Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/project-oncology/exploring-the-mechanisms-of-resistance-to-targeted-therapies-in-cll-mcl/12960/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Exploring the Mechanisms of Resistance to Targeted Therapies in CLL & MCL

Announcer:
You're listening to *Project Oncology* on ReachMD, sponsored by Lilly. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *Project Oncology*, and I'm Dr. Charles Turck. Joining me to explore key mechanisms of resistance to targeted therapies in chronic lymphocytic leukemia, or CLL for short, and mantle cell lymphoma, also known as MCL, is Dr. Andrew Lipsky. Dr. Lipsky is an assistant professor of medicine at the Columbia University Medical Center, and he specializes in caring for adult patients with hematologic malignancies, including CLL and lymphoma. Dr. Lipsky, welcome to the program.

Dr. Lipsky:
Nice to be with you.

Dr. Turck:
Let's begin by examining the CLL and MCL treatment landscapes. Can you tell us about some of the targeted therapies currently available?

Dr. Lipsky:
Sure, so starting with chronic lymphocytic leukemia, on the basis of the observation that the B cell receptor signaling, and mechanisms of apoptosis are aberrantly regulated in this disease, the field develops small molecule inhibitors that target either components of the B cell receptor pathway, or the cellular machinery that's associated with cell death mechanisms. And to that end, there are three main groups of targeted therapy in CLL.

First, there are the BTK inhibitors, which target Bruton's tyrosine kinase. Those are ibrutinib and acalabrutinib. BTK is a key molecule downstream of the B cell receptor, and those therapies are given as indefinite lifelong therapy.

The second group of targeted therapeutics in CLL involves targeting the protein BCL2, which is an anti-apoptotic protein. Venetoclax, the only currently approved drug that is a BCL2 antagonist, can be given as a time-limited therapy. For example, in combination with anti-CD20 antibody as given in the CLL14 study.

And finally, there are also the PI3K inhibitors, which inhibit phosphatidylinositol-3 kinase, and those are approved in relapsed and refractory disease.

With regard to mantle cell lymphoma, the BTK inhibitors, so that's ibrutinib, acalabrutinib, and zanubrutinib, those are a mainstay of treatment of mantle cell lymphoma in the relapsed and refractory setting.

Dr. Turck:
As we know, one of the primary challenges that comes with these therapies is the risk of acquired resistance. So, what can you tell us about that resistance and the factors that put patients at risk of developing it?

Dr. Lipsky:
Sure. So, the risk factors for progression on targeted therapies in CLL are really dependent upon the treatment context. I'll start with complex karyotype, which can be a tricky one. For example, we know that historically in the relapsed refractory setting where patients were pretreated with chemotherapy, complex karyotype was a predictor of disease progression and inferior progression-free survival. In the modern era, in some of the early phase clinical trials in the relapse setting, this appeared to hold true. However, with later studies

and studies of patients receiving BTK inhibition and BCL2 antagonism in the frontline setting, this seemed to indicate the complex karyotype may not impact PFS to the same degree as in earlier studies. Deletion 17p and TP53 mutation have also been highlighted as risk factors for progression on novel agents, particularly in the context of the CLL14 trial. Remember that this trial was time limited therapy with venetoclax and obinutuzumab. And in this study, deletion 17p was a significant risk factor for disease progression.

Additionally, in the context of mantle cell lymphoma, TP53 mutations are associated with worse outcomes and BTK inhibitor treated relapse refractory patients.

Dr. Turck:
And if we look at this at the microenvironment level, what role does B cell receptor signaling play in acquired resistance?

Dr. Lipsky:
So we know that in CLL, constitutive activation of the B cell receptor pathway is the main mechanism that underlies the pathogenesis of the disease. In the context of the BTK inhibitors, the development of bypass mutations and secondary mutations in the drug target has been shown to restore B cell receptor signaling in CLL cells.

In your question, you mentioned the role of the microenvironment. In CLL, I think the role of the microenvironment in acquired resistance remains an active area of investigation. Several researchers, including Nicholas Tarazi, have implicated IL-4 signaling as potential sources of drug resistance. For example, they found that IL-4 is a key survival factor in the CLL microenvironment that also improves leukemia cell adhesion to stromal cells expressing a surface membrane IL-4 receptor. And in some of my own work, we've looked at low VAF BTK progressors and saw some signs that this IL-4 interaction may also be the case.

With respect to mantle cell lymphoma, acquired resistance to ibrutinib has been shown to involve microenvironmental interactions, resulting in activation of the PI3K AKT pathway.

Dr. Turck:
You mentioned these a little bit before, but let's focus on two key mechanisms of resistance: secondary mutations within the drug target and activation of bypass pathways. What more could you tell us about those mechanisms?

Dr. Lipsky:
Right, so I'll start by addressing secondary mutations within the drug target. In the case of the BTK inhibitors, the most common resistance mechanism is a mutation in the binding site of BTK at position 41 in the protein. The most common is a cysteine residue that changes to a serine residue, we term this the so-called C-41S mutation. But multiple other mutations in BTK have since been characterized. These mutations often develop between the second and fourth year of the patient's treatment. And I think it's important to point out that there is some clonal heterogeneity here. So resistance or mutations are often what we call high-burden clonal variants with varying allele frequencies of 80%. But it's increasingly appreciated around half of the time the CLL patients who progress on BTK inhibitors have small subclones with these mutations with lower varying allele frequencies below 10%. And a better understanding of how the mechanisms of this low burden progression work has been an active area of interest in some of my research.

With respect to BCL2 antagonism and venetoclax, resistance can also take the form of acquired mutations in the drug target, specifically in what's termed the BH3 binding domain of BCL2. This can happen with a glycine 101 to valine mutation that disrupts the bond of venetoclax to BCL2, preventing the drug from competing with pro-apoptotic molecules that bind to BCL2, resulting in an evasion of apoptosis.

And now switching the focus to the second mechanism you referenced, bypass pathway activation with respect to the BTK inhibitors, a gain of function mutations in TLC gamma 2 are the second most common frequent mutations in CLL patients who have failed ibrutinib. This phospholipase C gamma 2 is the protein immediately downstream of BTK. And these mutations have an activating effect, resulting in continuous BCR signaling independent of BTK activation. These mutations can also occur in combination with BTK mutations at low varying allele frequency. And I think their role in acquired resistance in CLL is not fully elucidated.

With respect finally to venetoclax in bypass pathway activation, it's known that overexpression of prosurvival proteins such as BCL-XL, and MCL-1 can also be associated with acquired resistance via bypass of BCL2 and decreased overall levels of apoptosis.

Dr. Turck:
For those who is tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck. I'm speaking with Dr. Andrew Lipsky about acquired resistance and chronic lymphocytic leukemia and mantle cell lymphoma.

So Dr. Lipsky, now that we've talked about the mechanisms of resistance, let's focus on how we can avoid them. What are some strategies you recommend to prevent resistance in patients with CLL and MCL?

Dr. Lipsky:
Sure, so at this point, I don't think that the data clearly support a single winner among many strategies for avoiding acquired resistance, but I can comment on a few potential strategies in turn.

First, real-time monitoring is a strategy that's been utilized in the research setting and may end up proving useful. A few studies that have looked at surveilling patients by performing sequencing for BTK or PLC gamma 2 mutations throughout the course of therapy have been able to detect resistance mutations several months prior to a patient's clinical relapse. Yet I think it remains to be seen whether modification of therapy based on early detection of a resistance mutation translates into clinical benefit. And similar questions can be asked with respect to the cost benefit of doing monitoring with these techniques, giving the overall expense of genomic testing. So, for right now, I think it's a fair recommendation to send this type of genomic resistance testing when you have an overt clinical suspicion for disease progression.

Secondly, there have been a number of approaches deploying combinations of novel agents to try and target higher levels of MRD undetectability. So those type of approaches often personalize therapy and tailor the duration of therapy based on whether the patient is MRD negative. And included in these efforts would be combinations of both ibrutinib and venetoclax, which has been studied by the CAPTIVATE study investigators as well as Dr. Jain and colleagues at the MD Anderson as well as the CLARITY study investigators in the United Kingdom. Other groups have used strategies involving combinations of venetoclax with PI3K inhibitors. These types of efforts are also underway. But again, all of these are in the research setting, and none of them have made it to the clinic in an FDA approved manner.

While these types of strategies have been quite successful in getting patients to an MRD negative state, it's unclear if maintaining a clone in this state actually prevents resistance transformation to Richter syndrome or overall relapse.

And finally, there is a third possible strategy looked at in the research setting where investigators have looked at what is termed a drug holiday and asked whether this can limit acquired resistance. So evidence for this style approach is really inferred from other malignancies. And this involves stopping indefinite therapies for some particular interval and then reintroducing them at a later date in the hope that less resistance occurred, and these particular studies have not read out as of yet.

Dr. Turck:
Looking ahead to the future, what kinds of developments do we need in order to reduce or avoid the risk of acquired resistance?

Dr. Lipsky:
Sure. So first, I think it would be helpful to develop newer biomarkers that better predict response to treatment and acquired resistance. Multiple groups are certainly trying to do this by collecting better clinical and genomic data alongside prospective clinical trials. I think there are several potential candidates with large enough data sets that may be useful here. For example, I think BCR stereotypy is an underutilized example of a potentially promising biomarker.

Second, I think that determining the optimal duration of therapy for time-limited approaches would also go a long way to minimizing the risk of acquired resistance. And I think in this regard, undetectable MRD status has a clear prognostic value in predicting long-term outcomes at the end of a fixed duration approach. It remains an open question of what percentage of patients would likely derive additional benefit from longer duration therapy. And at this point with regard to studies like CLL14, I think that there are too few patients that have been retreated to comment on the potential for genetic evolution on treatment or the efficacy of retreatment.

I do think it's encouraging that we have new options for patients who have developed acquired resistance. For example, a recent study of a newer BTK inhibitor, pirtobrutinib, showed efficacy in patients with canonical BTK resistance mutations, and this also included some patients with the PLC gamma 2 mutation as well. Similarly, there are also next generation BCL2 antagonist in the works. And once patients progress, newer therapeutic modalities like car T cells and bispecific antibodies are also promising therapeutic strategies for these patients.

Dr. Turck:
Well with those forward-looking thoughts in mind, I want to thank my guest, Dr. Andrew Lipsky, for joining me to discuss some of the mechanisms behind acquired resistance to targeted therapies for chronic lymphocytic leukemia and mantle cell lymphoma. Dr. Lipsky, it was great having you on the program.

Dr. Lipsky:
Well, thanks so much. It's been a pleasure speaking with you.

Announcer:
This program was sponsored by Lilly. To revisit any part of this discussion and to access other episodes in this series, visit

ReachMD.com/projectoncology where you can Be Part of the Knowledge. Thanks for listening.