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Advanced Therapeutic Strategies and Resistance Mechanisms in CLL

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Dr. Paneesha:
Thank you very much for joining today's CLL Knowledge Hub Wiley session. I'm Dr. Paneesha, Consultant Hematologist at the University Hospital Birmingham NHS Foundation Trust, and the Honorary Associate Clinical Professor at the University of Birmingham. Thank you very much to the Wiley team for organizing. What I want to do over the next 15 minutes is to go through the treatment algorithm in patients who have been previously treated for CLL. We will look at the BTK resistance. We'll look at the new treatment options, and including cellular therapy and the T cell engagers.

As you all know, with the introduction of the BTK inhibitor and the BCL2, the landscape of the treatment for both frontline and the second- and third-line CLL has changed. With this changed treatment landscape, we also have now how best to choose the treatment decisions and the question of optimal sequencing of treatment. With this, I wanted to highlight how do we make the treatment decisions in our patient, both in the frontline and the subsequent line of treatment? So the key three factors which will be critical in coming to a treatment decision is things which are very specific to the patient, like their own individual clinical situation, including any other concurrent medical illness like diabetes, hypertension, and the need for any ongoing medication including anticoagulation. As with the current day treatment, with the median age of CLL being 72, there will be question of drug-to-drug interaction and any toxicities.

The next factor which will impact is the CLL-specific factors: the impact of the IGHV mutation status or the TP53, and regarding the presentation with either the bulky lymphadenopathy or cytopenias. And again, CLL does have a habit of presenting with an autoimmune hemolytic anemia or autoimmune thrombocytopenia, which will make the impact on the clinical decision-making. The third and the final is the patient choice and the regime-specific factors, like the choice among the patient and the clinician, whether they want to have a fixed duration or continuous treatment. As we are in 2025 and beyond, highly likely most patients and the clinician may prefer fixed duration over continuous treatment.

Because of today's topic is more the second and the subsequent line of treatment, how do we manage patients will be dependent on the previous treatment patient have received. And again, what is the reason for discontinuation of treatment? Because the options, if it is intolerance, is different too if they have progressed on the previous treatment and also the duration of how long the previous treatment had been working well.

This is my algorithm for how do we manage patient with relapsed CLL. Again, like the frontline CLL, the main question we do need to ask right at the beginning is, do patients need an indication for treatment? And again, like the frontline, even at the second and the subsequent line, the indication for treatment is dependent on the IWCLL criteria about the cytopenias, bulky lymphadenopathy, or CLL-specific symptoms.

And if we do have an indication for treatment, our options will be dependent on their prior treatment. Because we still have a lot of

patients who have been previously treated with the chemotherapy, for those cohort, we have the opportunity of all the BTK inhibitors. In majority of the world, we have ibrutinib, acalabrutinib, and zanubrutinib as the first- and the second-generation covalent BTK inhibitors available, and we also have an option of having venetoclax along with the anti-CD20. The only anti-CD20 we can use in majority the world is rituximab in the second and the subsequent line of treatment. But on the other hand, if patients had a covalent BTK inhibitor, then the treatment will be venetoclax-based—highly likely—which is a venetoclax-rituximab.

If patient had discontinued the treatment due to intolerance, we do have evidence, that alternative BTK inhibitors, as most of the patient would have been on previously ibrutinib—so either acalabrutinib or zanubrutinib. On the other hand, if patient progressed based on a prior venetoclax-based treatment, then they have the option of having the covalent BTK inhibitors. All the three are available in most parts of the world, but based on the toxicity profile, more likely we will be using the second-generation BTK inhibitors.

Now, the most difficult cohort would be the people who are double refractory. These are the patients who already had a BTK inhibitor and the BCL2. In the last 12 months, FDA have approved two important medications. So we'll discuss about the non-covalent BTK inhibitor pirtobrutinib, and also about the CAR T treatment—mainly the liso-cel is the only CAR T treatment that is approved for the treatment of the CLL by FDA.

With this, I just wanted to run through with you the current clinical guideline. The first one is the ESMO guideline, which highlights what I just went through—the pathway exactly dependent on what people had at the first-line treatment. And the second is the NCCN guideline, again, which is dependent on the presence or absence of the 17p deletion.

This brings us to the important point of discussion—what biomarker we do need to test when people are needing treatment for the second or subsequent line treatment. We do know in the first-line setting, about 12 to 15% of patients will have either the 17p deletion or the TP53 mutation, but the second and the subsequent line, this incidence will increase. So all patients at the point do need to have an assessment for the 17p and the TP53 mutation status.

Because of the increased recognition of the complex karyotype, which is three or more cytogenetic abnormality, it is good to have a stimulated karyotyping as a prognostic marker assessment. Based on the prior treatment, if patients had an exposure to BTK, it is good to have testing for the BTK resistance in the form of the BTK-resistant mutation or phospholipase C gamma 2 mutations, as which will help in terms of choosing the treatment. As IGHV is a static abnormality, once we know the IGHV status of a patient once, there is no need to be repeated at subsequent options.

What I have done here is summarize the key clinical trials of the BTK inhibitor and the BCL2 inhibitors in the relapsed setting. The most important trial in terms of the BCL2 is the MURANO trial, with a long median follow-up, which now we had more than 7-year follow-up already presented, which showed venetoclax-rituximab has got a median PFS of nearly 55 months as compared to 17 months. And the key important information we do need to know is that majority of patients in this trial had no exposure to BTK inhibitors.

As far as the BTK inhibitors, we have three important clinical trial. One, the RESONATE, which is between the ibrutinib and the ofatumumab. Then acalabrutinib we have the ELEVATE-RR, and for zanubrutinib we have ALPINE. I will go through these trial in a much greater detail now.

The ELEVATE-RR, nearly 268 patients randomized between ibrutinib and acalabrutinib. You know, the median follow-up is nearly coming up to 4 years. And in this trial, what we showed is there is no difference in the efficacy, as highlighted in the Kaplan-Meier curve, between acalabrutinib and ibrutinib. But what was different is acalabrutinib has a better safety profile in terms of the decreased incidence of cardiac and other side effects. Only side effect which is slightly more in acalabrutinib was the headache, particularly in the initial few weeks of starting acalabrutinib. The reduction in both atrial fibrillation and hypertension is statistically significant for acala as compared to ibrutinib. ALPINE study, again, over 325 patients in each arm, randomized between zanubrutinib and ibrutinib. And when the pivotal study was presented with a median follow-up of just under 30 months, as compared to ELEVATE-RR, in this study, zanubrutinib was superior to ibrutinib not only in terms of the efficacy but also in the side effect profile. And what was even more critical is the patient with complex genetics did significantly better, as highlighted in the second Kaplan-Meier curve, which shows people with the 17p or TP53 mutation did significantly better with zanubrutinib as compared to ibrutinib. And with the extended follow-up, we do know that this benefit is significantly getting even better. So with this, I wanted to show a graphic in which how can we optimally sequence all this novel treatment in 2025. So chemoimmunotherapy in majority of the world is now completely not used in the management of the patient with CLL, even though you could make an argument for some patients with the mutated CLL in the frontline setting. But in the second and subsequent line of treatment, I think none of us will be using chemoimmunotherapy. As I've highlighted before, the option for the second and the subsequent line of treatment will be dependent on what patient had in the first line and also the genetic factors.

Now the most important question is, what do we expect in terms of the BTK resistance? This all depends upon the half-life of the BTK

inhibitor. Both ibrutinib and acalabrutinib had a shorter half-life as compared to tirabrutinib or zanubrutinib, which have a longer half-life. Patients who are on a shorter half-life BTK inhibitor, they predominantly dial up mutation in the BTK kinase C481. But patient who are on longer half-life BTK inhibitor may develop mutation in the other BTK kinase pathway, in the K4310 or Y4762. And it is important to note that there can also be BTK resistance, which is because in the phospholipase C gamma 2 pathway, which is in the downstream pathway of BTK.

What do we have in terms of managing the BTK resistance? So the C481 mutation, which gives BTK resistance, can be overcome with non-covalent BTK inhibitor. One of the most widely used BTK inhibitor which is currently approved by the FDA is pirtobrutinib. As you can see in this graphic, the non-covalent BTK inhibitors are targeting the alternative site of binding to enable BTK inhibition in spite of C481 mutation.

The pivotal study after the phase 1 and 2 BRUIN studies is the BRUIN CLL-321 study, in which nearly 120 patients randomized between the pirtobrutinib and the investigator choice being the standard of arm. The investigator choice was either idela and rituximab as per the SBC of bendamustine and rituximab. With a median follow-up of significant duration, what we see is the PFS was almost double in the pirtobrutinib arm as compared to the idela/rituximab, so this is a median follow-up of over 1.5 years.

And what the investigators concluded, which is presented in the ASH 2024, is pirtobrutinib is significantly better PFS benefit as compared to investigator choice, idela/rituximab or bendamustine/rituximab. The most important is the time for the next treatment was significantly better with pirtobrutinib as compared to the standard of therapy arm. And the key is, because of using BTK inhibitors for a long time, we are well versed with the side effect profile. And pirtobrutinib is similar to other BTK inhibitors—is well tolerated with very low treatment discontinuation, with no additional toxicity signals as compared to the conventional covalent BTK inhibitors.

So now, the 2024–2025 has always been on looking at the cellular therapies and the T cell engagers. Now we have the TRANSCEND CLL 004 combination cohort, in which a combination of the ibrutinib and liso-cel treatment. So this again was presented by Professor Wierda in the ASH December 2024. This is 65 patients receiving ibrutinib and the liso-cel, with median follow-up of just over a year, shows that a significant complete response rate and the overall response rate is nearly 90%—so 9 out of 10 CLL patients who had gone through multiple treatment achieving the remission. And the key is, the median time to first response is just 1 month, and the median response to complete remission is 3 months. As I've highlighted here, there is a significant MRD—undetectable MRD—in the bone marrow in this cohort of patients undergoing CAR T treatment.

The other treatment—with the interest of time I'm not able to go in detail, but which is again presented in ASH 2024, is the new class of drugs called the BTK degraders. And both of them, with a median follow-up over 12 months, have shown significant overall response rate with no new toxicity. Some of the first-generation BTK degraders had a higher incidence of atrial fibrillation, which is now not seen in these two new class of the BTK degraders.

We have seen significant impact of the bispecific antibodies in the treatment of diffuse large B-cell lymphoma and follicular lymphoma. Same epcoritamab, glofitamab, and mosunetuzumab have also shown efficacy in CLL and Richter transformation. And we did had a presentation in ASH showing the efficacy of epcoritamab monotherapy in patients with relapsed or refractory CLL, with an overall response rate in the range of 70%.

So I hope in the last 15 minutes I've shown you how non-covalent BTK inhibitors have overcome the BTK resistance and given options for our patient previously exposed to both covalent BTK inhibitors and also the BCL2 inhibitors. For patients progressing on pathway inhibitors, we have at least two novel treatment approved by the FDA—one being the pirtobrutinib and the other being the CAR T therapy in the form of liso-cel. Because of these treatment options, we do need to look for BTK mutation along with the other cytogenetic analysis at the point of relapsed setting, so that we can be better informed and we can choose the optimal treatment options.

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