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Optimizing Outcomes for Patients with Relapsed or Refractory CLL/SLL

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Dr. Soumerai:
This is CME on ReachMD, and I'm Dr. Jacob Soumerai from Harvard Medical School and the Massachusetts General Hospital Cancer Center. In the last decade, we've seen a rapid evolution in the treatment of CLL, with promising results from trials examining chemotherapy-free regimens in the frontline setting. These targeted approaches utilize either BTK inhibitors or venetoclax-based therapy and have largely displaced chemoimmunotherapy in frontline management of CLL, leading to frequent, prolonged, multi-year remissions. Despite this success, there remains a clinically significant fraction of patients who will require subsequent therapy after developing drug intolerance or progressive disease. And today, Dr. Andrew Lipsky from Columbia University's Irving Medical Center and NewYork-Presbyterian Healthcare System, and I will be discussing available therapeutic options for relapsed/refractory CLL, and how to choose the best option for the patient that you're seeing in front of you. Dr. Lipsky, welcome to the show.

Dr. Lipsky:
Thank you, Dr. Soumerai.

Dr. Soumerai:
Dr. Lipsky, could you describe the mechanisms associated with treatment resistance in CLL or SLL? And do we know what is driving patients to relapse?

Dr. Lipsky:
That's an excellent question, Dr. Soumerai, and certainly we don't have all the answers, but for patients receiving first-line therapy, it's clear that certain features of the baseline tumor biology are relevant to how likely the patient is to do well in the long term.

For example, genetic features, such as the presence of a deletion 17p or a *TP53* mutation, have been associated with a higher risk of relapse in CLL. But of course, we should consider the prior lines of treatment that the patient has received, and really, there are 3 potentially overlapping categories to think about here. The first is patients who received prior chemoimmunotherapy, the second is patients receiving a BTK inhibitor, and the third is patients who have received venetoclax.

For patients who previously received chemoimmunotherapy, we know that clonal evolution is a common characteristic of disease relapse. These patients are more likely to relapse with high-risk features, such as complex karyotype and deletion 17p, and certainly I would recommend repeating FISH testing and *TP53* sequencing at the time of relapse. For patients who received targeted therapy, the patterns of resistance can be more drug specific. So, for the BTK inhibitors, we know that these drugs bind covalently to BTK, and that the C481S resistance mutations in the BTK protein are commonly observed. Also, since these drugs target the B-cell receptor signaling pathway, we can also see activating or bypass mutations in PLCgamma2, the kinase immediately downstream of BTK. Lastly, for

patients receiving venetoclax, BCL-2 mutations and upregulation of alternative pro-survival proteins have also been seen in relapsing patients. Here, I think it's important to find out that the duration of therapy is important when considering what resistance mutations may be driving progression, as venetoclax is often given as fixed-duration therapy, as in the CLL14 study in treatment-naïve disease and as in the MURANO study for relapsed/refractory disease. But it can also be given as indefinite therapy, where, really, resistance mutations are more likely to be seen. And so, I'm curious. In your practice, Dr. Soumerai, what additional thoughts do you have on resistance, and what diagnostic tests do you order at disease relapse and progression?

Dr. Soumerai:
Yeah, I think it's very important to order a CLL FISH panel, as well as *TP53* mutation testing for all patients at relapse and at any subsequent line of therapy, because these can be acquired, as you've stated, over the course of a patient's disease history. The targeted sequencing panel here also includes information on the development of specific resistance mutations, for example, BTK resistance mutations, although these are not mandatory at relapse.

So Dr. Lipsky, what are some of the currently approved agents that we use for the treatment of relapsed or refractory CLL?

Dr. Lipsky:
In the relapsed setting, there are currently 3 classes of targeted agents. We have BTK inhibitors, BCL-2 inhibitors, and PI3 kinase inhibitors. And across these 3 classes, there are currently 5 targeted agents approved. Of the BTK inhibitors, ibrutinib and acalabrutinib are currently FDA approved, and we also have zanubrutinib. That is not yet FDA approved for CLL, but its approval is widely expected later this year. Then, for BCL-2 inhibition, we have 1 approved inhibitor, and that's the drug venetoclax, which was approved on the basis of the MURANO study in combination with rituximab. And lastly, for the PI3 kinase inhibitors, we have 2 choices: idelalisib and duvelisib. From the standpoint of society guidelines, currently ibrutinib, acalabrutinib, and venetoclax/rituximab all have category 1 recommendations from the NCCN.

Dr. Soumerai:
Let's talk about some of the data underlying these approvals in relapsed or refractory CLL. So why don't we begin with the BTK inhibitors—ibrutinib and acalabrutinib being the currently FDA-approved agents. What were the relevant studies that established the efficacy of these agents?

Dr. Lipsky:
So, ibrutinib was approved on the basis of the RESONATE study. The RESONATE trial was a randomized study of ibrutinib versus ofatumumab, now keeping in mind, this is over 10 years ago, when ofatumumab was a reasonable comparator arm. If you look at the final analysis of this trial, and out to about 65 months, the median progression-free survival was 44 months with ibrutinib, compared to 8 months with the comparator, and this was in a very heavily pretreated population, who had received a median of 3 prior lines of therapy before going on ibrutinib. And so, thus, this study really established this class of medicines as effective single-agent therapy for relapsed/refractory CLL. In terms of acalabrutinib, this drug is a second-generation BTK inhibitor, with a more specific kinase binding profile for BTK.

And here, one of the studies in relapse, leading to the drug's approval was called the ASCEND study. This was particularly interesting because it randomized patients to receive either acalabrutinib or one of two control arms, with either bendamustine-rituximab or idelalisib-rituximab. And here, in this study, acalabrutinib was clearly superior to both control arms, in terms of progression-free survival.

Dr. Soumerai:
Now, with multiple covalent BTK inhibitors available in the clinic, this raises the next important question. Which agent should I be using? So can you comment on the available head-to-head data comparing BTK inhibitors in patients with CLL?

Dr. Lipsky:
Absolutely. There are two randomized studies that compare BTK inhibitors to each other in the relapsed/refractory setting. These are the ELEVATE-RR trial, in which patients with high-risk features, such as deletion 17p or 11q, were randomized to receive either ibrutinib or acalabrutinib, with a primary endpoint of noninferiority for PFS, and with almost 4 years of follow-up, both of these drugs had a median PFS of about 38.4 months, and thus acalabrutinib was deemed noninferior to ibrutinib. Importantly, there were differences in the side-effect profile of these agents. With ibrutinib, for example, 16% of patients developed AFib, compared to 9.4% with acalabrutinib. Likewise, there was also more low-grade bleeding with ibrutinib and higher rates of hypertension, for example, 23% with ibrutinib versus 9% with acala. There is a second head-to-head comparison study of BTK inhibitors, which is the ALPINE study; that study looked at relapsed/refractory CLL patients, regardless of genetic features when compared to the last study I mentioned. Patients were randomized to zanubrutinib versus ibrutinib. This study has relatively less mature data available at this time point, and the outcomes are investigator-assessed, but so far it seems that with an early readout, there are lower rates of atrial fibrillation seen with zanubrutinib compared to ibrutinib.

Dr. Soumerai:
So for those just tuning in, you're listening to CME on ReachMD. I'm Dr. Soumerai, and here with me today is Dr. Lipsky. We're discussing the therapeutic options for our patients in the relapsed/refractory CLL setting.

Dr. Soumerai:
What's the data for the use of venetoclax in these patients with relapsed CLL?

Dr. Lipsky:
So we have excellent data for the use of venetoclax that comes from the MURANO study, which was a really major study in the field. The MURANO study enrolled over 380 CLL patients, most of whom were heavily pretreated with chemotherapy. These patients were then randomized to receive bendamustine/rituximab which was certainly a reasonable and very appropriate treatment arm comparator, or the combination of venetoclax/rituximab as a fixed-duration therapy for 2 years.

Here, the venetoclax was given with a standard dose ramp-up, followed by 6 cycles of rituximab with continued venetoclax therapy for up to 2 years. Notably, the median progression-free survival was 53 months at 5 years for venetoclax/rituximab, which was statistically significant compared to 17 months for b/r. Even more remarkable was the fact that this trial also demonstrated an overall survival benefit for venetoclax, with a hazard ratio of 0.4, which is a notable achievement for a trial in CLL.

Dr. Soumerai:
Lastly, can you briefly comment on the approval data for the PI3 kinase inhibitors?

Dr. Lipsky:
Sure. So I'll briefly discuss duvelisib as an example. This drug was approved on the basis of the DUO trial, where it was compared to ofatumumab. Here the median PFS was around 13 months, and given this less robust data, I reserve this class of agents until patients have exhausted all other lines of available therapy.

So Dr. Soumerai, since I briefly mentioned sequencing, why don't we talk about this for a bit now. I'm curious—in your practice, how do you think about sequencing the available agents in patients with relapsed/refractory disease?

Dr. Soumerai:
Absolutely. And here, the most important factor is what the patient has received in terms of prior lines of therapy. And it's really important to point out that in the landmark trials that you've so well highlighted, that led to the approval of these agents, the vast majority of the patients enrolled had received only chemoimmunotherapy prior to study drug. And thus, randomized data on sequencing of targeted agents after chemo-free approaches in the frontline setting is actually quite limited.

And similarly, current NCCN treatment guidelines don't really offer in-depth guidance for tailoring which targeted treatment to pick based on patient or specific disease factors. I can highlight a few strategies for sequencing targeted therapies that have gained favor based on the available data for CLL.

So first, for patients who have received only chemoimmunotherapy, either a covalent BTK inhibitor, or venetoclax plus a CD20 antibody, are good options, and there is no definitive, randomized data to tell us which to recommend to a patient. Clearly, patients should receive these agents before a PI3 kinase inhibitor.

When choosing between a BTK inhibitor and venetoclax, I focus on a number of patient and disease-specific factors. So for example, a patient who presents with relapsed CLL and has comorbidities, including poorly controlled atrial fibrillation, concurrent need for anticoagulation, they have a bleeding history you know, these patients might not be the best candidates for a BTK inhibitor, whereas a patient who has very poor renal function, who's at high risk for tumor lysis syndrome on the basis of disease bulk, or who lives 4 hours away from the center and can't come in for frequent visits to get venetoclax started, might be a better patient for a BTK inhibitor as opposed to venetoclax-based therapy. When choosing either agent, it's very important to review the patient's medication list in detail. And if there are any drug-drug interactions identified, consult with a pharmacist and think about which of these drugs are absolutely critical or can potentially be held for a period of time. These are rarely hard stops, as we can typically get past these drug-drug interactions, either with drug or dose modifications.

Now, if a patient's received prior venetoclax in the frontline setting, if they've progressed while on therapy, it is clearly necessary to switch away from venetoclax to a covalent BTK inhibitor. If they progressed after completing planned venetoclax therapy, it's acceptable to either re-treat with venetoclax, or switch to an alternative therapy, in particular a covalent BTK inhibitor. The updated data from the MURANO study, as well as real-world analyses, have really shown us that re-treatment can be a successful approach, with about three-quarters of patients responding with venetoclax re-treatment. Thus, particularly in a patient with a long remission after completing venetoclax, this is a very reasonable approach.

Now, for patients who have received prior BTK inhibitors, current guidelines recommend switching to a venetoclax-based regimen. We have real-world, pooled data from multiple centers, suggesting high response rates—over 85%—for this strategy. It's also worth noting that another option may be on the horizon, as we recently saw data from the BRUIN study, utilizing a novel noncovalent BTK inhibitor, pirtobrutinib, which is able to overcome BTK resistance and extend the use of agents targeting BTK in patients with CLL. If this agent gets approved in the near future, switching to this noncovalent inhibitor would also be a promising option for this patient.

Dr. Lipsky:
That was an excellent summary of the relevant data for sequencing, and I completely agree with your enthusiasm for pirtobrutinib, and my management practices are quite similar. I wanted to ask you the question about PI3K inhibitors. In what specific circumstances do you consider these agents relevant to relapsed/refractory disease?

Dr. Soumerai:
At my institution we try to enroll patients on a clinical trial after they have progressed on both a BTK inhibitor and venetoclax. And here, we would think about emerging options, such as noncovalent BTK inhibitors, CAR T-cell therapy, other novel targets as well as bispecific antibodies. But for patients for whom a clinical trial is not the preferred approach, PI3 kinase inhibition is still a very important target, although it's important to note that in this double-refractory population the median progression-free survival has been quite limited. In the real-world setting, we've seen about 4 months in this population. Keeping in mind, of course, that these patients require ongoing monitoring given risk of infections including CMV viremia, as well as a potential for late immune-mediated toxicities including transaminitis, colitis, and pneumonitis.

This has been a great discussion, Dr. Lipsky. Unfortunately, that's all the time we have today, so I want to thank our audience for listening in, and thank you, Dr. Lipsky, for joining me and for sharing all of your valuable insights. It was really great speaking with you today.

Dr. Lipsky:
Thank you, Dr. Soumerai. It was great to speak with you as well.

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