CLL in Focus
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Use of Venetoclax Combination Regimens in Chronic Lymphocytic Leukemia

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H&O Is single-agent venetoclax a common treatment for chronic lymphocytic leukemia (CLL)?

CT In CLL, venetoclax (Venclexta, AbbVie/Genentech) is typically not used as a single agent; it is probably best used in combination with an antibody. In relapsed/refractory CLL, single-agent venetoclax leads to a partial response or better in approximately 75% of patients. Approximately 20% of patients will have a complete remission.

H&O How might the mechanisms of action of venetoclax and antibodies work together?

CT There is a suggestion that the resistance mechanism of venetoclax may be partly related to upregulation of other *BCL2* families. Some of this evidence experimentally has shown that antibody therapy lowers the apoptotic threshold of the cancer cells—which makes venetoclax work better—and also may help to mitigate some of the compensatory rise in other *BCL2* family members. Antibodies therefore help to mitigate some of the resistance to venetoclax.

H&O Which antibodies have been studied with venetoclax?

CT There are 2 main settings. Venetoclax has been combined with rituximab, an anti-CD20 monoclonal antibody, in the relapsed setting and with obinutuzumab in the frontline setting. The phase 3 MURANO study in relapsed/refractory CLL compared venetoclax plus rituximab vs bendamustine plus rituximab. The overall response rate was 92% with venetoclax plus rituximab vs 72% with bendamustine plus rituximab. The complete remission rates were 27% vs 8%, respectively. Progression-free survival was superior with prolonged follow-up, for a median of 54 months with venetoclax plus rituximab vs 17 months with bendamustine plus rituximab. The 5-year rate of overall survival was 82% vs 62%, respectively.

For the frontline treatment of CLL, venetoclax has been studied with obinutuzumab (Gazyva, Genentech), which is another anti-CD20 monoclonal antibody. The CLL14 trial compared venetoclax plus obinutuzumab against chlorambucil plus obinutuzumab. The overall response rate was 85% for venetoclax plus obinutuzumab vs 71% for chlorambucil plus obinutuzumab. The complete remission rates were 50% vs 23%, respectively. At the latest update of this study, the 4-year rate of progression-free survival was 74% with venetoclax plus obinutuzumab vs 35% with chlorambucil plus obinutuzumab. No difference in overall survival has been observed thus far.

H&O What is the toxicity profile when venetoclax is combined with antibody therapy?

CT The overall experience has been that the addition of an antibody to venetoclax increases the rate of neutropenia. However, in the vast majority of patients who

develop neutropenia, this event does not require a dose reduction or lead to infection. In general, the cases of neutropenia are asymptomatic. During the initial studies, there were some concerns that the addition of an antibody to venetoclax might increase the risk for tumor lysis. In fact, the reverse has been seen. For example, in the CLL14 study of venetoclax and obinutuzumab in the frontline setting, patients were treated with obinutuzumab before they received their first dose of venetoclax. In this study, starting treatment with obinutuzumab first led to debulking of the tumor before administration of venetoclax. No cases of clinical tumor lysis syndrome were reported.

H&O Was anything learned about venetoclax as it moved from trials to the clinic?

CT There is often a suspicion that trial populations were cherry-picked, and that outcomes among patients in the clinic may be inferior. For venetoclax, however, real-world analyses from multiple groups have shown that the data from trials translate very well to the clinic. In both the relapsed and frontline settings, the available evidence suggests that the response rates, as well as the duration of response and tolerability, are just as good in the real world as in the clinical trials. The only difference concerns tumor lysis syndrome, which is the major side effect seen with venetoclax. In the longer clinical trials, especially in the early stages, the investigators adopted a very conservative, aggressive monitoring schedule for tumor lysis syndrome. The protocol followed in trial centers was not reproducible in the community. Therefore, a simplified version of the monitoring schedule (as detailed in the package insert) was tested and shown to be safe, and then rolled out to the community. Based on the cumulative experiences throughout the community, the simplified monitoring schedule for tumor lysis syndrome is safe. There have been no reports of excess tumor lysis syndrome associated with venetoclax.

H&O Are there patient subgroups more likely to benefit from treatment with venetoclax in combination with antibody therapy?

CT Venetoclax plus an antibody works across all types of patients with CLL, including those who are refractory to fludarabine and those who have *TP53* mutations, the 17p deletion, or a complex karyotype. The combination is effective across the spectrum of patients with poor prognostic features. Patients who are particularly suitable for venetoclax-based therapy are those with high-risk genomic features, such as 17p deletion and complex karyotype, because they are more likely to be resistant to chemotherapy. Having said that, this same group of patients are probably just as likely to respond to Bruton's tyrosine kinase (BTK) inhibitors. There are no data to guide selection of venetoclax-based therapy vs BTK inhibitor–based therapy. The choice is largely based on physician preference and patient circumstances.

An advantage to venetoclax-based therapy is the limited duration. Patients receive treatment from 12 to 24 months. In contrast, treatment with BTK inhibitors is indefinite. There is a slight belief, albeit unproven by phase 3 studies, that in the frontline setting in patients with 17p-deleted CLL, the treatment experience with continuous BTK inhibitors may be more favorable compared with fixed-duration therapy with venetoclax plus obinutuzumab. This observation, however, is based on comparisons across clinical trials, as there is no head-to-head comparison.

Venetoclax plus an antibody works across all types of patients with CLL, including those who are refractory to fludarabine and those who have *TP53* mutations, the 17p deletion, or a complex karyotype.

H&O What are the schedules for venetoclax plus antibody therapy?

CT There are 2 schedules. In the relapsed setting, venetoclax is administered first, and then rituximab is given afterward as consolidation. This strategy works well, but it does not protect against tumor lysis syndrome because patients are exposed to venetoclax right from the start. This regimen was evaluated in the MURANO clinical trial.

In the CLL14 trial in the frontline setting, obinutuzumab was administered before venetoclax. It appears that this schedule may be better at mitigating the risk for tumor lysis associated with venetoclax vs the schedule in which the antibody is given after venetoclax. Having said that, clinicians should follow the schedules established as the standard of care by the trials: the antibody after venetoclax in the relapsed setting, and the antibody before

venetoclax in the frontline setting. However, if I were able to redesign the study in the relapsed setting, I would probably administer the antibody first.

H&O Is there any promising research in this setting?

CT Currently, the most promising studies are evaluating the combination of BTK inhibitors and venetoclax. These 2 classes of drugs have different mechanisms of resistance. By combining them, it may be possible to overcome most mechanisms of resistance in a tumor. In several phase 2 studies, this 2-drug combination has led to a very high clearance rate of minimal residual disease (MRD), at approximately 75%. There are now fixed-duration regimens of the 2 drugs together. Patients in these clinical trials will receive 12 months of combination therapy with venetoclax plus ibrutinib or a similar drug. It is hoped that this type of combination will lead to a high MRD clearance rate that will allow patients to discontinue therapy after a fixed duration of, say, 12 to 24 months.

Disclosure

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Suggested Readings

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