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The Challenge of BCL-2 Resistance in CLL: Treatment Strategies and Emerging Therapies

Announcer:
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Dr. Kipps:
Hello. Hi, this is CME on ReachMD. I'm Dr. Thomas Kipps from the University of California at San Diego, and I'm here to discuss the challenge of BCL-2 resistance in the era of targeted therapies for patients with chronic lymphocytic leukemia.

We have actually seen, with the advent of targeted therapies, an improvement in progression-free survival and overall survival. And notable has been the drug venetoclax, which is a very potent inhibitor of the protein BCL-2, which regulates the degree of apoptosis that cells have. By inhibiting BCL-2, it actually causes the cells to undergo apoptosis and we see dramatic clearance of leukemic cells upon initiation of therapy, so much so that we have to be careful when we initiate therapy.

Nonetheless, this drug has been very helpful in achieving very high-quality and deep remissions that have allowed for fixed-duration therapy, allowing for patients to stop therapy after 1 or 2 years of venetoclax therapy, usually in combination with an anti-CD20 antibody, such as obinutuzumab, or in combination with the BTK inhibitors, such as ibrutinib. Now patients can develop resistance to venetoclax. On therapy, we had patients who were undergoing treatment in the early clinical trials. They continued on venetoclax for years after therapy was initiated, and we've noted that some patients were developing resistance to therapy. However, we've had also patients develop resistance in as short as 18 months after initiation of venetoclax therapy.

I think one of the key factors that appears to be associated with the development of resistance to venetoclax really is the deletion in chromosome 17, the short arm of chromosome 17, 17p, which also is associated with mutations in the gene TP53.

The gene TP53 is very important in policing the cell. It halts the cell division if there's any mutations that need to be repaired, and it may actually trigger the proapoptotic factors, which induces cell death in patients with functional TP53. It accounts for the effectiveness of chemotherapy, which is a strong inducer of TP53. However, when TP53 is mutated, then it may not respond appropriately, and patients become resistant to chemotherapy.

Now, although patients with deletion 17p or mutations in TP53 can respond to and do well on venetoclax, these patients are at higher risk for developing resistance over time with treatment, and that's something that we have to watch for.

Another factor that might be important is the expression of unmutated antibody genes by the CLL cell. This typically is associated with the higher proclivity of the leukemic cell to proliferate and divide, and we see the development of resistance in patients with unmutated antibody genes to be more frequent than those patients with unmutated antibody genes.

So what accounts for resistance? I think that we and others have noted that patients can acquire mutations in BCL-2, and typically these mutations are at the pocket at which the drug, venetoclax, can bind to BCL-2. And that limits the ability of that drug to bind BCL-2 and inhibit its function. However, there are other mechanisms that might account for resistance independent of mutations in BCL-2. Because

BCL-2 itself belongs to a family of both pro-death and anti-death factors, proapoptotic and antibiotic factors, and it's the balance between the proapoptotic factors, which are like the executioners, and the survival factors, such as BCL-2, that balance has to be kept. What the inhibitors of BCL-2 do is turn the balance to favor the executioners and therefore the cell undergoes apoptosis. So one can consider a decrease in the level of the expression of the executioner proteins. And this is seen sometimes in patients with lower levels of BAX, which is a pro executioner protein, or higher levels of some of the proteins that can take the place of BCL-2 to counter that balance and protect the cell from undergoing cell death. These include protein such as MCL1 and BCL-xL. These proteins can substitute for BCL-2 and help promote the survival of the leukemic cells. So the balance of the executioner proteins and the proteins that protect a cell can be altered in some patients who develop resistance to this remarkable drug, venetoclax.

I must say that there is also a lot of work in this area to improve second-generation BCL-2 inhibitors. There's a number of compounds that are undergoing development; some are in clinical trials. These have been tested. Some may have higher levels of binding activity for BCL-2 and, therefore, may be more resistant against certain mutations that might develop in BCL-2. And then there's also other drugs which may inhibit not just BCL-2 but some of these other proteins that can actually promote the survival of the leukemia cell.

And I think this is a very active area of research and we hope to see more develop in this area because it truly has transformed how we treat patients and allow them to achieve a fixed-duration therapy without continued drug therapy, and that's very notable.

So our time is up. I thank you for tuning in. I hope this information is useful for your practice.

Announcer:
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