and HLA-DR15 as predictors of response.[34] Associations with marrow cellularity have been equivocal.[32,33] We found an association between response and hypocellular marrow, MDS subtype favoring hypocellular MDS, and low blast counts. Borderline associations were seen with short duration of transfusion dependence, short interval between diagnosis and treatment, and young age. In this study, marrow hypocellularity had the strongest impact on response, where patients with hypocellular marrow had a 50% RR to ATG+CSA. A significant treatment effect was confirmed by multivariable analysis adjusting for marrow cellularity. Other variables were not significant, but the power of the multivariable analysis is limited because only 88 patients were analyzed. This study was started before the information on HLA-DR15 became available; therefore, HLA typing was not included in the patient work-up.

As was expected, adverse events were significantly more frequent in the ATG+CSA arm compared with the BSC arm and included various infectious, inflammatory, and hemorrhagic complications.

Response to immunosuppression in MDS requires explanation, and even though the pathophysiology is not fully elucidated, effects observed in this and other studies point to the importance of an immune-mediated component of MDS hematopoiesis being driven to apoptosis and the potential to remove this drive by immunosuppressive treatment. Immunosuppression is associated with malignancy in many clinical situations, although no evidence that ATG+CSA accelerates leukemic transformation in patients with MDS is shown here.

Medical resource use does not provide much information other than stating that these patients do use resources. Transfusion needs were not diminished in the ATG+CSA arm within the first 6 months possibly because only one third of patients were responders, and this is likely to be compensated by increased use in the active treatment phase.

This study has several limitations. The main limitation is that, by today's standards, the patient groups are heterogeneous, reflecting the ongoing progress in diagnostic classification of MDS.[32] We had intended to accrue mainly patients with low-risk MDS but had to allow patients with more advanced disease, thus including intermediate-2–risk patients. Finally, 18% and 12% of patients in the ATG+CSA and BSC arms, respectively, had IPSS intermediate-2 and high-risk disease and 20% and 31% of patients, respectively, had MDS type RAEB-I or RAEB-II by WHO classification. We allowed for cross over to the active treatment arm for patients receiving BSC. The cross-over design is not optimal because it precludes any definite conclusions on the risk of leukemic evolution and differences in survival. Patients were allowed to cross over if progression occurred before 6 months or after 6 months if there was no response. Difficulties in accrual made this design necessary because it was difficult to convince patients referred to a tertiary care center and already on BSC to remain on BSC alone. In fact, three patients crossed over before 6 months, two because of progression and one because of alloimmunization refractory to transfusion support. To adjust for all problems inherent in this design, analysis was carried out both by intent to treat and by treatment per protocol, censoring patients at the time of cross over.

This phase III trial shows significant response to ATG+CSA compared with BSC in approximately one third of treated patients, confirming results of a series of phase II trials. It will be the task of future research efforts to more precisely define responders to limit this treatment, which is not devoid of toxicities, to the cohort of patients most likely to benefit from this intervention.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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