

NEW DRUG REVIEW

Perspectives on Recent FDA Drug Approvals in Hematology and Oncology

Recent Experience With Decitabine in MDS

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The myelodysplastic syndromes (MDS) are a group of disorders characterized by increased proliferation of the bone marrow and ineffective hematopoiesis. In many cancers, including MDS, several processes interfere with the cells' ability to differentiate normally, which leads to insufficient production of normal cells. Two of these processes are methylation, meaning insertion of methyl groups at critical sites of gene expression, and histone deacetylation. Decitabine (Dacogen, SuperGen/MGI Pharma) is a drug that induces hypomethylation. Hypermethylation is a process common in MDS and is promiscuous to many other cancers. MDS was thus used as a paradigm for research into decitabine, which is a drug that has been in use for decades. It was used in the 1980s at high doses, 1–2 g/m², which were prohibitive in terms of suppressing the bone marrow. In our recent research, we developed a low-dose decitabine schedule that can still produce the process of hypomethylation without inducing the excessive myelosuppression: approximately 100 mg/m² daily per course, which is 5–10% of the dosages that were used in the 1980s. A randomized study in MDS then proceeded, in which patients were randomized to receive either decitabine at a dose of 15 mg/m² given intravenously over 3 hours every 8 hours for 3 days (at a dose of 135 mg/m² per course), repeated every 6 weeks, or best supportive care. A total of 170 patients were enrolled. This study, reported in the April 15, 2006, issue of *Cancer*, showed that patients who received decitabine did better in terms of improved blood cell counts, reduced need for blood transfusions, and delayed time to disease progression to acute myeloid leukemia (AML). These results led to the approval by the US Food and Drug Administration of decitabine in May 2006 for the treatment of MDS. The approved schedule requires a 3-day continuous infusion of the drug in the hospital over four cycles.

Decitabine has been shown to be safe in the treatment of MDS. Toxicities outside the bone marrow are

uncommon. Diarrhea or temporary abnormalities in the liver chemistry have been observed, but these toxicities are minor. The one toxicity of note is suppression of the blood counts, which is not of great concern either. Approximately 20% of patients on any course of decitabine become febrile and require hospitalization, which is considered a manageable toxicity.

Since the approval of decitabine, additional work has been undertaken with a modified infusion schedule. In this study, patients received decitabine 100 mg/m² per course every 4 weeks in 3 different schedules: either 20 mg/m² intravenously daily for 5 days, 20 mg/m² subcutaneously daily for 5 days, or 10 mg/m² intravenously daily for 10 days. The short infusion given over 1 hour daily for 5 days produced the best results and was quite effective. In that regimen, which is now the standard regimen in use at the University of Texas M. D. Anderson Cancer Center, we obtained complete remissions in 35% of patients with MDS, and approximately 70% of patients improved in terms of their low blood counts. These results were published in the January 15, 2007, issue of *Blood*. The results with decitabine in MDS were then compared to those with intensive chemotherapy: decitabine produced lower mortality and better survival than intensive chemotherapy, which is one of the standards of care in MDS. The responses seen with decitabine therapy were correlated with the degree of hypomethylation.

The next step in research with decitabine is to try to improve upon the results seen thus far. One way to improve the results is to target the other process in MDS, histone deacetylation. Histone deacetylase inhibitors also show activity in MDS. Valproic acid and vorinostat (Zolinza, Merck) are two histone deacetylase inhibitors of interest. We have opened a study of decitabine with or without valproic acid, which will ultimately show whether valproic acid in combination with decitabine will improve the results over decitabine alone. Another avenue of research is the expansion of the experience with decitabine to AML. Decitabine will be administered to elderly patients with AML and will also be used as maintenance therapy in patients who achieve a complete remission.

Suggested Readings

Kantarjian H, Oki Y, Garcia-Manero G, et al. Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. *Blood*. 2007;109:52-57.

Kantarjian H, Issa JB, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer*. 2006; 106:1794-1803.