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ReachMD
www.reachmd.com
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(866) 423-7849

Exploring Therapeutic Updates for Lymphoma

DR. SANDS:
While lymphoma can sometimes be difficult to treat, therapeutic updates and clinical developments could lead to tailored treatment and improve outcomes. Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands. And here to share current treatment updates in lymphoma is Dr. Joseph Tuscano, physician and Professor of Hematology and Oncology at UC Davis Comprehensive Cancer Center. Dr. Tuscano, thanks for joining me today.

DR. TUSCANO:
You're welcome. Happy to be here.

DR. SANDS:
Let's begin by taking a look at indolent lymphoma. Can you tell us about some of the newest targeted agents?

DR. TUSCANO:
So there's a lot going on in all of lymphoma, particularly in indolent lymphoma. Indolent lymphoma really is comprised of a number of different histologies, including the most common follicular lymphoma, marginal zone lymphoma, small lymphocytic, which is the lymphomatous counterpart of CLL, and lymphoplasmacytic lymphoma, at least those are the most common. Now it used to be the clinical trials would encompass all of indolent lymphomas in those trials. And now we're really starting to do trials that really target those specific subsets of indolent lymphomas. I'll focus on follicular lymphoma and marginal zone since those are the most common and there is a lot happening there.

I think that right now, still the standard of care for the initial management of indolent lymphomas is bendamustine/rituximab. I mean, that's based on two trials, the StiL trial by Rummel et al., and the BRIGHT trial by Flinn et al. And those showed progression-free survival benefit and a lot less toxicity for bendamustine/rituximab. Now we still use a lot of single-agent rituximab for those that are infirm or do not want chemotherapy as initial therapy but not that often anymore.

But in terms of patients with relapsed disease, there are a lot of targeted agents. And probably in first relapse, the most common regimen that's used these days is lenalidomide and rituximab. And that was based actually on some data here at UC Davis over 15 years ago. We saw dramatic responses even in patients that were rituximab refractory with an overall response rate around 78 percent and about 50 percent complete remission rates.

Subsequently, there was a large, randomized trial called the AUGMENT trial that was published by John Leonard in the *Journal of Clinical Oncology,* and in that trial, they compared lenalidomide/rituximab to rituximab as a single agent. And there was a big advantage for lenalidomide/rituximab. So that's really become the standard of care in terms of relapse disease.

Now, in terms of third line, it's a pretty crowded space. But I'd say the majority of patients will be treated with either a PI-3 kinase inhibitor or a EZH2 inhibitor. So, in terms of what to use in that third-line setting, currently there are at least four PI-3 kinase inhibitors that are FDA-approved in that setting. So, I think it can be challenging for the practitioner to decide, “Which PI-3 kinase inhibitor should I use, or should I use the EZH2 inhibitor tazemetostat?” So, that can be a little bit challenging.

DR. SANDS:
So, you've mentioned various newer drugs, albeit over the last 15 years. How would you compare those to prior standard chemotherapy sequencing and then CAR T therapy?

DR. TUSCANO:
That's another challenging question, primarily because there aren't a lot of clinical trials comparing those two. In fact, most of the trials that led to the FDA approval of the PI-3 kinase inhibitors and the EZH inhibitor, tazemetostat were based on Phase 2 trials. So, it's difficult to know which is superior. I think that most practitioners or lymphoma specialists will go look at the patient profile, their comorbidities, and try and make a choice depending on their comorbidities, in terms of the relapse. Rarely in the relapse setting will we use chemotherapy any longer; we'll really reserve that for patients that have failed the targeted agent, that have failed lenalidomide, that have failed the PI-3 kinase inhibitor, and failed tazemetostat. And then will potentially go back to the older chemotherapeutic drugs because they're a lot more toxic.

In terms of CAR T-cell therapy, now that is a challenging one. There was recently a trial called the ZUMA-5 trial, and that looked at axicabtagene, or Axi-Cel is what we like to call it. Axi-Cel is FDA-approved for the treatment of diffuse large B cell lymphoma and was recently FDA-approved for the treatment of relapse follicular lymphoma. And the ZUMA-5 trial showed a very impressive overall response rate of greater than 92 percent and a CR rate of over 70 percent. And at the last follow-up, the median progression-free or overall survival had not been reached. So it's very, very effective.

The data for aggressive lymphomas and acute leukemia is very impressive, but with long-term survivals of anywhere from 35 to the low 40 percent range in patients that had failed very aggressive regimen, so they may be cured. But we do need longer follow-up. So, we're hopeful that the same will be true with Axi-Cel for follicular lymphoma. What we call the lymphodepleting chemotherapeutic regimen that we use to treat patients with CAR T-cells is a combination of Cytoxan and fludarabine. And those are very effective drugs for the treatment of indolent lymphoma and can produce durable remissions, particularly in patients that have not been exposed to Cytoxan or fludarabine, and the vast majority of patients have not because they all receive these targeted agents initially.

I think it's promising, but there are selected patients with follicular lymphoma that you should consider for CAR T-cell therapy and those are patients that are highly refractory to initial therapy. And we do subcategorize those patients into a group called POD24. And those are patients that have relapsed within 24 months of receiving CHOP, which we rarely use anymore, or bendamustine/rituximab, because those patients have a very poor overall survival. So that's one patient population that we would maybe consider it after they failed at least two lines of therapy, and that's the FDA approval requirement. Or patients that have failed a number of regimens that relapsed very quickly after targeted agents and chemotherapy those are the patients that you would consider for Axi-Cel or CAR T-cell therapy with follicular lymphoma.

DR. SANDS:
So, you mentioned aggressive lymphoma—let's transition now to focus on that. The FDA recently approved four new agents for this type of lymphoma, what can you tell us about them?

DR. TUSCANO:
There's really some interesting agents for aggressive lymphoma, and those include an antibody drug conjugate and that's called polatuzumab. Polatuzumab, a target CD79b, which is a counter receptor for the B-cell receptor, and as a single agent with rituximab, produced response rates around 40 to 50 percent. When it was combined with bendamustine, response rates were better than that. And there was a large, randomized trial that compared bendamustine/rituximab to polatuzumab/bendamustine/rituximab, and there was a big overall survival benefit and response rate benefit. So that became FDA-approved. And so, we use that pretty frequently in patients with relapsed disease, it's pretty well tolerated. It's a very effective regimen. Very well tolerated because it's the lower dose of bendamustine with the polatuzumab and rituximab. It does have some neurotox, because it uses the same toxin MMAE, monomethyl auristatin E that's used for brentuximab that's FDA-approved for Hodgkin's lymphoma.

So, one of the other ones loncastuximab, a CD19-targeted antibody drug conjugate and kind of similar to brentuximab, similar to polatuzumab, but really uses a different toxin. It's called the PBD, and it's a very, very potent alkylator. It was looked at in patients with highly refractory diffuse large B-cell. Overall response rate was 48 percent and the CR rate was 24 percent, some of those being

durable, and that was FDA-approved recently as a single agent.

The other agent is called tafasitamab. And tafasitamab—this is also CD19-targeted—but this is an engineered antibody. And what we mean by that is it's an antibody that's been engineered at both ends, at the FAB, or the antigen-binding domain, to the variable segments have been engineered to increase affinity for CD19. Then the FC portion has been modified as well to increase affinity for the FC receptor. So, not only potentially do you get better direct killing effects, or apoptotic effects, but you get better recruitment of host immune effector mechanisms. So based on that, they combined it with lenalidomide.

The last agent I wanted to mention is selinexor. And this is a completely different—actually a new class of compounds. It's called a nuclear export inhibitor, XPO, or exportin is the name of the protein inhibitor. So, it modulates the export of proteins from the nucleus, and we know that that's dysfunctional. And that actually causes dysregulation of the apoptotic regulators, something that I have developed an interest in. And so selinexor is FDA-approved for multiple myeloma. But also, recently FDA-approved for relapsed diffuse large B-cell lymphoma, in the SADAL trial that was presented at ASH has been published now, looks at Selinexor. Again, it heavily pretreated diffuse large B-cell patients. And in those patients, they found an overall response rate of really about 28 percent and a CR rate of 13 percent. And so, that might not seem like that high, but it is an oral agent. It's moderately toxic, has some mild suppressive effects, and it can cause diarrhea as well. But those patients that responded, even those patients that just had stable disease, and that's closer to about over 40 percent of patients had very durable remissions.

DR. SANDS:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Joseph Tuscano on current treatment updates in lymphoma.

Dr. Tuscano, going back a bit. Let's take a look at CAR T therapy for lymphoma. How does this type of immunotherapy compare to autologous stem cell transplant?

DR. TUSCANO:
That's a really good question. So there are three CAR T-cell products approved for relapsed diffuse large B-cell lymphoma that have failed at least two prior regimens. And that is axicabtagene, the one I already mentioned for follicular lymphoma, the other one is tisagenlecleucel, and the other one is lisocabtagene. And so those three CAR T-cell products are all FDA-approved for relapsed diffuse large B-cell lymphoma.

The most notable trial that people look to is the ZUMA-1 trial. That was the first one that was published. And that produced an overall response rate of 82 percent with over 50 percent of patients achieving a complete response. And I had already mentioned the fact that many of those responses are durable upwards of higher 30s, low 40 percent are disease-free about 18 to 24 months after treatment, so very, very effective. And maybe curative in some of those patients. So that's very, very exciting.

Now when somebody fails induction therapy for diffuse large B-cell, the standard for chemosensitive-eligible patients is salvage therapy. And those patients that respond to salvage therapy, auto transplant—you can cure probably about 40 percent of patients with an auto transplant. So, CAR T, those patients that fail auto transplant, they can be salvaged with CAR T-cell therapy. So, it's a nice sequence of events.

But the nice thing about CAR T is it's a little bit less toxic, and it's getting much less toxic with time or we're learning how to manage the cytokine release syndromes to make it less toxic. So, it's potentially something that more patients can receive, elderly patients, patients with other comorbidities.

So right now, there's some trials comparing auto transplant with all the CAR T-cell products, auto transplant to CAR T, and so we'll have the answer to that pretty soon. But I think that right now, auto transplant remains the standard for those patients that are candidates for auto transplant.

Now, if you have a patient that may not be a good candidate because of comorbidities or is refractory to salvage therapy, those patients should be considered directly for CAR T-cell therapy, because some of those patients even with refractory disease can be salvaged. And there's a study looking at elderly patients with comorbidities, and they can tolerate CAR T and have very good outcomes with CAR T-cell therapy as well, so it really expands it. Now, I'm a little nervous about replacing auto transplant with CAR T, primarily because CAR T provides a nice salvage option for patients that fail auto transplant.

DR. SANDS:
It's exciting to hear so many things going on in lymphoma. Dr. Tuscano, do you have any final takeaways for our listeners?

DR. TUSCANO:
Okay, so in a nutshell, I think that for indolent lymphoma the upfront regimen is still bendamustine/rituximab. I didn't mention but there is good data for lenalidomide rituximab actually for upfront. It was actually compared to chemotherapy, rituximab, very effective. But standard still is bendamustine/rituximab, relapse disease, lenalidomide/rituximab. When you fail, you have a number of choices that include various PI-3 kinase inhibitors and EZH2 inhibitors, but I think it's important to consider clinical trials at every step.

In terms of diffuse large B-cell lymphoma, R-CHOP remains a standard except for maybe double-hit lymphomas where it's probably R-EPOCH. Look to ASH this year maybe to see an update. It'll be exciting if there's a change in the way we manage untreated diffuse large B-cell in the relapse setting. I think it's salvage therapy and auto transplant for most patients. And those that aren't eligible or that don't respond to salvage therapy, CAR T-cell therapy. Those that fail auto transplant should be considered for CAR T-cell therapy. And again, progressive lymphomas, please consider clinical trials because that's how we make progress.

DR. SANDS:
Well, we have covered a lot of ground. But that's all we have time for today. I want to thank my guest, Dr. Tuscano, for joining me and sharing his insights on treatment developments in lymphoma.

DR. TUSCANO:
Happy to be here. Thanks for the invitation.

DR. SANDS:
I'm Dr. Jacob Sands. To access this and other episodes in our series, visit ReachMD.com/ProjectOncology where you can Be Part of the Knowledge. Thanks for listening.