

NEW DRUG REVIEW

Perspectives on Recent FDA Drug Approvals in Hematology and Oncology

Intravenous Azacitidine for MDS

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Azacitidine (Vidaza, Pharmion) was first synthesized in 1974 in Czechoslovakia. It was originally studied as a high-dose chemotherapeutic agent in the setting of acute leukemias, for which it did not achieve regulatory approval in the United States. Subsequently, via *in vitro* experiments, azacitidine was found to inhibit DNA methylation and induce cell differentiation. In the late 1980s, Dr. Lewis R. Silverman and colleagues of the Cancer and Leukemia Group B (CALGB) began to examine azacitidine in myelodysplastic syndromes (MDS) as a presumed inducer of terminal differentiation. In this setting, azacitidine was found to be quite active clinically. The early studies in this setting administered azacitidine intravenously as a continuous infusion, due to its instability in an aqueous solution. In the interest of offering a more convenient route of administration, a subcutaneous regimen, which could be administered on an outpatient basis, was developed. After a series of phase II trials, a CALGB trial (9221) randomized patients with MDS to either subcutaneous azacitidine or observation alone. Responses to azacitidine were conclusively demonstrated in this trial, along with findings that azacitidine delayed progression to more dense forms of leukemia. Furthermore, quality of life was shown to be improved by azacitidine in comparison to observation alone. These data led to the initial regulatory approval for azacitidine in MDS in the United States.

The US Food and Drug Administration (FDA) required, at the time of the initial application for azacitidine for the treatment of MDS, a small bioequivalence study. In that study, patients received either intravenous or subcutaneous doses of azacitidine, and patients' pharmacokinetics were assessed. This study was intended to demonstrate the bioavailability of the drug. Intravenous administration was shown to have similar pharmacokinetics to subcutaneous administration.

Based on these data as well as a study of stability and compatibility and a pharmacokinetic modeling study, the FDA recently granted regulatory approval to the intravenous regimen of azacitidine. Like the subcutaneous regimen, the dose administered is 75 mg/m². This intravenous dose is given over a period of 10–40 minutes for 7 days every 4 weeks in a clinic.

The systemic toxicities seen are similar with each formulation. The most common adverse reactions with subcutaneous administration are nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, fatigue, injection site erythema, constipation, neutropenia, and ecchymosis. Other adverse reactions seen with intravenous administration are petechiae, rigors, weakness, and hypokalemia.

Because the intravenous formulation of azacitidine is as efficacious as the subcutaneous formulation and is not associated with any skin reactions, it offers a viable alternative available to clinicians treating patients with MDS. Furthermore, the intravenous formulation may be associated with some improvements in quality of life by avoiding skin reactions.

Suggested Readings

Silverman LR, McKenzie DR, Peterson BL, et al; Cancer and Leukemia Group B. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol*. 2006;24:3895-3903.

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Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. *J Clin Oncol*. 2002;20:2429-2440.