ADVANCES IN LLM

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

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Lenalidomide in CLL: What Is the Optimal Dose?

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H&O What are the current treatment approaches for chronic lymphocytic leukemia (CLL)?

CW In Europe and the United States, the standard frontline treatment for patients with CLL and no relevant comorbidity is chemotherapy with fludarabine and rituximab (Rituxan, Genentech/Biogen Idec). In Europe, cyclophosphamide is also added to this regimen. For the many patients with CLL who suffer from significant comorbidity and/or are over the age of 65, there is some debate over whether this approach should be considered the standard. Aside from chlorambucil, bendamustine (Treanda, Cephalon) monotherapy is also being used in these patients, but more studies are needed.

There is medical need for other treatment options in patients with relapsed CLL or patients who are refractory to purine analogues. We still need improvements for patients with very high-risk cytogenetic alterations, such as p53 mutation or 17p deletion. Maintenance therapy in CLL remains undefined as compared with other indolent lymphomas. Elderly patients are still a group we need to focus on.

H&O How is the novel agent lenalidomide being used in patients with CLL?

 ${\bf CW}$ Lenalidomide (Revlimid, Celgene) is a new candidate in the field of CLL therapy, and we are learning

more and more about this interesting drug. Right now, most evidence supports continuous dosing over a 3 plus 1 regimen with 3 weeks of treatment followed by 1 week off the drug, as has been used before. There has been a fair amount of discussion regarding the best starting dose, and I think there is some consensus as to what is safe, but improvements are needed.

H&O What is the mechanism of action of lenalidomide?

CW Lenalidomide is generally considered to be an immunomodulating agent, so it is not a classic cytotoxic drug. It is thought that lenalidomide works not through direct effects on the tumor cell but rather through modulation of tumor cells, especially of immune cells—specifically CD4 T cells and natural killer cells. It has recently been observed that during treatment, lenalidomide boosts immunoglobulin levels, which is not seen with classic cytotoxic drugs.

H&O What do data suggest about the use of lenalidomide in patients with CLL?

CW At the M.D. Anderson Cancer Center, Ferrajoli and colleagues found that an objective response could still be induced in approximately half of the pretreated patients. Chen and coworkers from the University of Toronto observed that first-line use of lenalidomide in patients with CLL is well tolerated with a conservative approach and slow dose escalation. Lenalidomide-induced molecular changes, such as restoration of so-called immune synapses, revealed promising insights into the drug's immunomodulatory mechanisms in CLL, as Dr. Gribben's group in London has nicely demonstrated.

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The elderly are one group of patients in whom I think this drug should be more developed. Several trials have studied lenalidomide in the elderly population, alone or in combination with rituximab. In a study by Badoux and associates in elderly patients with untreated CLL, lenalidomide was safe and induced complete responses and partial responses. Other groups of patients who might benefit from lenalidomide include those who are at high risk or who are refractory to fludarabine. Lenalidomide, perhaps in combination with antibodies, might be able to produce remissions in these patients.

H&O Is lenalidomide associated with adverse events?

CW There are some very specific side effects that can be attributed to this drug, such as tumor flare reaction. This toxicity seems to be associated with infiltration of immune cells in the lymph nodes, so there is swelling at the beginning of therapy—which should not be misdiagnosed as progressive disease. The other side effect we have had to learn to address is tumor lysis syndrome, which can occur when the drug is not used appropriately. Lenalidomide is also associated with some of the doselimiting toxicities that are seen with other chemotherapy agents, such as myelotoxicity, especially neutropenia and thrombocytopenia.

H&O What were the results of your phase I study of lenalidomide in patients with relapsed/refractory CLL?

CW We presented the final results of this study at the 2010 American Society of Hematology meeting. The goal was to find the maximum tolerated dose (MTD) for patients with relapsed/refractory CLL. This study was a worldwide effort and included 52 heavily pretreated patients. The majority of patients had high-risk genomic abnormalities and bulky disease.

We started with a very low dose of lenalidomide (2.5 mg/day) and during the trial, we safely titrated the dose up to 20 mg/day. The MTD was not even reached at this dose. We found that 2.5 mg was a safe starting dose, but it was associated with low efficacy. The partial

response rate was approximately 12%. The conclusion was that we have to further optimize the dosing regimen with lenalidomide in patients who have relapsed/refractory CLL.

H&O What is known about the efficacy and safety of lenalidomide in the treatment of CLL, and how do dosing regimen changes affect these factors?

CW Neutropenia and thrombocytopenia are concerns with this drug, as are severe tumor flare and tumor lysis syndrome. I think we have learned that step-wise dosing is one clue to solving this problem. Another approach is to start very low. I do not think that 2.5 mg has to be used; in reality, the starting dose can probably be in the range of 5–10 mg, followed by a step-wise escalation. This question will be addressed in the ongoing phase II CLL-009 trial, which is examining 3 different starting doses: 5 mg/day, 10 mg/day, and 15 mg/day. The doses will increase in a step-wise fashion every 28 days, according to tolerability, to a maximum of 25 mg/day.

Suggested Readings

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