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CLL & MCL Patient Management Strategies: A Review of the NCCN Guidelines

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

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck and joining me to take a look at patient management strategies for chronic lymphocytic leukemia and mantle cell lymphoma, is Dr. Thomas Kipps, a Professor of Medicine at the UC San Diego Moores Cancer Center. Dr. Kipps, welcome to the program.

Dr. Kipps:
Well, thank you very much. It's a pleasure to be here.

Dr. Turck:
Let's dive right in, Dr. Kipps. What are some key prognostic factors for patients with chronic lymphocytic leukemia, or CLL for short and how do they differ for patients with mantle cell lymphoma, also known as MCL?

Dr. Kipps:
I think that it's very important when recommending therapy that a full discussion be with the patient and the patient's family regarding the potential adverse events that might occur with the use of any therapy. The patient and the patient's family are with the patient 24/7 and they can look for adverse events early and bring them to the attention of the medical team so that we can mitigate the more serious consequence of not recognizing these adverse events earlier.

With the use of chemo immunotherapy, we know that there can be adverse effects of myelosuppression with anemia and thrombocytopenia and neutropenia. This may require transfusion support, blood product support, and the use of recombinant growth factors such as G-CSF. Patients need to be carefully monitored with their complete blood counts and potentially given prophylactic antibiotics to mitigate the risk of opportunistic infection.

With the use of some of these newer targeted therapies there's fewer adverse effects but there's still adverse effects. And these could be mostly low grade 1 or 2 including myalgias, arthralgias, a rash, sometimes diarrhea, and general malaise. However, the patients typically can work through these and often times I've noted that some of these adverse effects do attenuate over time. A more serious complication could be one of bleeding complications because the BTKi drugs typically may interfere with platelet function. There's also the risk of cardiac arrhythmias, notably atrial fibrillation, which can occur spontaneously, particularly in older men, but the incidence of the use of these drugs when the use of these drugs actually seems to be higher. And so that's something that has to be called out and if the patients experience irregular heart rhythms or difficult cardiac issues, they should be evaluated not only by their hematologist/oncologist, but also by their cardiologist and to determine whether this may require systemic anti-coagulation therapy, which then perhaps may increase the risk for bleeding complications.

The risk of the use of BCL2 inhibitors is most profound with the potential for tumor lysis syndrome. So, patients who have bulky disease, high white counts may risk having the tumor actually undergo cell death all at once and that could increase serum potassium levels and that could be very adverse to cardiac conductivity. That has to be very closely monitored to keep the potassium level down so it doesn't have lethal consequences. That's only with the initiation of therapy after the therapy is maintained into the level of where you would maintain patients. We have to look for neutropenia, which may itself increase the incidence of opportunistic infection and that has to be then addressed potentially with the use of G-CSF to improve the neutrophil counts during therapy. But it's not necessarily an indication

for stopping therapy if the patient is responding to G-CSF to improve the neutrophil count.

Dr. Turck:
Keeping those features in mind, let's take a look at the updated NCCN guidelines for both CLL and MCL. Starting with CLL, what do the guidelines recommend for treatment?

Dr. Kipps:
Well, the NCCN guidelines have undergone many recent revisions. And notably, the use of chemo immunotherapy is not listed as a primary indication for frontline or second-line therapy. The advent of these newer targeted therapies, namely inhibitors of Bruton's tyrosine kinas or BTK have actually become put at the forefront for a consideration of primary or initial therapy.

There's another category of drug which has also been introduced and is very effective in the treatment of patients with chronic lymphocytic leukemia and that is the drug venetoclax, which is a small molecule that can inhibit BCL2. This molecule can induce cell killing or apoptosis of leukemia cells quite dramatically, making the major risk of that drug the initiation of therapy where patients may suffer tumor lysis syndrome. With the proper management of that, however, it's a relatively well-tolerated drug and it can induce very deep clinical remissions with complete responses and eradication of detectable minimal residual disease. The outcome of patients treated with venetoclax-based treatment regimens typically in concert with an anti-CD20 antibody, such as rituximab or obinutuzumab have really helped to define this as an important initial therapy for patients with chronic lymphocytic leukemia. So, in the NCCN guidelines, we have a choice between initiation of inhibitors of BTK, which the primary first drug to introduce in that category was ibrutinib and now we have also acalabrutinib and now more recently zanubrutinib that have been approved for the treatment of patients with CLL. And patients can choose that verus a therapy that can induce deeper remissions and potentially can give the option for fixed duration therapy with venetoclax-based treatment regimens which typically include venetoclax and either rituximab or obinutuzumab.

So, this is a game changer for chronic lymphocytic leukemia patients. Namely the NCCN guidelines is not mentioning the use of chemotherapy as a primary frontline treatment option for patients. And so targeted therapies have clearly shown themselves to be superior in randomized clinical studies, making the NCCN guidelines community give these recommendations.

In mantle cell lymphoma, however, we have still to grapple with the fact that it's a more aggressive disease by and large and patients typically are recommended to have multi-drug chemo immunotherapy regimens such as CHOP-R or maxi-CHOP-R, which is including more dose-intense treatment option. There's also treatment options with oxaliplatin as well as daunorubicin containing regimens. Obviously these regimens are more difficult to take, particularly as we get older and one has to do a detailed assessment of cardiac function, marrow status, and the like, prior to giving such treatments to patients who are elderly with mantle cell lymphoma. So, there are less intensive regimens which might be deemed as mainly palliative including agents such as bendamustine and rituximab.

The stratification of patients with mantle cell, as I mentioned earlier, really is based on the ECOG performance status, as well as the LDH and the serum beta-2 microglobulin level, along with the white blood cell count. It's clear that patients with more aggressive disease will advance more quickly and typically, more intensive regimens are recommended for such patients. It's not until the patients have gone through such therapy that there has been the exploration of use of these targeted therapies, such as the BTK inhibitors or venetoclax as I mentioned to you earlier. And I think that this may change as we are able to introduce these drugs in very well-conducted and tightly-controlled clinical trials that can assess the outcome of patients treated with these agents versus multi-agent chemotherapy.

Some of the multi-agent chemotherapy regimens used in mantle cell lymphoma are considered a segue to allogeneic stem cell transplantation and so this is a very intense treatment regimen, but if there's a suitable matched related or unrelated donor and the patient's performance status and age is one that is amenable for use of allogeneic transplantation, then that could be consideration following intensive chemo immunotherapy with an attempt to irradicate the disease and provide a more long-lasting clinical remission.

Dr. Turck:
And what do we need to know about NCCN treatment recommendations when it comes to MCL?

Dr. Kipps:
Well, one of the exciting developments, too, is the use of some of the targeted therapies that have been transformative for treatment of patients with chronic lymphocytic leukemia and patients with mantle cell lymphoma. So, I mentioned the inhibitors of BTKi have clearly demonstrated activity in patients with mantle cell lymphoma and these agents typically are easier to take and with less adverse events than we find with chemo immunotherapy and clinical trials certainly are ongoing to establish potentially a primary role for use of some of these targeted agents in the treatment of patients with mantle cell lymphoma. I'm talking about drugs such as ibrutinib, acalabrutinib, or now more recently, zanubrutinib clearly have demonstrated clinical activity in patients with the disease allowing for oral therapy and that's much less toxic in terms of myelosuppression or immune suppression.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck and I'm speaking with Dr. Thomas Kipps about managing chronic lymphocytic leukemia and mantle cell lymphoma.

So, Dr. Kipps, if we keep our focus on the NCCN guidelines for just another moment, what do you think are some of the more salient characteristics of the therapeutic agents you had mentioned for CLL and MCL?

Dr. Kipps:
Well, some of the more salient features of the agents recommended for use in the treatment of patients with chronic lymphocytic leukemia are the fact that these are targeted therapies which really are not your typical chemotherapy, which has basically been developed through advances in drugs that can inhibit more rapidly dividing cells. They have certainly proven themselves to be effective and useful. However, the use of some of these newer agents, namely inhibitors with BTK or inhibitors to BCL2, these regimens in head-to-head comparisons with standard chemo immunotherapy regimens have shown themselves to have a superior outcome with less toxicity, less myelosuppression, and improved progression-free survival, and yes, improved overall survival. So, this is now been a change in terms of replacing the recommendation for chemo immunotherapy as a frontline to give way to these new targeted therapies as the indication for primary treatment.

Whereas in mantle cell lymphoma, we are still in the issue of recommendations for patients being consideration of some of these multi-agent chemo immunotherapy regimens as a primary consideration. The thought being that the disease perhaps is more aggressive and there's an attempt then to obtain control of the disease and some patients may have a good performance status and good progression-free survival after the use of such regimens. However, I look forward to the day when we can make the recommendation for initial therapy being again some of these more targeted therapies which are more selective and able to interfere with either key signaling pathways or survival pathways that are used by the lymphoma cell and therefore we can get a more specific and targeted treatment of the disease in patients with mantle cell lymphoma.

Dr. Turck:
And what are some strategies you recommend to help patients manage the adverse effects of these treatment regimens?

Dr. Kipps:
I think research in chronic lymphocytic leukemia has defined two types of CLL essentially. One type is derived from a more primitive B-cell and this type expresses unmutated immunoglobulin genes or antibody genes. The other type is derived from more differentiated B-cell that has mutations in the antibody genes. So, by looking at the leukemic cells, we can distinguish patients as to whether they have leukemia cells that express mutated versus unmutated antibody genes. In the former, we know that the disease tends to be more aggressive and patients typically require therapy withing three to five years of diagnosis. Whereas patient with leukemic cells that express mutated antibody genes typically may have five to nine years of waiting before the require therapy and some patients may not require therapy at all. So, this has been very helpful. Obviously, there are exceptions to this rule but it's been very useful in distinguishing two different types of patients.

The strategies for looking at how to stratify patients has incorporated many different types but, one of the oldest one, the Rai Binet staging system really looks into the fact that patients who have evidence of marrow suppression, namely anemia or thrombocytopenia typically are considered to have more advanced disease and a poorer prognosis than patients who have not advanced that particular stage.

With regard to mantle cell lymphoma, the disease tends to be derived from more primitive B-cell. These cells typically will express mutated, unmutated antibody genes, rather. The prognostic index of mantle cell, namely the Mantle Cell International Prognostic Index, or MIPI, has been shown to be of value in stratifying patients who have different outcomes in response to therapy or outcomes in general. And that involves the assessment of the patient's performance status, the ECOG performance status, for example, the serum lactate dehydrogenase level, the serum beta-2 microglobulin level and also the white blood cell count.

I think this MIPI index has been validated, particularly in reference to the era of chemo immunotherapy where many of the frontline recommendations still reside within the use of chemo immunotherapy. What's been a very important outcome is the fact that with the advent of newer targeted therapies, some of these prognostic features may be falling by the wayside. Namely, in chronic lymphocytic leukemia, patients with ether mutated or unmutated antibody genes appear to have a very similar progression-free survival on these drugs and therefore the adverse prognostic influence of this disease characteristic may be attenuated by the use of these newer agents. I'm optimistic that we'll see similar changes in patients of mantle cell lymphoma as targeted therapies are validated to serve patients even as initial therapy for the treatment of their disease.

Dr. Turck:

Now, we're almost out of time for today, Dr. Kipps, but before we close what are some recommendations you can offer your colleagues to help them incorporate the NCCN guidelines into practice with the goal of optimizing outcomes in CLL and MCL?

Dr. Kipps:
Well, I think it's important, I know that sometimes we often times take ourselves too seriously. I'm on the NCCN guideline committee for chronic lymphocytic leukemia and we do make recommendations based upon our critical review of outcome data based largely on phase 3 clinical trials and if very rarely is it based upon single arm trials because of the need to compare efficacy between different treatment regimens. This is often times taking into account the considerations of risk, as well as the potential benefit and the recommendations are based upon evidence that we have been able to assimilate from the literature.

I think that it's helpful for physicians to heed the recommendations of the NCCN guideline committee because it does incorporate then the recommendations made based upon the analysis of the evidence. I think however, sometimes patients may be treated perhaps in ways that are not according to the NCCN guidelines and I think that this is probably based upon historic preference choices that oncologists may have for treating patients with different regimens. There's also the assumption that treatment could be perhaps delayed with the use of these newer agents until you actually need them after having failed chemo immunotherapy. I have a hard time understanding the rationale for such measures because often times the use of chemo immunotherapy repeatedly can lead to increased incidence of mutations in genes such as TP53, which can obviously make the patient less amenable or less sensitive to chemotherapy but also may mitigate the activity of these newer targeted agents.

Now, in terms of the use of chemo immunotherapy for mantle cell lymphoma, it's often times said that your first shot on goal is your best chance for obtaining a deep remission. Obviously if you're using regimens which are not able to induce a very dramatic response in patients, I think that using a different regimen may be more complicated because the patient may have incurred toxicity from the initial regimen. And that is a very important consideration to choose wisely and to perhaps monitor the response because typically the initial responses over the first two cycles can actually almost predict what the outcome is going to be if you go the distance. And a patient who is clearly not responding to the initial few cycles of chemo immunotherapy should perhaps be considered for alternative treatments sooner than going the distance and completing the full six cycles of treatment. That's a way of mitigating some of the risk that you might have with use of those regimens.

Dr. Turck:
Well, with those tips in mind, I want to thank my guest, Dr. Thomas Kipps for joining me to discuss the NCCN guidelines for the treatment of chronic lymphocytic leukemia and mantle cell lymphoma. Dr. Kipps, it was great having you on the program.

Dr. Kipps:
Well, thanks very much.

Announcer:
This program was sponsored by Lilly. To revisit any part of this discussion and to access other episodes inthis series, visit ReachMD.com/projectoncology where you can Be Part of the Knowledge. Thanks for listening.