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Azacitidine in Myelodysplastic Syndromes

A Viewpoint by Valeria Santini

Department of Haematology, University of Florence, Florence, Italy

Therapy for myelodysplastic syndromes (MDS) remains nonspecific and based on supportive care for the great majority of patients, while only a very small subgroup of young patients can anticipate a cure by high-dose chemotherapy and bone marrow transplantation. MDS are a heterogeneous group of diseases characterised by several different molecular abnormalities, but hypermethylation of CpG islands in the promoter region of genes critical for cell cycle seems to be the most encountered, and thus possibly significant, alteration from a pathophysiological point of view. For this reason, a hypomethylating drug, such as low-dose azacitidine (50–100 mg/m^2), has been reckoned to be active and employed in the treatment of MDS.

Azacitidine is a pyrimidine analogue – a drug synthesised several decades ago and endowed with strong myelosuppressive potential – which is now experiencing a second, more productive 'youth', thanks to a better understanding of its mechanism of action at low doses as an inhibitor of DNA-methyltransferase. In fact, azacitidine has shown impressive efficacy (60% haematological improvement) in the treatment of all MDS subtypes in an otherwise desolate panorama. Most interestingly, azacitidine can be given as subcutaneous injection and it is reasonably well tolerated, inducing only a mild and transient myelotoxicity and infrequent nausea. These characteristics are fundamental to preserving and possibly improving quality of life in often depressed patients experiencing a chronic disease without any effective treatment. The dual advantage of being actively treated with a drug specific for MDS and of being at home, combined with the real improvement in haematological parameters shown in the majority of patients, makes azacitidine treatment a big step forward in the treatment of MDS patients.

Results of azacitidine therapy are striking in terms of overall haematological improvement, but still not in terms of complete response. Although azacitidine is the only drug known to modify the natural history of MDS (and thus has been approved by the US FDA for the treatment of any MDS FAB subtype), we still think that a more rigorous selection of patients to treat with this drug could boost the percentage of complete responders from 12% to more substantial figures. Using a molecular basis for selection of patients for treatment is obviously possible only if hypermethylated target genes relevant to the development of MDS are precisely determined. This is a hard and complicated task, but it could permit, in the future, the employment of azacitidine as a precisely targeted drug and allow the epigenetic therapy of MDS to have even more successful results. ▲