

ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Lenalidomide in Myelodysplastic Syndromes

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H&O How does lenalidomide achieve its therapeutic effects in patients with myelodysplastic syndromes?

AL Lenalidomide (Revlimid, Celgene) is part of a proprietary class of drugs called immunomodulatory drugs (IMiDs) that share a structural backbone with thalidomide (Thalomid, Celgene) as well as its cytokine- and immune-modifying properties. The name of this class is somewhat misleading because the effects of these drugs are not only immunologic; rather, they have broad pharmacologic effects. The unique pharmacologic profile includes the modulation of a number of ligand- and receptor-induced signals in the microenvironment surrounding the diseased clone and the clone itself. This dual effect accounts in part for the superior activity of these agents in myelodysplastic syndromes (MDS) as well as multiple myeloma. The IMiDs' biologic effects extend from the suppression of inflammatory cytokine elaboration, angiogenic response, and cell adhesion to potentiation of antigen-induced immune response. In the setting of MDS, lenalidomide has other effects that contribute to its hematopoiesis-promoting effects—such as enhancement of erythropoietin receptor signaling, which is usually suppressed in MDS erythroid precursors—thereby restoring effective erythropoiesis in normal and malignant progenitor cells. Additionally, in MDS characterized by deletion of chromosome 5q [del(5q)], lenalidomide is directly cytotoxic and, as a consequence, suppresses the clone. Our laboratory presented findings at the 2007 annual meeting of the American Society of Hematology (ASH) that identified two genes that are deleted within

the common deleted region of del(5q) MDS that result in allelic haploinsufficiency of two critical cell-cycle regulatory enzymes that are sensitive to inhibition by lenalidomide. These findings may account for some of the selective cytotoxicity of lenalidomide for del(5q) MDS clones.

H&O How has lenalidomide's efficacy compared to that of thalidomide in MDS?

AL The initial trial of thalidomide in patients with MDS by Dr. Azra Raza and colleagues included 83 patients and yielded a 19% hematologic improvement rate, most of which was erythroid in nature. A comparison of thalidomide and lenalidomide in the laboratory, showed that lenalidomide has 1,000-fold or more potency than thalidomide in suppressing endotoxin-induced tumor necrosis factor generation from monocytes. Also, thalidomide has a less specific effect in del(5q) MDS. There does not appear to be a cytokine-specific predilection associated with thalidomide.

H&O Which patients are the best candidates for therapy with lenalidomide?

AL Lenalidomide has been approved by the US Food and Drug Administration for the treatment of patients with del(5q) MDS with transfusion-dependent, low- or intermediate 1-risk disease by the International Prognostic Scoring System (IPSS). For such patients in the registration trial that included 148 participants, 76% had a transfusion response and 67% became transfusion-free, with a median duration of transfusion independence of 2.5 years. Interestingly, approximately 73% of patients evaluable for cytogenetic response achieved at least a 50% reduction in the abnormal clone. Overall, approximately 45% of patients achieved a complete cytogenetic remission after 6 months of therapy. There is close concordance between cytogenetic response and achievement of transfu-

sion independence. All patients who achieved complete or partial cytogenetic response achieved transfusion independence. Suppression of the del(5q) clone therefore appears to be necessary to achieve the robust erythroid response required for transfusion independence.

The multicenter MDS-002 trial had the same design and was performed in 214 MDS patients without del(5q). This trial administered lenalidomide in the same fashion as the registration trial to transfusion-dependent patients who had lower-risk disease. Among these patients, 43% had a transfusion response according to International Working Group (IWG) 2000 criteria (ie, $\geq 50\%$ reduction in transfusions). Overall, 26% of patients achieved transfusion independence that was sustained for a median of 41 weeks. Cytogenetic and pathologic responses were infrequent in this population. Only 19% of patients had cytogenetic improvement, and complete cytogenetic remission was rare. There was no specific cytogenetic abnormality that appeared to be more responsive than any other. Toxicity also differed between the del(5q) patients and the non-del(5q) patients in MDS-002 study. Less than 25% of the latter patients experienced grade 3 or higher neutropenia or thrombocytopenia, whereas over 50% of del(5q) patients experienced these toxicities in the initial 8 weeks of therapy. In del(5q) MDS, this toxicity profile would be expected, given lenalidomide's action to rapidly suppress the clone. A recent analysis of the two trials showed that those del(5q) patients who experienced a 50% or greater reduction in platelet count in the first 8 weeks of therapy had a significantly higher probability of achieving transfusion independence. Early myelosuppression therefore represents a surrogate marker for successful suppression of the clone, leading to transfusion independence in del(5q) patients. There is no similar relationship in patients who lack del(5q), in whom lenalidomide acts to directly potentiate erythropoiesis in the existing MDS clone.

H&O Can myelosuppression be used as a prognostic marker by clinicians?

AL Myelosuppression in the first 8 weeks is a good marker that clonal suppression is occurring. Therefore, it is an indicator of the likelihood of achieving transfusion independence. Additionally, an understanding of the prognostic value of early myelosuppression should allay fears that it is an unnecessary toxicity.

H&O Have the pivotal data on lenalidomide been updated based on longer follow-up?

AL The data from the del(5q) registration trial have been updated as recently as November 2007. Furthermore, all

168 patients with del(5q) who have been treated on all trials of lenalidomide in the United States have been analyzed for long-term outcome. The first safety and efficacy trial began in 2002, and the registration trial began in 2003. The median follow-up is more than 4 years. Some patients have been receiving lenalidomide for over 6 years. Taking this treated population, the median duration of response (ie, transfusion independence) was 2.2 years. There are patients who are still transfusion-free and continuing lenalidomide treatment after 6 years. In a multivariate analysis of features associated with longer transfusion independence, it was found that 5q- syndrome, lower transfusion burden, low-risk IPSS, and younger age all predicted for longer response duration. It is interesting to note that among covariates associated with longer overall survival, cytogenetic response was by far the most powerful independent variable, with a hazard ratio of 5.2. In fact, Kaplan-Meier estimates of overall survival adjusting for the interval from diagnosis to the date of initiation of therapy showed that cytogenetic response was the most powerful predictor for extended survival. Cytogenetic responders had not reached the median duration of overall survival, with a 10-year survival estimated at 78% compared to 4% for nonresponders or those not evaluable for cytogenetic response. Furthermore, there was a lower risk for transformation to acute myeloid leukemia (AML) in cytogenetic responders compared to nonresponders. Based on these retrospective long-term follow-up data, it appears that lenalidomide may have the potential to alter the natural history of the disease, particularly in those patients with higher-risk features, such as greater cytogenetic complexity, and, as a consequence, favorably affect clonal evolution.

H&O What treatment options are available for patients who lose response?

AL Many patients who lose their response to lenalidomide experience it when receiving lower doses of the drug (eg, 5 mg every other day or 5 mg three times per week). The question therefore arises whether these patients are simply receiving an inadequate dose to sustain suppression of the clone. Or, are they resistant to the drug as patients with chronic myelogenous leukemia may become while receiving imatinib (Gleevec, Novartis) due to emergence of mutations in the drug binding site (ie, true intrinsic clonal resistance)? The answers to these questions are unclear. There are anecdotal reports that responses have been restored upon dose escalation to 10 mg/day, but, in my opinion, many patients who lose their response are likely to be truly resistant. Therefore, using a different therapy is indicated. Such lower-risk patients are candidates for therapy with a methyltransfer-

(Continued on page 311)

(Advances in LLM, continued from page 272)

ase inhibitor. Given its favorable toxicity profile, azacitidine (Vidaza, Pharmion) would be a reasonable agent to consider for the next therapeutic option.

H&O What research is ongoing with lenalidomide in patients with different risk profiles?

AL There are several ongoing studies in this setting. Preliminary results from a French MDS Study Group trial were presented at the ASH annual meeting in 2007. This trial enrolled higher-risk (ie, intermediate 2- and high-risk) patients with del(5q) MDS. This study showed a 20–25% response rate to lenalidomide. As would be expected, these patients had a prevalence of cytopenias at the outset, and given that the trial employed the same guidelines as the pivotal trial for stopping treatment when platelet counts dropped below 50,000/ μ L or neutrophil counts below 500/ μ L, most patients were not exposed to a sufficient duration of lenalidomide treatment to achieve clonal suppression necessary for response. A phase I trial led by Dr. Mikkael Sekeres at Cleveland Clinic is evaluating the safety and preliminary activity of combination therapy with lenalidomide and azacitidine in patients with higher-risk MDS. A trial by the Southwest Oncology Group (SWOG) is currently investigating an augmented dose of lenalidomide in the treatment of elderly patients with AML with del(5q). Patients with this disease historically have an overall complete remission rate with standard induction chemotherapy of 17%. Case reports of complete remissions in patients with del(5q) AML have been previously reported with lenalidomide. Other studies are beginning that combine vaccine therapy with lenalidomide in higher-risk non-del(5q) MDS, with the notion that an immune potentiator may augment the response to the vaccine. Also, one trial is testing lenalidomide in sequence with standard induction chemotherapy in patients with del(5q) MDS. In lower-risk MDS, given the effect of lenalidomide to enhance erythropoietin activity, the Eastern Cooperative Oncology Group, SWOG, and Cancer and Leukemia Group B are investigating lenalidomide alone or in combination with epoetin- α (Procrit, Ortho Biotech) in patients who have failed erythropoietin or have a poor response profile.

H&O Have other analogs of thalidomide been investigated in MDS?

AL Actimid (Celgene), also known as pomalidomide or CC4047, and lenalidomide have similar effects on CD34-positive progenitor cells, promoting expansion of the erythroid burst population. Actimid has been studied more extensively in multiple myeloma. Its greater erythropoietic effect is attractive for research in MDS, however, experience in myeloma suggests that it is more myelosuppressive than lenalidomide. CC11006 (Celgene) is a less myelosuppressive agent, based on animal models, with comparable potency to lenalidomide that is currently completing initial investigation in MDS.

Suggested Readings

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