The Evolving Landscape of Chronic Lymphocytic Leukemia: Selecting and Managing Targeted Therapy

Announcer:
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Here is your host, Dr. Paul Doghramji.

Dr. Doghramji:
Chronic lymphocytic leukemia, or CLL is the most common leukemia in western countries. In the United States, alone, CLL is responsible for 21,000 new cancer cases and 4,000 deaths every year. The availability of targeted therapies has dramatically transformed the therapeutic landscape for CLL, allowing for the personalization of treatment based on a variety of patient and disease-related factors. In this educational activity, we will review current and emerging strategies for the treatment of patients with newly-diagnosed and relapsed or refractory CLL. We will also review emerging approaches to therapy and strategies for individualizing the selection of treatment regimens for the first and subsequent lines of therapy.

I’m your host, Dr. Paul Doghramji, and I would like to welcome my guests, Drs. Seema Bhat and Nina Wagner-Johnston.

Dr. Bhat is an Associate Professor in the Division of Hematology at the Ohio State University Comprehensive Cancer Center. Dr. Bhat, thank you for joining us.

Dr. Bhat:
Thank you very much Dr. Doghramji. Thank you for having me.

Dr. Doghramji:
OK, and Dr. Wagner-Johnston is an Associate Professor of Oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University. Thanks for being here, today, Dr. Wagner-Johnston.

Dr. Wagner-Johnston:
Thanks so much. It’s a pleasure to be here.

Dr. Doghramji:
Let’s begin. One of the most frequently asked questions among healthcare providers in community practice is, ‘When is treatment warranted in the patient with CLL?’. Starting with you, Dr. Wagner-Johnston, what factors do you consider when you are weighting the choice of treatment versus observation?

Dr. Wagner-Johnston:
Thank you for the question. There are some misconceptions about when to start treating. For example things like 17p deletions do not automatically indicate the need for starting therapy. If the patient’s counts are normal and the patient is feeling well, observation is completely appropriate.

More specifically, for patients with low and intermediate risk CLL at presentation, we actually look for indications for starting therapy. These could be disease-related symptoms like severe fatigue, night sweats or weight loss. We also look at end organ function and consider treatment in patients with progressive bulky disease or progressive cytopenias, such as anemia or thrombocytopenia, or in the case of autoimmune cytopenias, those that are steroid refractory. Once an indication is present, then we would evaluate things like 17p deletion, TP53 status, as well as the IGHV mutational status that can be important in treatment decision-making.

In patients with high-risk CLL, progressive cytopenias would be an indication for treatment. Though even in this case, observation may be appropriate if the cytopenias are mild and stable.

Dr. Doghramji:
Dr. Bhat, when treatment of CLL is warranted, what treatment regimens do you currently consider most often as first line systemic therapy?

Dr. Bhat:
If we look to current clinic practice guidelines, preferred first-line regimens for CLL with or without deletion 17p or TP53 mutation, are currently either based on BTK inhibitor or BCL-2 inhibitors.

These include acalabrutinib with or without obinutuzumab, ibrutinib and venetoclax with obinutuzumab. Age and functional status are important factors that we use to guide therapy, which we can talk about later in this activity.

For patients who do have a response to BTK inhibitor therapy, we may continue to treatment until progression. By contrast, we may go with observation if the patient has response to chemo-immunotherapy or FCR, which is an option that we would consider for patients with ig-h3 mutation CLL without other high-risk features, or a targeted therapy with fixed duration treatment.

Dr. Doghramji:
Dr. Bhat, it’s interesting that you mentioned continuous therapy and fixed duration treatment. Dr. Wagner-Johnston, what are the key issues when considering whether to give timed, limited, or continuous therapy?

Dr. Wagner-Johnston:
One of the real challenges in treating patients with CLL is balancing efficacy with the tolerability of that treatment. We know that treatment with BTK inhibitors is very effective, but usually requires continuous therapy. In other words, the treatment continues until the patient progresses.

Continuous treatment can lead to resistance and disease relapse, as well as increased side effects. Balancing efficacy with toxicity is particularly important in the elderly who more often have comorbidities, functional impairment, as well as reduced organ function. These observations highlight the need for therapies that have improved efficacy, yet without increased toxicity in our elderly patients who do represent the majority of patients with newly-diagnosed CLL.

We also know that venetoclax has remarkable efficacy in CLL so the combination of venetoclax plus obinutuzumab as studied in the CLL14 trial is a very compelling regimen.

Dr Bhat, why don’t you summarize here the results of the CLL14 trial?

Dr. Bhat:
Certainly. As you noted, CLL14 is the multinational, open-label, phase 3 trial, which enrolled patients with CLL and coexisting conditions. CLL14 compared venetoclax plus obinutuzumab to well-established regimen of chlorambucil plus obinutuzumab. The 24 month, progression-free survival was superior for the venetoclax/obinutuzumab arm at 88% versus 64% for chlorambucil plus obinutuzumab arm with a hazard ratio of 0.35. The benefit was seen regardless of TP53 or IGHV mutations status. There were no significant differences in the safety endpoints, with similar incidences of neutropenia and infections.

Dr. Wagner-Johnston, what’s your take on the choice of time-limited versus continuous therapy?

Dr. Wagner-Johnston:
Yeah, Dr. Bhat, I really feel that that decision needs to be individualized, whether you are going to choose time-limited therapy versus continuous therapy. Fortunately, there’s an ongoing phase 3 study which is directly comparing the efficacy of continuous ibrutinib monotherapy with fixed duration venetoclax plus obinutuzumab, as well as fixed duration ibrutinib plus venetoclax. And the primary endpoint in this trial will be progression-free survival. So, we anxiously await those results to help, help inform this decision.
Dr. Doghramji:
For those who are just joining us, this is ReachMD. I’m your host, Dr. Paul Doghramji and joining me to discuss targeted therapies for chronic lymphocytic leukemia are Drs. Seema Bhat and Nina Wagner-Johnston. Earlier we spoke a bit about key issues when considering first-line therapies for CLL.

Now, let's shift our focus to treatment options in the setting of relapsed or refractory CLL. Dr. Wagner-Johnston, what’s your approach to managing disease progression?

Dr. Wagner-Johnston:
Although some of our patients may experience prolonged remission, CLL remains incurable. And so, for most patients, the disease course is marked by disease progression that requires additional therapy. In the past, we had very few options for these patients. But that’s changed due to the introduction of novel agents with proven efficacy beyond the first line. This includes treatments such as acalabrutinib and ibrutinib, BTK inhibitors, as well as venetoclax, the BCL-2 inhibitor, and then lastly, the PI3-kinase inhibitor, such as duvelisib and idelalisib. So, I look at the second and subsequent lines of therapy, the list of preferred treatment regimens is somewhat longer than in the first line. However, note that the regimens with category one evidence in the NCCN guidelines include acalabrutinib, ibrutinib, and venetoclax plus rituximab. Duvelisib and idelalisib are available and approved in this setting, though we don’t often use them and that’s specifically because of concerns regarding toxicity.

Dr. Wagner-Johnston:
Dr. Bhat, perhaps you could chime in and go over some of the supporting evidence?

Dr. Bhat:
Yes, thank you. It would be worthwhile to review some of the evidence from randomized controlled trials, supporting these category 1 recommendations. We know ibrutinib is approved for the treatment of adult patients with CLL, including those with 17p deletion. It can be given as a single agent, or in combination with rituximab, with obinutuzumab, or with bendamustine and rituximab. We recently saw the final analysis of RESONATE, which included up to seven years of follow-up of patient’s with CLL who received single-agent ibrutinib treatment. Updated results showed median progression-free survival remaining significantly longer for ibrutinib versus ofatumumab with up to 7 years follow-up. At 6.5 years, progression-free survival was 61% in patients treated with ibrutinib versus 9% in patients treated with chlorambucil. Progression-free survival benefit was observed across all sub-groups, including in ibrutinib-treated patients with high-risk genomic features of unmutated IGHV. Overall survival at 6.5 years was 78% with ibrutinib treatment. Overall response rate was 92% for ibrutinib-treated patients. CR/CRi rate increased to 34% with this follow-up. Safety profile was consistent with previous reports, with grade 3 or higher hypertension and grade 3 or higher atrial fibrillation remaining same as previous reports. These long-term results confirmed that ibrutinib has robust efficacy, regardless of high-risk features in patients with relapsed refractory CLL.

We also need to be aware of results from ASCEND, the phase 3 randomized trial demonstrating the efficacy of acalabrutinib monotherapy versus investigator’s choice of either idelalisib plus rituximab or bendamustine plus rituximab in patients with relapsed or refractory CLL.

The primary endpoint of progression-free survival, as assessed by independent review committee and intention to treat population, was significantly longer with acalabrutinib at median of 16.1 months follow-up. Progression-free survival was not reached for acalabrutinib was a 16.5 months for investigator’s choice of treatment with hazard ratio of 0.31. Estimated 12 month progression-free survival was 88% for acalabrutinib was a 68% for investigator’s choice of treatment. Thus, acalabrutinib significantly improved progression-free survival and had an acceptable safety profile compared to, especially idelalisib plus rituximab.

Finally, venetoclax is approved for treatment of adult patients with CLL. It can be given as monotherapy in combination with obinutuzumab or in combination with rituximab. Returning to the theme of time-limited treatment, we recently saw a very significant update of MURANO, a global phase 3, open-label, randomized study that evaluated the fixed duration combination of venetoclax plus rituximab, followed by venetoclax monotherapy up to a maximum of 2 years. This update was significant not only for the updated PFS and OS results, but also for analysis of minimal residual disease, as we will review, next.

The main point regarding progression-free survival and overall survival is that the benefits previously observed were sustained. With this update, we now have the median progression-free survival of venetoclax/rituximab-treated patients of 53.6 months, compared to 17 months with a control arm of bendamustine plus rituximab. At 5 years, overall survival was 82% for venetoclax plus rituximab-treated patients, and 62% for bendamustine plus rituximab-treated patients. Also, no new safety signals were identified.

Dr. Wagner-Johnston, would you like to discuss the MRD results from MURANO?

Dr. Wagner-Johnston:
Sure. Thanks, Dr. Bhat. As, as you mentioned, the update was sign, not only for the PFS and OS results but also for analysis of MRD.
You can see that among patients who completed venetoclax monotherapy, the majority had undetectable MRD at the end of therapy and remained undetectable at the end of this follow-up. You can see that for patients who are undetectable, highlighted by the green curve, they had significant prolongations of PFS compared to those with low MRD versus high MRD. In some, MRD status is a robust predictor of outcomes in patients with CLL.

Dr. Doghramji:
Thank you both for reviewing the treatment options in the setting of relapsed or refractory CLL and the supporting evidence. So, regarding the BTK inhibitors, namely ibrutinib and acalabrutinib, Dr. Wagner-Johnston, is there any evidence to suggest that one would be preferred over the other in the treatment of relapsed or refractory CLL?

Dr. Wagner-Johnston:
Thanks, it's a good question. Certainly, the availability of BTK inhibitors has dramatically changed the CLL treatment landscape. And as just described, we have phase 3 randomized, controlled data from both RESONATE, in the case of ibrutinib and ASCEND in the case of acalabrutinib. Results from ELEVATE, a randomized, phase 3, open-label, non-inferiority study of acalabrutinib versus ibrutinib in patients with previously treated high-risk CLL were just presented as ASCO this year. While survival rates were similar, acalabrutinib had lower rates in the atrial fibrillation and other adverse events than ibrutinib for previously-treated CLL.

Dr. Bhat:
I would like to add in here that, ELEVATE-RR was designed as a non-inferiority study and, both ibrutinib and acalabrutinib were equally effective in this. And what that means is that for a patient who has no cardiac risks and for ibrutinib, at least for now, we have the longest follow-up available. For someone who has no cardiac risk, I would still pick ibrutinib as my frontline choice for those patients. And for someone who has cardiac risks and are more prone to, risks for atrial fibrillation, for those, I would prefer acalabrutinib. So, yes both these drugs are available to us, and I would pick the right patient for these two medications. And it’s good that we have options available for the right patient.

Dr. Doghramji:
Earlier we discussed the important current and emerging treatment regimens for frontline and relapsed refractory CLL, so Dr. Bhat, are there other treatment options that need to be considered besides what we have already discussed?

Dr. Bhat:
Yes, absolutely. Our previous discussion of CLL treatment options made the choice of regimen seem relatively simple, though as the slide shows, there are quite a few potential regimens we could consider. This is not a complete list, just to be clear. In addition to these treatments settings, we also may need to consider maintenance treatment, therapies, like lenalidomide or ofatumumab as an option for patients who have a CR or PR after second line, therapy. Although this list is long, familiar things are underlying the list, like chemotherapunotherapy, BTK inhibitors, BCL-2 inhibitors, PI3-kinase pathway inhibitors, as you guys can see on the list in the slide.

Dr. Doghramji:
Dr. Wagner-Johnston, what impacts your treatment selection when you are considering therapeutic options for a specific patient?

Dr. Wagner-Johnston:
Selecting therapy really requires us to consider a number of patient and disease-related factors. And even socio-economic aspects of care. Age and functional status are very important. Some key factors to consider include frailty or comorbidity and age. So, specifically, comorbidity comes into play quite frequently when considering frontline therapy. So, for example, if somebody has cardiac issues, then treatment with a BTK inhibitor may be, reserved in preference you would choose venetoclax because of that concern.

We also need to consider risk markers, including 17p deletion, as well as their TP53 status and their IgVH mutational status. Some commonly used treatments have characteristic toxicity that need to be considered, as I just mentioned. And then we can’t forget about patient preferences. We need to recognize the importance of patient communications, as well as shared decision-making in this important process.

When it comes to treatment sequencing, we also need to think about prior therapy. So, for example, if somebody has progressed on ibrutinib, then treatment with acalabrutinib really may not be wise. And similarly, if somebody had progressed on a venetoclax-based regimen, the second line therapy is likely then to be switched to a BTK inhibitor.

Dr. Doghramji:
Dr. Bhat and Dr. Wagner-Johnston, this would be a good time for our audience to hear some patient examples. Could you provide some examples of how these factors might be considered to individualized treatment selection and sequencing for specific patients with CLL? Dr. Bhat let’s start with you.
Dr. Bhat:
Sure, we can discuss for example a 75-year-old male who has a SIRS score of 8 with an EGFR of 45 presenting with mild fatigue and dyspnea, has a mutated ig-h3 that means good risk, has a del(13q) by FISH, which again is a good risk prognostic marker no TP53 mutation on NGS, so what would I choose for initial treatment and what would be second line treatment on disease progression if the patient progresses, on initial treatment? So, let's go, step-by-step. So, this patient has fatigue and dyspnea, so probably needs treatment. So, looks like this is a good risk disease mutated ig-h3, no TP53, FISH shows probably there's no mention but looks like only del(13q), though IGHmutated del(13Q), no TP53. So, older patient, 75, so, what would be my initial choice of treatment? So, looking at the comorbidities has a high SIRS score, has a low EGFR, so, what would I choose? With a low EGFR, I get a little bit concerned about giving the BCL-2 inhibitor venetoclax which needs hydration there's a risk of TLS, although I do not have a mention of the tumor bulk in this patient. If the patient has a high tumor bulk, there's a risk of tumor lysis syndrome, there is a need for hydration, so I get a little bit worried about TLS and need for hydration. So that I would explore that a little bit more with scans, what's the lymphocytic count in this patient, again high SIRS scores states there are maybe a little bit more organ dysfunction in this patient. What's the cardiac status? I would like to know that about this patient. Given the good risk, I would go either with BTK inhibitor or BCL-2 inhibitor. But given the renal dysfunction, I would choose, BTK inhibitor in this patient, as my initial treatment. That being said, it's an indefinite treatment. Of course, if I use that as my initial treatment in a 75-year-old between the two, BTK inhibitors in a 75-year-old given the recent head-to-head study, that was in relapsed refractory setting I could extrapolate that in an up-front setting, I would use acalabrutinib in this patient.
So, for second line, if this patient were to progress in a couple of years, obviously we have the choice of BCL-2 inhibitor if this patient were to progress. As sequencing from, BTK inhibitor to a BCL-2 inhibitor.

Dr. Wagner-Johnston:
I agree with Dr. Bhat. I would likely start this patient on a BTK inhibitor, and I would probably start with acalabrutinib in the first line setting. And at the time of progression, as long as the patient didn't have bulky disease, ideally I would then switch to venetoclax, at that time.

Dr. Doghramji:
So, Dr. Wagner-Johnston, do you have a patient case example to share?

Dr. Wagner-Johnston:
Sure. We can talk about a 51-year-old female with a SIRS score of 2, an EGVR-a GFR, which is preserved at 95, unmutated, IgVH, trisomy 12 by FISH, no TP53 mutation on NGS. So, this would actually be considered a fairly good risk patient. And one could discuss the, you know, opportunity to give this patient, sort of, standard chemo-immunotherapy treatment and I would say that my preference still, kind of, follows that same paradigm of looking at more of the targeted treatment approaches. And so, for this patient, I would likely start her on venetoclax with obinutuzumab and then should she progress at some point in the future, at that point, I would then initiate therapy with a BTK inhibitor and likely that would be, at least currently, with acalabrutinib. Things are changing so much that it's hard to predict years out from now whether or not it would still be with acalabrutinib or with an alternative BTK at that time.

Dr. Doghramji:
Dr. Bhat, your thoughts on this case presentation?

Dr. Bhat:
Agreed. This is a prototype case for a time-limited, targeted agent, younger patient, probably doesn't want to be on indefinite treatment. Given this is unmutated IgF3, I would stay away from chemo-immunotherapy, that would have been a mutated IgHV without any other high risk features. Would go with obin for one year and has kidneys look good, low SIRS score, ren/obin for one year and yeah, if and when patient progresses after that, re-treatment with ren/obin is definitely an option for second line or at our BTK inhibitor as second line. Definitely an option. Agree with that.

I actually do have another patient that we can talk about. A 65-year-old female with previously treated high-risk CLL and atrial fibrillation. So, this patient has atrial fibrillation and as we know, our BTK inhibitors do have the risk of causing or worsening pre-existing atrial fibrillation. Now, we have to understand that atrial fibrillation, firstly is not a contraindication for using BTK inhibitors. If atrial fibrillation is well under control, we can use both ibrutinib and acalabrutinib. So, that's something that we have to understand that it's not a contraindication. However, now that we have acalabrutinib available, which has lesser incidence of atrial fibrillation compared to ibrutinib, we can favor that, given that we have had to have data available, we can favor that. The only contraindication is that if the patient has to be on warfarin for some reason, that is my only contraindication for using, or patients have uncontrolled atrial fibrillation. Those are the two, only two contraindications where we cannot use BTK inhibitors. So, we can very well use ibrutinib, acalabrutinib. I favor acalabrutinib over ibrutinib, for our patients. But for any reason you cannot use these, we definitely have BCL-2 inhibitor venetoclax that we can use for our patients.
Dr. Wagner-Johnston:
Yes, Dr. Bhat, I agree, this would be somebody that I would prefer to use the BCL-2 inhibitor, although we can, if necessary proceed cautiously with BTK inhibitors in these situations.

Dr. Bhat:
Especially if we have someone with 17p, um, minus, those are some patients where I still prefer the BTK inhibitors, or complex carrier type.

Dr. Doghramji:
Before we move on to the end of our discussion, is there another example either one of you want to share with our audience?

Dr. Wagner-Johnston:
Sure, I actually have a patient that I’ve been dealing with this week who’s an older gentleman, who presented to the hospital, as a transfer with, very bulky adenopathy, as well as an LDH that was elevated. Initially there were concerns that this was going to be an aggressive lymphoma, however, peripheral bloodflow just came back demonstrating that this is CLL. And so, there’s significant concerns for tumor lysis in this patient. The patient is thrombocytopenic, he is anemic and, and certainly needs to initiate therapy. And although I’ve said that often times in the frontline setting, I like to treat with venetoclax/obinutuzumab, I’m really concerned that this individual is going to encounter significant tumor lysis syndrome. So, in this scenario, I recommended frontline therapy with a BTK inhibitor and I’m trying to work on getting acalabrutinib, as we speak, actually.

Dr. Doghramji:
As we wrap up, what are your concluding remarks and key take-aways to share with the audience? Dr. Wagner-Johnston let’s hear from you first.

Dr. Wagner-Johnston:
Sure, I think it’s, again, very important to remember that not all patients need treatment. We really need to consider, those cases where observation is completely appropriate. We know that the pathway inhibitors, particularly BTK and BCL-2 have widely expanded our treatment option and significantly improved outcomes for patients. We do need to balance out the decision of whether or not we want to start with either time-limited versus continuous therapy and further data are needed to really drive that decision. And as mentioned, the CLL17 trial will really help inform that decision. Head-to-head study data are really needed to help inform the choice of a pathway inhibitor. And then lastly, treatment selection must be individualized based on careful consideration of patient, as well as disease-related factors.

Dr. Doghramji:
OK. And, Dr. Bhat, I’ll give you the final word.

Dr. Bhat:
Again, I agree that head-to-head study data is needed to help inform choice of pathway inhibitors. CLL17 will further define, in a head-to-head analysis, whether BTK inhibitor versus BCL-2 inhibitor, whether it will be time-limited versus indefinite treatment. Until then treatment selection must be individualized based on careful consideration of patient and disease-related factors. I agree with that. So, there’s still some data that we are waiting for.

Dr. Doghramji:
Well, with that, I would like to thank my guests, Drs. Seema Bhat and Nina Wagner-Johnston for joining me to discuss treating patients with newly-diagnosed and relapsed or refractory CLL. Dr. Bhat, Dr. Wagner-Johnston, thank you both for being here.

Dr. Wagner-Johnston:
Thanks for having us.

Dr. Bhat:
Thank you for having us.

Announcer:
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