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Decitabine in Myelodysplastic Syndromes

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5-aza-2′-deoxycytidine (decitabine) is a nucleoside analogue with the capacity to induce global and gene-specific DNA hypomethylation. It exerts this effect by trapping DNA methyltransferase to DNA. This hypomethylating effect is DNA replication dependent. DNA methylation is an epigenetic modification of DNA that has a role in the control of gene expression regulation. Aberrant DNA methylation of multiple promoter cytosone phosphoguanine (CpG) islands is a common characteristic of cancer and leukemia, and in particular of myelodysplastic syndrome (MDS). Interest in the use of hypomethylating in MDS is derived from the realisation that aberrant DNA methylation is reversible, and that this process is associated with gene reactivation. Based on this concept, a significant effort is underway to develop drugs with hypomethylating activity as antineoplastic agents. Indeed, the first drug approved for MDS was 5-azacitidine, another hypomethylating nucleoside analogue.[1]

The use of decitabine in MDS was pioneered by Wijermans and Lübbert in Europe.[2] In their trials, decitabine was administered at a dose of 15 mg/m^2 intravenously (IV) over 4 hours every 8 hours, daily for 3 days. Based on the results of their studies, a randomised clinical trial comparing decitabine with supportive care was conducted in the US; this study was recently published.[3] In this trial, decitabine was superior to supportive care in terms of response, time to acute myeloid leukaemia (AML) transformation and quality of life. These results were similar to those observed with the initial randomised study of 5-azacitidine in MDS.[1]

One of the main limitations of the schedule of decitabine administration used in these studies is that it requires hospital admission. To overcome this problem, and based on *in vitro* data suggesting that lower doses of decitabine are more effective at hypomethylating DNA, a low-dose outpatient schedule of decitabine, initially tested in a phase I study,[4] has been developed. With this schedule, decitabine is infused IV at a dose of 20 mg/m^2 over 1 hour, daily for 5 days. This schedule has shown significant activity in a randomised phase II study. In this study, Kantarjian et al.[5] demonstrated a complete response rate of 47% with a 2% mortality at 6 weeks. Overall survival with decitabine was superior to that observed with intensive chemotherapy in a similar cohort of patients.[5]

In summary, a low-dose schedule of decitabine has an excellent toxicity profile and significant activity in MDS. Further studies are ongoing to confirm the activity of decitabine in MDS and elderly patients with AML. ▲

References

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