The Practical Implications of the Rise of Targeted Therapies for Chronic Lymphocytic Leukemia: A Q&A With Alexey V. Danilov, MD, PhD

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***AJMC®*: Could you discuss the challenges and opportunities resulting from the rise of targeted therapies for chronic lymphocytic leukemia (CLL)?**

DANILOV: We are now in an age of transition from standard chemoimmunotherapy treatment to novel therapies. Although this era is exciting, it comes with its own challenges in addition to opportunities. Overall, CLL treatment will develop in this new age because of an increasing transition toward targeted therapies, as well as combinations of targeted therapies. Several targeted therapies have been approved now for CLL, and there is a lot of debate regarding how to administer those treatments in combination and whether they are more effective in combination or alone. One challenge with targeted therapies—ibrutinib, for example—is chronic administration of the drug, as opposed to [what we do with] chemotherapy, which is typically to treat the patient for 4 to 6 cycles and then monitor them off treatment for years. The combination approach offers an opportunity to administer those targeted therapies similarly to chemotherapy, wherein targeted therapies are continued for a year or two in combination with a CD20 antibody, for example, and then the patients are monitored off treatment. Another challenge with targeted therapies is cost. The financial burden can be quite substantial, and not everyone can afford it.

In general, there will be more transitions toward targeted therapies, particularly with new data coming out at the American Society of Hematology [ASH] 2018 Annual Meeting, particularly in up-front therapy of CLL. There will be new combinations that will, hopefully, result in less exposure to drugs.

Yet another challenge with targeted therapies is management of adverse events [AEs], which can be quite severe. We are now learning who could be the best candidate for certain targeted therapies and how to manage those AEs. The variety of AEs is broader than with chemotherapy, mostly due to infection, and there are some to which we are not accustomed to managing.

***AJMC®*: To what extent do factors not related to the drugs themselves, such as drug vehicle and delivery mechanism, affect treatment selection?**

DANILOV: One factor that affects treatment selection is oral versus intravenous therapy. I find it easier to use oral therapies in most patients. I practice at an academic institution, where we get referral from outside clinics and many patients may travel for an extended number of hours. From what I hear from my colleagues, it may be less of a concern for some local practices, but still, most patients do prefer an oral agent if it is available. There is no scheduling involved, and there are no regulated strict visits. The challenge with oral therapies is compliance, as we cannot necessarily control adherence. However, I think most of my patients tend to be compliant with oral therapies because they are easier to administer.

***AJMC®*: How important is the conversation with patients when it comes to adherence, when they are taking therapy at home versus in a clinic or a hospital setting?**

DANILOV: If I had a suspicion [regarding adherence] based on how they are responding, then I would have a conversation with them about whether they are taking the drug. I have had a few patients who had co-pays and potentially would try

to space out drug doses to save money, and most of the time, that does not necessarily make a whole lot of sense, because there is not the full target inhibition. Therefore, I talk to the patient about the nature of novel therapies and that we need to fully inhibit the target. I think for most patients it is helpful to know and, hopefully, understand the data.

AJMC®: What are the advantages and disadvantages of having such a variety of modalities? How do you see that landscape playing out in practice through combination therapies as well as multiple therapies in a treatment sequence?

DANILOV: The advantage [of having so many treatment options] is that they all have distinct AE profiles, so we can better tailor those drugs to patients' individual goals and needs, based on factors such as comorbidities. They all are active agents. I think we will see a lot of combination studies in the next few years, similar to what happened in myeloma 3 or 4 years ago when several new drugs came out, for example. There will be different combination studies with different maintenance regimens. Clearly, there are already good data combining venetoclax and ibrutinib, with or without CD20 antibodies, suggesting this is a highly active combination resulting in high levels of minimal residual disease eradication in the bone marrow.

Several questions still remain: What will be the progression-free survival, as some of the data [are] still early? How long will this regimen work for off treatment? What happens when patients relapse? How well will they respond to the same or alternative regimens?

Regarding combinations, there is focus on venetoclax and ibrutinib, mostly. Phosphoinositide 3-kinase [PI3K] inhibitors generally have a well-described but often more toxic AE profile compared [with] BCL2 inhibitors and Bruton tyrosine kinase [BTK] inhibitors. However, PI3K inhibitors are also very effective medications, and with appropriate monitoring for AEs, they can be used very successfully. One legitimate question seems to emerge: Can we use PI3K inhibitors in relapse, and how do we combine them with other new agents? The advantage of combinations is that you block multiple pathways and thereby neutralize some of the resistance mechanisms that emerge early, such as resistance to BTK inhibition, and potentially block emergence of resisting clone based on genetics, based on mutations in BTK. Despite lingering questions, combinations with targeted therapies still represent the future, and that's where a lot of studies will go.

In terms of sequential use, a lot of data are emerging now. We know that venetoclax works well in patients who progress on ibrutinib. Data [are lacking] to show that the same may be true in reverse. Ibrutinib will be expected to be effective in venetoclax relapses. Thus, until we come up with a combination strategy that is effective and suppresses the disease for many years, sequential use of the drugs will be preferred.

AJMC®: Can you talk about the practical implications of this fast-developing field?

DANILOV: There will be an increasing transition away from chemoimmunotherapy regimens toward novel targeted agents. I'm already seeing a significant pickup of targeted therapies being used in relapsed or refractory CLL. Ibrutinib has become one of the most prescribed drugs in CLL. I think this will continue to increase. I do see that community practices, particularly larger ones, are pretty good at uptake of the new novel agents. Some of the smaller, rural practices may experience a delay in their use. [Another reason] I anticipate there will be an increase in use of novel agents over chemotherapy [is that] many patients with CLL are older and present with multiple comorbidities. Most patients have at least 1 serious comorbidity, so often we are limited in terms of how we can use chemotherapy, how much chemotherapy we can give, [and] whether we can give a full dose to achieve high advocacy. In that sense, targeted therapies are often easier and safer, which is why their use will likely increase over the next few years.

AJMC®: What are the most significant unmet needs in the CLL treatment spectrum, and how do you see those being addressed in the next couple of years?

DANILOV: Relapses of disease represent a significant unmet need. Patients with high-risk disease, particularly those with del(17p), complex karyotype, are those who relapse sooner on ibrutinib and are less likely to respond to subsequent treatments. Also, patients with multiple comorbidities do not do well on ibrutinib. I think the way this will be addressed is through early use of drug combinations and early achievement of responses, so that there's no time to develop a genetically mutant clone.

The other approach would be taking full advantage of PI3K inhibitors. This development has been a little slower, but these agents have high efficacy and well-described AE profiles, and we anticipate they work in patients who develop *TP53* and *BTK* mutations. In terms of patients with high-risk disease with del(17p), the use of novel agents in an earlier setting and avoidance of chemotherapy will improve outcomes in the future [for those] chromosomally prone to acquiring new mutations. By completely eliminating chemotherapy in that patient subgroup, we are already making a significant impact.

Finally, I think chimeric antigen receptor [CAR] T cells are getting more and more momentum in CLL. New research presented at the ASH meeting is offering insights into CAR-T as a potential approach to patients' resistance to novel therapies and to patients with high-risk disease. In general, the future is bright, and there are many emerging strategies for how we can approach those unmet clinical needs.