Determining which patients with myelodysplastic syndrome will respond to immunosuppressive treatment

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Anecdotal observations of hematologic improvement in patients with myelodysplastic syndrome (MDS) given immunosuppressive treatment and a greater than chance association of MDS with autoimmune disorders[1] led us, in 1995, to start a prospective trial of antithymocyte globulin (ATG) to treat the cytopenia of MDS. We reported a 33% response, defined as a durable freedom from transfusion requirement, in 61 patients given a 4-day course of ATG. Responders also had improved platelet and neutrophil counts and fewer of these patients had transformation into acute leukemia when compared with non-responders.[2]

In 1998, cyclosporine A (CSA) was also reported to improve cytopenias in MDS.[3] *In vitro* findings supported the hypothesis that immunosuppressive treatment worked by blocking a clonally expanded CD8 T-cell population, which suppressed progenitor cell proliferation.[4] Subsequently a number of trials of immunosuppressive treatment in MDS patients with cytopenia confirmed that therapy with ATG, CSA, or combinations of the two can produce substantial clinical improvement in cytopenias in some patients with MDS (reviewed in Barrett *et al)*.[5] The multicenter study from Scandinavia reported in this issue by Broliden and colleagues[6] is further evidence that ATG and CSA can improve cytopenias in MDS.[6] Broliden *et al*. found that 6/20 (30%) patients had improvement in their blood counts, and responses were sustained beyond 3 years in two of these patients. The authors conclude that immunosuppressive treatment is only effective in a minority of younger patients with low risk MDS.

Reported response rates in published series for immunosuppressive treatment vary between 0-66%.[6] These differences could be due to heterogeneity and small study group size, as well as to variations in treatment approach and response criteria. Within the constraints of small case series, investigators have sought to determine factors predictive for response. There is a consensus that immunosuppressive treatment is mainly effective in refractory anemia (RA), but a few patients with RA and excess blasts have responded and also some with RA with ringed sideroblasts.[7-9] Other criteria for response are patient's age and cytopenia: in our first report of risk factors in 61 patients treated with ATG, low platelet counts and younger age were independent factors for response in a multivariate analysis.[2] These two features recur in responders described in other reports, notably in the current report from Scandinavia. Factors with no independent prognostic value in our series were PNH abnormality, karyotype and marrow cellularity. Nevertheless, because of the assumption that immunosuppressive treatment is only effective in borderline MDS overlapping with severe aplastic anemia, there remains a popular misconception that marrow hypocellularity is the most important predictive factor for response to immunosuppressive treatment. Genetic factors may also be important: the DR15 HLA type was found to be strongly predictive for response to ATG/ATG+CSA in MDS patients treated at the NIH.[9] In a more recent analysis of 105 NIH MDS patients given immunosuppressive treatment, only DR15, patient's age, and interval between first transfusion and treatment with immunosuppressive treatment were independent factors in multivariate analysis. A simple score combining HLA-DR type, age and transfusion interval sufficed to define the probability of response as low (0-40%) or high (41-100%).[10] The score was validated in our own series of patients, but it will be important to see whether its strong predictive value is upheld in treatment series from other centers. The powerful predictive value of these factors has prompted us to speculate about the biological basis for responsiveness to immunosuppressive treatment. Is MDS in younger people a different disease? Do genetic differences in immune responsiveness govern the response and why is it important for success to start immunosuppressive treatment early in the course of anemia? In re-examining our recent data on 129 MDS patients treated with immunosuppression we noted that 33/39 responders were under the age of 60 years and age was the most significant factor predicting response to therapy ($p<0.0001$). Interestingly, the responders included nine of the 12 patients with trisomy 8 (*unpublished data*). We have recently found that patients with trisomy 8 MDS have marked clonal CD8 T-cell expansions, and that such T cells strongly inhibit growth of trisomy 8 but not residual normal progenitors. Paradoxically, trisomy 8 cells appear to escape Fas-mediated death and persist in the marrow despite hematologic recovery after immunosuppressive treatment. Our working hypothesis is that a T-cell attack on the marrow creates a selection pressure for clonal expansion of a trisomy 8 population, supporting the hypothesis that autoimmune attack on hematopoiesis can be provocative for the development of MDS.[11,12] The association of MDS with HLA-DR15 is intriguing in this respect: not only is HLA-DR15 a favorable prognostic factor for response to immunosuppressive treatment, it is also increased in frequency in MDS

patients.[9] DR15 may be a marker for, or function directly as an immune response gene; it is associated with a reduced frequency of acute GVHD and several autoimmune syndromes.[13] It is thus possible that responsiveness to immunosuppressive treatment in MDS identifies a subset of individuals who have an autoimmune disorder which drives the marrow to develop MDS.

Apart from the etiological unknowns, there are still unanswered questions about the best way to deliver immunosuppressive treatment. Would more powerful immunosuppressive schedules increase the response rates? Is ATG best combined with CSA? Tumor necrosis factor (TNF) is elevated in MDS, probably as a result of T-cell activation during the autoimmune attack on marrow cells. Deeg and colleagues[14] recently combined ATG with the anti-TNF agent etanacerpt as a way to enhance the blockade of T-cell-induced myelosuppression. Their results are promising because the treatment combination had low toxicity, but achieved a 46% response rate.[14]

Until the pathogenesis of cytopenia in MDS is better understood, the predictive algorithm, which requires only a knowledge of the patient's age, duration of transfusion and HLA-DR type, remains the most easily tested means for making treatment decisions in cytopenic MDS patients. Improved treatment strategies could then be explored in a targeted, responsive subgroup.

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