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Uncovering Unmet Needs in Relapsed/Refractory ALL Care

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Kite Pharma. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss the current unmet needs in the treatment of relapsed or refractory acute lymphoblastic leukemia, or ALL, is Dr. Ryan Cassaday. He's an Associate Professor in the Division of Hematology and Oncology at the University of Washington School of Medicine in Seattle and an Associate Professor of the Clinical Research Division at the Fred Hutchinson Cancer Center. Dr. Cassaday, it's great to have you with us today.

Dr. Cassaday:
Thank you, Dr. Turck. It's great to be here.

Dr. Turck:
Well, to set the stage for us, what kind of prognosis do patients with relapsed or refractory ALL typically face?

Dr. Cassaday:
Historically, patients with relapsed refractory ALL have a relatively poor prognosis. Survival is generally measured in months. Many patients will ultimately succumb to their disease, even with aggressive treatment and curative-intent treatment. But that being said, there are still treatments that we can offer with the goal of cure. So even though that median survival may only be measured in months, there is a subset of patients that can be cured in that setting, in which case, depending on their age, of course, they could live for years, despite having relapsed refractory disease.

Dr. Turck:
So you mentioned treatment. Would you tell us about the current standards of care in the treatment of relapsed or refractory ALL?

Dr. Cassaday:
Unlike in the front-line setting where the treatment is relatively similar for patients with the two key subgroups of ALL, which is the T-cell subtype and the B-cell subtype, in the relapsed refractory setting, the treatment really starts to change significantly.

We've seen significant advances in new options for patients with relapsed refractory B-cell ALL, where there's a number of immunotherapy-based treatments that are now available. That is definitely where a lot of evolution has occurred, and a lot of changes have developed, particularly for those practicing oncologists that maybe don't see this disease very often. It may have changed a lot since the last time you saw a patient with this. I'll come back to that in a moment, but just so I don't forget to touch on it for the folks with T-cell ALL, unfortunately, we still have to rely primarily on traditional cytotoxic chemotherapy for patients with that situation. That is a critically unmet need, and unfortunately, there's not a whole lot to say about that setting because frankly, there's really not a lot of great options.

But getting back to B-cell ALL, the general treatments that we have in that setting come in three different groups: there's the drug inotuzumab ozogamicin, which is an antibody drug conjugate that targets CD22, and there's blinatumomab, which is a bispecific T-cell engager that links CD3 on effector T-cells and CD19 on the malignant B lymphoblasts, the first by specific agent of any sort approved for cancer treatment. And then the last therapeutic option we have are CD19-targeted CAR T-cells that currently includes two different products. There's tisagenlecleucel, which is approved for children and young adults up to age 25, and then there's brexucabtagene autoleucel, sometimes called brexu-cel. That's approved for adults, so age 18 and up.

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Dr. Turck:
And what are some of the limitations associated with those treatment options?

Dr. Cassaday:
Well, they all have very excellent early response rates. Unfortunately, as I alluded to before, when you look at survival based on populations of folks, it still remains suboptimal, to say the least. So I would say the first important limitation across the board is we are still not able to provide long-term remission for the majority of patients who receive these therapies.

When you drill down a little further, each of these treatments has its own sort of unique limitations. For example, inotuzumab ozogamicin has a black box warning associated with sinusoidal obstructive syndrome or veno-occlusive disease, a very severe form of liver toxicity. Admittedly, it's not very common. In the registrational trials, it was seen in about 10 percent of patients. There's better knowledge about how to select patients and limit the risk, whether it's reducing the number of cycles and things of this nature, but it still remains a serious problem, particularly for patients that have underlying liver disease or develop liver disease in the course of their treatment.

Blinatumomab, one of the important limitations for that drug is it is relatively less effective in patients that have had a higher burden of disease when the treatment starts. So response rates are generally less, and the toxicity is also probably a bit worse. Furthermore, because of the nature of this agent and its pharmacokinetics, it has a very short half-life, so it has to be given as a 24-hour continuous IV infusion for 28 consecutive days.

Lastly, CAR T-cells. Obviously, these have been a really important treatment advancement in a lot of different hematologic malignancies. The issues that are germane to CAR T-cells for B-cell ALL are the similar ones that we see in lymphoma and myeloma. It's largely access. Can you get patients from their local treatment facility, whether that's a smaller community or a local oncology office to the large academic center or the large medical center that can offer CAR T-cell therapy? It might take several weeks for that to happen, during which time the patient's disease may be progressing. Then there's the unique toxicities that come with this that can really only be managed at specialized centers.

So there's a lot of unique limitations for each of these therapies that are actively being explored. But I would say across the board, there's still a lot we've got to learn in terms of trying to improve survival.

Dr. Turck:
For those just joining us, this is *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Ryan Cassaday about challenges and unmet needs in the care of patients with relapsed refractory acute lymphoblastic leukemia, or ALL.

Now in addition to treatment related limitations, Dr. Cassaday, what other challenges do clinicians face in the real-world treatment of patients with relapsed refractory ALL?

Dr. Cassaday:
One of the most challenging practical issues is the fact that this is such a rare disease. And some of these treatments that are available in this setting are relatively unique across all of oncology that to find someone who has experience with the disease and those therapies can be pretty challenging. I am fortunate to work at a large center that can be very, very specialized, so our clinical team is very accustomed to these things and sees a lot of these patients. But if you are a general oncologist doing the hard work out there in the community and seeing the breadth of the human condition, you may not have seen a patient with ALL in any disease state in a year. So to have somebody with relapsed refractory disease who might be a candidate for some of these therapies, you maybe have never used a bispecific agent of any sort, much less blinatumomab specifically. You may have to refer a patient for CAR T-cells and may have only done that a few times.

So even just the practical aspects of logistically delivering these therapies and some of their nuances require a certain amount of experience and comfort that may not be immediately at your disposal. Then when you factor in the fact that this is a very aggressive malignancy often affecting young people, that adds to the level of stress and anxiety for the clinician because time is of the essence and patients are usually very eager to move along with whatever treatment is trying to be offered. So learning a lot of those nuances can be quite challenging.

Dr. Turck:
And are there any strategies you could share to help us overcome some of the treatment challenges we've been discussing?

Dr. Cassaday:
Yeah. So I think a really important strategy would be to engage the opinion of a disease expert early, particularly if it looks like there is a patient that you're treating in your practice who either hasn't responded as well to initial therapy or appears to have relapsed disease. It

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may be that that expert is able to provide some guidance with respect to choosing among the different therapies available. They may be able to suggest a specific treatment that could be given locally while something more complex or not available locally could be explored at their referral center. So for example: CAR T-cell therapy. It may be that a patient that you're treating would be a really good candidate for that treatment, but it might take several weeks for us to set up that treatment in order to be able to deliver it. While we're waiting for that time to pass, whether it's because of the insurance authorization or whatever, there may be some suggestions that can be offered for local therapy to be delivered that is more comfortable in your practice while we're working out all the logistics of trying to get the CAR T-cells set up. So even though it doesn't necessarily mean that the patient is immediately going to come to the referral center right away, we can try to help provide a little bit of a runway to try to make that transition a little easier. Alternatively, we might be able to say, you know, "Unfortunately for this, that, or the other reason, these therapies really aren't a good strategy. I think you should give X, and that could be delivered locally," and we just cross our fingers and hope for the best.

Dr. Turck:
Now if we look ahead for a moment just before we close, Dr. Cassaday, how might emerging therapies help address some of the unmet needs we discussed today?

Dr. Cassaday:
Again, just to circle back to T-cell ALL briefly, even though not a whole lot has changed there, really, any new advance in that disease is going to be a welcome improvement. So there are a number of agents that are in investigational stages at various levels. There are some CAR T-cell therapies, for example, that are being explored in T-cell ALL. None of these are close to primetime, but certainly if some of these early phase trials read out favorably, it might be that we've got better options for these folks. But unfortunately for now, we're still stuck largely with traditional chemotherapy.

As it pertains to the agents that we do have for B-cell ALL, one of the things that is currently happening—and we're already seeing it in terms of FDA approvals and updated guidelines and so forth—is some of these agents are starting to move forward into the frontline space. While that is really exciting and may lead to fewer patients relapsing and more patients staying in remission after their first treatment, it's going to potentially select-out for patients that, when they do relapse, it becomes even harder to treat them. It may be that we lose options later. So trying to understand for these folks that are treated with these agents upfront, how does that impact things later if they do relapse. Obviously, if we're curing more people in the long run, that's better, but if all we're doing is kind of picking off the lowest-hanging fruit and only making our job that much harder when patients do relapse, that may not necessarily be as great of advance as it seems right now. So obviously, further studies and longer follow-up from some of these recently presented and published studies is going to really inform some of those decisions, so that we can better understand how can we sequence these therapies? Is it better to start with this one and then follow with that one or vice versa?

The last one I'll mention because it is relatively late in terms of its development and thus may become available—it seems like it's a bit of an embarrassment of riches now—but there's actually potentially a third CD19 CAR T-cell product that could become available, maybe even by the end of this calendar year: a product called obecabtagene autoleucel, or obe-cel. It's currently under review by the FDA. A lot of folks in our field expect that it's going to get approved, so that's going to mean potentially a third CAR T-cell product for this really, really rare disease. So then it'll be should we choose brexu-cel verses obe-cel, and where does tisagenlecleucel fit in? Again, studies are going to be needed to sort that out, but until we have that, it's going to be a lot of opinion and expertise that needs to be used to sort that out.

Dr. Turck:
Well, with those forward-looking thoughts in mind, I want to thank my guest, Dr. Ryan Cassaday, for joining me to discuss unmet needs in the treatment of relapsed or refractory acute lymphoblastic leukemia. Dr. Cassaday, it was great having you on the program.

Dr. Cassaday:
Thank you, Dr. Turck. Really appreciate it.

Announcer:
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