CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Choosing Between CAR T-Cell Therapy and Pirtobrutinib in Double-Refractory CLL

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H&O What does it mean to have double-refractory chronic lymphocytic leukemia (CLL)?

KR We do not have a definition that everyone in the field agrees with completely. In general, double-refractory CLL refers to CLL that has become resistant to both a covalent Bruton tyrosine kinase (BTK) inhibitor and the BCL2 inhibitor venetoclax (Venclexta, AbbVie/Genentech). Covalent BTK inhibitors comprise ibrutinib (Imbruvica, Pharmacyclics/Janssen), acalabrutinib (Calquence, AstraZeneca), and zanubrutinib (Brukinsa, BeiGene), whereas pirtobrutinib (Jaypirca, Lilly) is a noncovalent inhibitor that can be used in double-refractory CLL.

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Definitions can vary, however. Some studies or discussions will refer to double-exposed CLL, which means that the patient has been exposed to both a covalent BTK inhibitor and venetoclax but their CLL is not necessarily resistant to the treatments. For example, the patient may have stopped taking an agent because of side effects or because the planned treatment has been completed. True double-refractory disease usually implies that the CLL has shown resistance to both those drugs, but we still need to be careful to look at the eligibility requirements when we interpret individual studies because definitions vary in the field.

H&O How often does CLL become double-refractory?

KR The answer to the question of how often double-refractory CLL develops is extremely variable, depending on the patient and what treatments they have received. For example, a patient in their mid-80s who is on their first treatment for CLL is unlikely to use a second treatment in their lifetime, so the risk that double-refractory CLL will develop in that patient is low. A patient in their 40s who has high-risk CLL has a much greater chance that their CLL will become refractory to both classes of drugs because they are likely to use both during their lifetime. We do think that if patients were to live long enough and undergo enough treatments, double-refractory CLL would eventually develop in all of them.

One of the reasons double-refractory CLL is a growing problem is that covalent BTK inhibitors have been in routine clinical use for a decade. Given that the median progression-free survival (PFS) with first-line ibrutinib was 8.9 years in one study[1] and that the median PFS with venetoclax monotherapy is approximately 2 years when

it is used after ibrutinib, we are now seeing large numbers of people whose disease progressed on ibrutinib and venetoclax. We will continue to see increasing numbers of patients with double-refractory CLL because covalent BTK inhibitors are being used more and more.

CAR T-cell therapy is not always easy to use in CLL because the T-cell quality can be impaired by the CLL itself or by older treatments patients might have received.

H&O What treatment options are available for patients with double-refractory CLL?

KR The 2 main options are chimeric antigen receptor (CAR) T-cell therapy with lisocabtagene maraleucel, also known as liso-cel (Breyanzi, Bristol Myers Squibb), and pirtobrutinib. Both these treatments have received accelerated approval from the US Food and Drug Administration (FDA) for use in the setting of double-exposed CLL. In CAR T-cell therapy, patients' peripheral T cells are collected by apheresis. The T cells are then sent to the manufacturer to be modified to contain CARs. After conditioning chemotherapy, patients receive the modified CAR T cells as an infusion. They can become very sick after the procedure, with cytokine release syndrome a common side effect. The procedure feels like a less-intense version of a transplant. Depending on the manufacturing time, bridging therapy may be necessary between the time of T-cell collection and reinfusion.

Although CLL is one of the first diseases in which CAR T-cell therapy was studied, it is one of the diseases for which the therapy has most recently been approved. CAR T-cell therapy is not always easy to use in CLL because the T-cell quality can be impaired by the CLL itself or by older treatments patients might have received, such as fludarabine-based chemotherapy.

The major study of liso-cel in CLL is TRANSCEND CLL, in which just 18% of patients experienced a complete response.[2] In most of the patients with a complete response, the response lasted, so when liso-cel works, it works well. It is important to explain to patients that CAR T-cell therapy is a challenging process with a chance of working that is slightly less than 1 in 5.

The major study of pirtobrutinib in CLL is the phase 1/2 BRUIN trial, in which 73% of patients with pretreated CLL responded to pirtobrutinib.[3] This is an oral medication that is very easy to take, so treatment is very different from going through several weeks of very intensive visits to receive CAR T-cell therapy. As a noncovalent BTK inhibitor, pirtobrutinib binds BTK in a way that is different from that of covalent BTK inhibitors; it is able to bind and unbind BTK as a target. The data we have so far suggest that pirtobrutinib has fewer side effects than ibrutinib, acalabrutinib, and zanubrutinib. Although patients may experience side effects such as infections (in 71%), bleeding (in 43%), and neutropenia (in 33%), they are generally able to continue with work and other activities. Another difference between CAR T-cell therapy and pirtobrutinib is that most patients who take pirtobrutinib experience a response. Unfortunately, the median PFS with pirtobrutinib in BRUIN was only 20 months, meaning that resistance to pirtobrutinib does eventually develop. To summarize, the experiences of taking CAR T-cell therapy and taking pirtobrutinib are very different. Some patients will end up receiving both treatments, either CAR T-cell therapy followed by pirtobrutinib or pirtobrutinib followed by CAR T-cell therapy. New treatments are still needed, so I encourage patients to enroll in clinical trials of investigational therapies that may produce higher success rates.

H&O How can clinicians decide between CAR T-cell therapy and pirtobrutinib in double-refractory CLL?

KR One of the most important steps in choosing between therapies when patients are eligible for both is to review with the patient what to expect with each treatment. I explain that CAR T-cell therapy is an intense process that may produce a long-term benefit but is more likely not to, whereas pirtobrutinib treatment simply requires taking pills but may work for only 1 to 2 years. In my clinic, I find that many patients have a strong preference for one way or the other after this discussion. One patient may be in the middle of an important activity and want to do pirtobrutinib, whereas another patient may decide that it is a good time to take advantage of an opportunity to receive CAR T-cell therapy. Geography can play an important role as well. My practice serves a rural community surrounding Columbus, Ohio, which means that the number of appointments needed for CAR T-cell

therapy makes it unfeasible for some of my patients. CAR T-cell therapy is also a poor option for patients who are elderly or otherwise unfit. A consideration of where your patient is in their disease course and their lifespan, along with their comorbidities and personal considerations, will answer that question in most cases.

H&O What questions remain to be answered?

KR We need to learn how to boost the number of people who respond to CAR T-cell therapy. We have seen a great deal of improvement in the safety of CAR T-cell therapy, and I would like to see the effectiveness improve as well. Approaches that might improve effectiveness include using different types of cell therapy or different targets. The current efficacy is not what I would hope for. Regarding targeted agents, we need to look at how newer targeted agents can be used and how they can be sequenced with existing agents to reduce the risk of resistance.

It will take a long time for us to answer these important questions because CLL currently takes approximately a decade to progress. Although this makes things difficult from a research perspective, it is very good news for our patients because it means they are doing well. The challenge of doing research in an area where patients do well is that it takes a longer time to learn the answers to our questions.

Disclosures

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