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Incorporating guideline-concordant care for patients with CLL/SLL relapsing after 2 prior lines of therapy

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Dr. Abramson:
Hello, this is CME on ReachMD, and I'm Dr. Jeremy Abramson.

Dr. Bhat:
And I'm Dr. Seema Bhat.

Dr. Abramson:
Let's start today's discussion with a case of a patient with CLL. This is a case from my practice. It's a 76-year-old woman who was initially treated 4 years earlier with venetoclax and obinutuzumab as her initial treatment for CLL. Her CLL at that time had both a 13q deletion and a trisomy 12, and next generation sequencing had shown no presence of a TP53 mutation.

She resulted in a CR on venetoclax/obinutuzumab, and that lasted a few years. But after 3 years, she relapsed and again developed symptomatic anemia which required treatment. At that time, she still had her 13q deletion as well as trisomy 12, and repeat next generation sequencing actually showed a low-level TP53 mutation. At that time, I treated her with single agent zanubrutinib.

She achieved a partial response but had evidence of progressive disease after 1 year of treatment. I resent next generation sequencing at that time, which showed a higher level of the TP53 mutation, but now also showed a BTK cysteine 481 mutation. At this time, she felt generally well, although she was developing progressive anemia as well as thrombocytopenia, but she had an ECOG performance stat of 1, and good organ function.

Dr. Bhat:
So, Dr. Abramson, this patient by definition has double refractory CLL because patient has received venetoclax previously, as well as a covalent BTK inhibitor, and now has progressed, and now has a BTK mutation. So, we currently have two FDA approved therapies for such patients in the third-line setting, we have pirtobrutinib and liso-cel. Pirtobrutinib is a noncovalent BTK inhibitor that inhibits both the wild-type and the C481 mutant BTK. It's effective against BTK mutations that have developed on a covalent inhibitor and being a select inhibitor, it has a very favorable safety profile.

FDA granted accelerated approval to pirtobrutinib for patients with CLL or SLL who previously received two or more prior lines of therapies, including a BTK inhibitor and a BCL-2 inhibitor, and approval was based on results from the BRUIN Phase 1/2 study, which included a CLL and SLL cohort of 247 patients who had been previously treated with a covalent BTK inhibitor. Overall response was 72% in the study for dual refractory patients, and the median progression-free survival was 19.4 months. Treatment was safe with side effects that are consistent with what could be expected of BTK class, with bruising and some diarrhea seen. And notably, cardiac events were low and so was discontinuation rate.

Liso-cel is also FDA approved for a similar dual refractory population. It's the first and only chimeric antigen receptor, or CAR T-cell

therapy, available for CLL or SLL patients. And the accelerated approval was based on the TRANSCEND CLL-004 trial. This trial also included patients who had a double refractory disease. Response rate was 45% with 20% complete responses, and those patients with complete responses had durable responses with no progressions. Side effects were expected with cytokine release syndrome seen in most patients, and almost half of the patients had neurotoxicity and almost all recovered.

So, how do we choose between these two treatments? One of the important considerations is safety. Pirtobrutinib is fairly well tolerated and easy to administer, though the treatment is continuous just like other BTK inhibitors. On the other hand, CAR T-cell therapy is associated with cytokine release syndrome as well as neurotoxicity, so it should be done at specialized centers. Patients must also be fit enough to undergo lymphodepletion that's required for CAR T-cell therapy.

Other factors to consider include disease burden and time needed for CAR T-cell manufacturing. Pirtobrutinib may be a better option for patients with rapid disease progression, where there's limited time to get the CARs manufactured. And patient factors to consider include caregiver support, transportation and insurance coverage.

So, in summary, for patients with double refractory patient, like the one you presented, both pirtobrutinib and liso-cel can be effective treatments. Selection of therapy should include both clinical and patient specific factors.

Dr. Abramson:
Yeah, I agree. I think an essential point in this case is that the disease can undergo clonal evolution over time, and if a patient progresses after initial treatment, I think it's always helpful to resend FISH, as well as next generation sequencing, as patients can acquire high risk changes such as 17p deletions or TP53 mutations. For patients progressing on or after a covalent BTK inhibitor, we'd also be looking for BTK inhibitor resistance mutations such as the BTK cysteine 481 mutation that this patient acquired on treatment.

In selecting among these options, I entirely agree with the decision-making. I will say that if I have a patient who prefers a CAR T-cell treatment option, such as liso-cel, but they have rapidly progressive disease or disease that requires disease control prior to getting the CAR T-cell administered, then I will consider pirtobrutinib as a bridging therapy, help control and cytoreduce the disease on route to their liso-cel infusion.

With that, our time is up. We hope you found this brief case review useful. Thanks so much for listening.

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