CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Should Venetoclax Be Used With or Without Anti-CD20 Therapy for CLL?

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H&O Which patients with chronic lymphocytic leukemia (CLL) are eligible for treatment with venetoclax?

RF Nearly all patients with CLL are eligible for treatment with venetoclax (Venclexta, AbbVie) because the safety and tolerability of novel agents like venetoclax, Bruton tyrosine kinase (BTK) inhibitors, and phosphoinositide 3-kinase (PI3K) inhibitors do not depend on patient fitness. Factors that make me cautious about the use of venetoclax are a large tumor load and impaired creatinine clearance because of the risk for tumor lysis syndrome. BTK inhibitors and venetoclax are my first choices for the treatment of CLL. In those patients with contraindications to BTK inhibitors, such as bleeding or cardiac issues, venetoclax is the better option.

H&O Is the use of venetoclax a requirement with anti-CD20 therapy for CLL?

RF We have never had a trial that compared venetoclax alone with venetoclax plus an anti-CD20 agent, and therefore we do not know what contribution the anti-CD20 makes to venetoclax. The trials that led to the approval of venetoclax in CLL always included an anti-CD20 agent—either obinutuzumab (Gazyva, Genentech) or rituximab—which is why the US Food and Drug Administration approved venetoclax in combination with these agents for CLL. I do not think it is necessary to use an anti-CD20 agent with venetoclax; the efficacy of venetoclax/anti-CD20 regimens depends almost entirely on the venetoclax. The use of venetoclax and anti-CD20 monoclonal antibodies is driven by the way the trials were designed. Although 2 rationales exist for a benefit from the combination—reduction in risk for tumor lysis and synergy between the agents—the tumor lysis mitigation strategy outlined in the package insert has shown that venetoclax is safe without the use of anti-CD20 agents, and no study has demonstrated an improvement in outcomes with the addition of an anti-CD20 agent.

H&O Are there certain circumstances in which anti-CD20 therapy is useful in these patients?

RF I do think that anti-CD20 agents may be beneficial as tumor debulking agents, to obviate some of the risks for tumor lysis. Giving a patient 1 or 2 doses of obinutuzumab, for example, can make a dose escalation of venetoclax safer, so that hospitalization for tumor lysis monitoring is unnecessary. In most cases, however, anti-CD20 agents are not being used as pretreatment to avoid tumor lysis. When anti-CD20 agents are initiated at the same time as venetoclax, the benefits of reducing tumor lysis and hospitalization are not realized.

H&O What are the disadvantages of using anti-CD20 agents in combination with venetoclax?

RF Anti-CD20 agents are responsible for most of the toxicities associated with the combination regimen, which include depletion of normal B cells, hypogammaglobulinemia, an elevated risk for infection, and infusion reactions. Given that these agents add toxicities and do not

have a proven benefit, I think that they should not be used together with venetoclax until we have more data.

H&O Is the elevated risk for infection a special concern during the COVID-19 pandemic?

RF COVID-19 creates special concerns regarding the use of anti-CD20 agents, for 2 reasons. First, we know that anti-CD20 agents impair the body's ability to mount an immune response to a virus. If a patient receives an anti-CD20 agent and is then infected with SARS-CoV-2, the impaired ability to generate a humoral immune response can lead to a more severe course of infection. Likewise, if a patient has been vaccinated and then receives an anti-CD20 agent, any benefit from the vaccination in terms of humoral immunity may be lost.

Second, because anti-CD20 agents are administered via infusion, patients must come into the infusion center for prolonged appointments rather than stay in isolation. In addition, venetoclax treatment necessitates in-person visits for tumor lysis monitoring, although these visits are brief and should entail a low risk for viral exposure.

H&O How effective is venetoclax on its own?

RF Venetoclax is very effective when used as a single agent. The data on single-agent venetoclax have been generated in patients with relapsed/refractory CLL, who have demonstrated high response rates and long progression-free survival (PFS). The results for the single-agent studies are not as good as those for the combination studies, but that is primarily a consequence of differences in the populations studied: either relapsed vs treatment-naive or relapsed vs 17p-deleted. As a result, I think that the data we have underestimate the value of single-agent venetoclax. The most positive data we have are from the CLL14 study, which shows excellent long-term PFS with venetoclax plus obinutuzumab in patients who have treatment-naive CLL and a Cumulative Illness Rating Scale (CIRS) score above 6 or a creatinine clearance rate below 70 mL/min.

H&O Can you talk more about the CLL14 study?

RF CLL14 is a randomized phase 3 trial comparing 6 cycles of obinutuzumab plus venetoclax followed by 6 cycles of venetoclax vs 6 cycles of obinutuzumab plus chlorambucil followed by 6 cycles of chlorambucil in patients with treatment-naive CLL who are considered unfit for chemoimmunotherapy owing to a CIRS score above 6 or a creatinine clearance rate below 70 mL/min. The 432 enrolled patients, with a median age of 72 years, a median CIRS score of 8, and a median creatinine clearance rate of 66.4 mL/min, were randomized in a 1:1 ratio. At the American Society of Hematology (ASH) 2020 Annual Meeting, Dr Othman Al-Sawaf presented updated results demonstrating a 4-year PFS rate of 74.0% for venetoclax plus obinutuzumab vs 35.4% for chlorambucil plus obinutuzumab.

This study is important for 2 reasons. First, it demonstrates how effective venetoclax plus obinutuzumab is in patients with treatment-naive CLL. Second, and more importantly, as a fixed-duration regimen for treatment-naive CLL, it represents a paradigm shift in treatment strategy. Chemoimmunotherapy regimens were of fixed duration out of necessity, given the toxicities resulting from repeated treatments. Novel agents have thus far been investigated as continuous therapy until progression. The data from CLL14 provide an option for patients to receive 1 year of treatment followed by years of remission.

One caveat that needs to be considered when the fixed-duration venetoclax data are examined is that we really do not know what is the optimal duration of treatment. The use of 12 cycles of venetoclax was rather arbitrarily decided upon, and we do not know whether results would be even better if treatment were to be extended further. We might be, in essence, leaving efficacy on the table. Of course, if effective salvage therapy is possible after disease progression, there is no harm in holding therapy.

> We need to establish whether anti-CD20 agents really add to the benefit of venetoclax treatment.

In his presentation at the ASH virtual meeting, Al-Sawaf presented data on the deepening and lessening of responses during months 7 to 12 in patients on single-agent venetoclax in the CLL14 study, derived by using next-generation sequencing techniques to detect minimal residual disease (MRD) to a sensitivity of 10^{-6}. The more sensitive assessment of MRD allows the generation of data regarding changes in disease status that would not otherwise be available, and eventually it could provide insight into the clinical utility of MRD monitoring.

A second aspect of the study of Al-Sawaf and colleagues was to examine the proliferation of CLL cells after treatment discontinuation. Data could be generated because of the use of more sensitive MRD monitoring. The researchers demonstrated that the proliferative index

of the residual cells following chlorambucil treatment was higher than before treatment; the same did not occur with venetoclax. This finding provides early evidence on the cellular level that chemotherapy selects for more aggressive disease and lends further support to avoiding chemotherapy.

H&O What questions remain to be answered?

RF First, we need to establish whether anti-CD20 agents really add to the benefit of venetoclax treatment. Second, we need to determine the optimal duration of treatment with venetoclax.

H&O Is there anything that you would like to add?

RF One of the important questions we need to answer regarding the management of CLL is whether a policy of watch and wait is still beneficial for all patients. I am concerned that during the period of watch and wait, patients with what might be considered genomic instability will acquire mutations and other changes that will make their disease more difficult to treat later on. This could be in the form of resistance mutations or the development of a Richter transformation. By starting to treat patients with genomic instability earlier, before the development of a large tumor burden, we might be able to prevent progression on novel agents. In addition, for venetoclax specifically, the early initiation of treatment would avoid the issues with tumor lysis syndrome. If we can predict which people are going to need treatment, we can avoid holding off and creating an increased risk for tumor lysis syndrome.

Disclosure

Dr Furman has consulted for AbbVie, AstraZeneca, BeiGene, Genentech, Janssen, Pharmacyclics, Oncotarget, MorphoSys, Sanofi, and TG Therapeutics; has received speaker fees from AstraZeneca, Janssen, and AbbVie; has received research support from TG Therapeutics and AstraZeneca; and has participated in a data and safety monitoring board for Incyte.

Suggested Readings

Al-Sawaf O Zhang C, Robrecht S, et al. Clonal dynamics after venetoclax-obinutuzumab therapy: novel insights from the randomized, phase 3 CLL14 trial [ASH abstract 127]. *Blood*. 2020;136(1)(suppl):22-23.

Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2020;21(9):1188-1200.

Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2018;378(12):1107-1120.

Stilgenbauer S, Eichhorst B, Schetelig J, et al. Venetoclax for patients with chronic lymphocytic leukemia with 17p deletion: results from the full population of a phase II pivotal trial. *J Clin Oncol*. 2018;36(19):1973-1980.