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Azacitidine in Myelodysplastic Syndromes

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The median age at diagnosis of the myelodysplastic syndromes (MDS) is approximately 70 years. As MDS represents a chronic leukaemia, and early initiation of therapy has never been shown to provide a survival advantage over treatment started when signs or symptoms progress, therapy should be initiated under one of two conditions:

- the disease has advanced to a 'late' phase (patients with >5% myeloblasts in their blood or bone marrow, or those classified by the International Prognostic Scoring System [IPSS][1] as Int-2 or High, in whom progression to acute myeloid leukaemia or death from MDS is a *fait accompli*); or
- the disease is at an 'early' phase (patients with <5% myeloblasts or IPSS classifications of Low or Int-1) and patients require blood transfusions so frequently that their quality of life suffers and this outweighs the potential adverse effects of chemotherapy.

Azacitidine is a nucleoside analogue that works through hypomethylation to induce cell differentiation and expression of silenced genes, and is the only drug approved by the US FDA for the treatment of MDS. This approval is based on the results of a randomised, controlled trial in which patients who received azacitidine showed response rates (complete and partial) of 23%, with a further 37% experiencing haematological improvement.[2] Response rates were similar in patients with early or late phase MDS. Important caveats to the interpretation of this study include the response criteria used, which preceded the International Working Group criteria[3] (and which would have called for maintaining a response for 8, rather than 4, weeks), and the inclusion of early-phase MDS patients who were not all transfusion-dependent. These patients did not necessarily require therapy and should not be exposed to the adverse effects of azacitidine, which included grade 3 or 4 leukopenia in 59%, granulocytopenia in 81%, thrombocytopenia in 70% and infection related to therapy in 20% of patients. It is not known from this study how many patients were able to receive the full 7-day cycle of therapy every 28 days, though, in practice, this dosage schedule is difficult, as most clinics are not open 7 days continuously. The optimal number of cycles of therapy has not been defined.

Azacitidine represents an exciting advance in therapy for MDS, and it is the first agent to show combined response rates and haematological improvements in >50% of patients. It should be considered a first-line therapy in patients with late-phase MDS, and should be given for a minimum of four cycles before response is assessed and at least three additional cycles, depending on subsequent response. ▲

References

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