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Immunosuppressive Therapy: Exploring an Underutilized Treatment Option for Myelodysplastic Syndrome

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Abstract

Immunosuppresive therapy in low risk myelodysplastic syndrome can achieve sustained hematologic improvement but is underutilized due to lack of selection criteria. We completed a retrospective analysis of sixty-six patients treated with immunosuppressive therapy to investigate treatment outcome and clinical co-variables that influence response. Overall hematologic improvement was 42%, comparable to other treatment options for lower risk MDS. The response rate was higher in low risk disease, treated early on in the disease process with immunosuppressive therapy as the first line treatment.

Background: Immunosuppressive therapy (IST) in low risk myelodysplastic syndrome (MDS) is known to achieve hematologic improvement but remains an underutilized treatment option. We report our experience using antithymocyte globulin (ATG) and cyclosporine A (CSA) to explore clinical predictive response factors. **Patients and Methods:** Patients treated with IST identified in the Moffitt Cancer Center MDS database were analyzed using baseline data, IST details, and response rates. **Results:** Sixty-six patients treated with IST were identified. The median age was 61 years; the majority were at low risk and had a good karyotype. The median time to start IST was 1 year. All patients received ATG, 60% rabbit (r-ATG), 32% equine ATG (e-ATG), and 60% received CSA. Overall hematologic improvement was 42% with a trend favoring e-ATG over r-ATG (52% vs. 39%; $P = .09$). Erythroid improvement was evaluated in 30 patients, and 60% responded; neutrophil improvement was evaluated in 15, and 39% responded; platelet improvement was evaluated in 18, and 57% responded. Six of 18 pancytopenic patients experienced trilineage response. Mean time from ATG to next therapy was 12 months. None of the patients with very high risk or high risk revised International Prognostic Scoring System (IPSS-R) responded. Poor karyotype had a lower response rate, 25%, compared to 41% for intermediate and 44% for good karyotype. No difference in predicting response was found based on the National Institutes of Health Response Model; 38% with low and 45% with high probability responded. A trend favored treatment within 2 years from diagnosis, with 46% responding compared to 33% treated after 2 years. First-line ATG or after lenalidomide responded better than after azacitidine or third-line therapy. CSA provided an advantage: the disease of 51% responded compared to 27% with ATG alone ($P = .05$). Ten patients experienced transformation to acute myeloid leukemia, 7% with disease that responded to therapy and 24% with disease that did not respond to therapy ($P = .08$). Overall survival was 67.2 months without difference between those with and without response. Adverse events were reported in 55 patients. Infusion reactions occurred in 85% but was similar between ATG types. Infection rate was 25% and higher with e-ATG. Serum sickness was reported in 18% and significantly higher with r-ATG. **Conclusion:** IST has a hematologic improvement response rate in the range of other therapies approved for lower risk MDS. High risk IPSS-R, poor karyotype, and treatment after 2 years from diagnosis have unfavorable response trend. ATG with CSA has higher response than ATG alone. First-line ATG or after lenalidomide had better response trend compared to third-line therapy or azacitidine therapy.

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Introduction

The treatment options for patients with lower risk myelodysplastic syndrome (MDS) are limited. In a subset of patients, an immune mechanism is thought to contribute to disease pathobiology, thus prompting the use of immunosuppressive therapy (IST) as a treatment modality.[1] It was first used in patents with hypoplastic MDS under the assumption that the disease process mimicked that of aplastic anemia.[2,3] IST with antithymocyte globulin (ATG) with or without cyclosporine A (CSA) is known to achieve hematologic improvement, including trilineage response. In fact, hematologic improvement is observed in approximately one third of patients treated with IST.[4] Despite achieving durable responses, there is a lack of appropriate selection criteria for MDS patients to receive IST, and this modality is underutilized in community practices. In evaluating the selection criteria for treatment, several factors have been linked to IST response. The National Institutes of Health (NIH) Response Model incorporates age, duration of transfusion dependence, and HLA-DR15 genotype, dividing patients into low and high probability of response categories.

A study combining equine ATG (e-ATG) with etanercept and another evaluating alemtuzumab alone demonstrated response in MDS patients with low International Prognostic Scoring System (IPSS) risk, younger age, shorter transfusions duration, and HLA-DR15 genotype positivity.[5,6] Molldrem et al[7] reported that 34% of 61 transfusion-dependent MDS patients treated with e-ATG became transfusion independent, with durable responses for a median of 3 years in 81% of the patients whose disease responded to therapy. An updated analysis by Sloand et al[1] on an NIH cohort revealed that response to therapy was associated with a better outcome in intermediate risk patients and those younger than 60 years old. Those who experienced response also had a decreased risk of transformation to acute myeloid leukemia (AML).

Komrokji et al[4] evaluated rabbit ATG (r-ATG) in MDS patients in a phase 2 multicenter trial in 2012. Hematologic improvement was achieved in 33% of patients across all IPSS risk categories. In this study, there was no difference in response with age less than 60 years. The disease of a majority of HLA-DR15-positive patients responded. The study also noted that a shorter interval between diagnosis and initiation of therapy was associated with a higher response rate. The group evaluated biomarkers in an effort to identify a T-cell profile associated with ATG response. An increase in $CD8^+$ terminal memory T-cell percentage and $CD4^+$ T-cell proliferative index were associated with higher response.

We report our experience using ATG and CSA in patients treated at the Moffitt Cancer Center. The purpose of the study was to evaluate response rates, clinical predictors of response, and the safety of therapy as well as its impact on outcome.

Patients and Methods

This was a retrospective study conducted at a single institution. The MDS database was reviewed to identify all patients with MDS who received treatment with immunosuppressive therapy in the form of ATG with or without CSA. Sixty-six patients were identified and reviewed. Patient baseline characteristics including demographics, pretreatment laboratory tests, and bone marrow biopsy pathology reports with karyotype and cytogenetics were recorded. Prior treatments, including transfusions, erythropoietin stimulating agents, and hypomethylating agents, were also recorded. Treatment dates, type of ATG received, and whether CSA was used as well as the timeline of treatments were recorded. Hematologic response and duration of response were assessed. Transformation to AML and overall survival were recorded.

Table 1 Patient Characteristics

Characteristic	n (%)
WHO Classification	
RA	8 (12%)
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RCMD	37 (56%)
RAEB I	5 (8%)
RAEB II	3 (4%)
MDS	5 (8%)
IPSS	
Low	21 (32%)
Intermediate I/II	40 (60%)
High	5 (8%)
IPSS-R	
Very low/low	39 (59%)
Intermediate	19 (29%)
High/very high	5 (8%)
Missing	3 (4%)
Global MD Anderson Risk	
Low	24 (36%)
Intermediate I/II	38 (58%)
Poor	3 (5%)
Missing	1 (1%)
Karyotype	
Good	45 (68%)
Intermediate	17 (26%)
Poor	4 (6%)
PNH clone present	4 (6%)
Hypocellular bone marrow	13 (20%)
Grade 2 or 3 BM fibrosis	6 (9%)
LGL clone present	4 (6%)
Median CD4/CD8 Ratio	168
NIH Response Model Probability	
Low	32 (49%)
High	20 (30%)
t-MDS	5 (8%)
Autoimmune disease	
Yes	15 (23%)

Abbreviations: BM = bone marrow; IPSS-R = revised International Prognostic Scoring System; LGL = large granular lymphocyte; MDS =myelodysplastic syndrome; NIH = National Institutes of Health; PNH = paroxysmal nocturnal hemoglobinuria; t-MDS = therapy-relatedmyelodysplastic syndrome; WHO = World Health Organization.

Hematologic Response Criteria and Adverse Events

Hematologic response was assessed using the International Working Group 2006 response criteria for patients with pretreatment hemoglobin < 11 g/dL, platelets $< 100 \times 10^9$/L, or