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

Targeting CD123 in AML: The Latest Therapeutic Advancements

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Dr. Caudle:
This is *Project Oncology* on ReachMD, and I am your host, Dr. Jennifer Caudle. And here with me today to share his insights on the rationale behind targeting CD123 in acute myeloid leukemia, or AML for short, as well as the latest therapeutic developments is Dr. Naval Daver. Dr. Daver is a Professor and Director of the Leukemia Research Alliance Program in the Department of Leukemia at MD Anderson Cancer Center in Houston. Dr. Daver, thank you so much for being here today.

Dr. Daver:
Thank you very much. It's a pleasure to be here with you today.

Dr. Caudle:
Well, we're excited that you're here. So if we start by taking a look at CD123 at the molecular level, Dr. Daver, what can you tell us about its structure within the IL-3 receptor complex?

Dr. Daver:
CD123 is one of the major antigens that's expressed on the surface of various tumors, including myeloid tumors, such as acute myeloid leukemia, chronic myelomonocytic leukemia, and myelodysplastic syndrome, but also in certain lymphoid tumors, like acute lymphoblastic leukemia. And basically, CD123 plays an important role, we believe, in proliferation as well as expansion and tumor spread.

In fact, tumors that have a higher CD123 seem to be associated with a higher proliferation and may be more resistant to standard chemotherapy phenotypes. So it is, clinically, a very relevant and important marker both prognostically and then potentially, of course, therapeutically as well.

Dr. Caudle:
Thank you for that, and as a quick follow-up, how does the expression of CD123 differ in normal versus leukemic cells?

Dr. Daver:
CD123 is one of the very commonly expressed markers on the surface of leukemic blasts, including both mature leukemic blasts, but also on primitive leukemic stem cells, as well as hematopoietic progenitor population. This is very important because when we use any antibody-based targeting treatment, we want to address not just the mature blast population, but also ideally the stem cell population, so we can get a much deeper remission, what we call a minimal residual disease clearance.

And among the various antigens that have been tested, CD123 seems to be one of the antigens that is most widely expressed in general across various AML patient populations, but also widely expressed on the different AML subsets, including the mature blasts, the primitive hematopoietic stem cell, and the progenitor population. Also important to note that the expression of CD123 is less on the normal, healthy hematopoietic stem progenitor population, and so this differential gradient makes it a favorable target to be attacked using antibody-based therapies.

Dr. Caudle:
Right. And with all that in mind, let's apply this knowledge to the clinical setting. How can we test AML patients for CD123 expression?

Dr. Daver:
The testing is actually standard and quite simple. This can be done by one of two ways. One is called the flow cytometry, which is an automated machine that can look at the various populations of cells in either the blood or the bone marrow sample and identify both the frequency of CD123 among what we call the mononuclear cell population as well as the intensity of the expression.

The other way to look at it is with immunohistochemistry, or IHC. This is another approach that is quite standard and done in most hematopathology labs where they're able to stain using particular stains, such as CD123, that can, again, identify both the frequency and intensity of expression on the leukemic population either in the bone marrow or the blood.

Dr. Caudle:
Now, if a patient's test does confirm the presence of CD123, what kind of impact can this have on their prognosis, their disease progression, and treatment outcomes?

Dr. Daver:
So CD123 is not a very well-established prognostic marker per se. However, there have been previous studies and data showing that in patients who have a higher CD123 expression, it does seem to be associated with a more proliferative phenotype as well as resistance to standard therapy such as cytarabine-based therapies.

So in general, it does seem to be associated with a more difficult, more adverse disease profile. There are certain mutations as well where we have seen that CD123 expression may be higher, such as FLT3 mutation. These patients seem to have a higher CD123 in the acute myeloid leukemia population, and that is a mutation that is also associated with more proliferative as well as a more resistant disease.

So we think, based on a lot of this data, that high CD123 is associated with more disease that is proliferative and resistant to standard therapies.

Dr. Caudle:
Thank you for that. And, for those of you who are just tuning in, you're listening to *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle, and I'm speaking with Dr. Naval Daver about the clinical significance of CD123 in acute myeloid leukemia.

So, Dr. Daver, now that we have a better understanding of its structure and potential impacts on AML patients, can you tell us about the latest therapeutic approaches targeting CD123 that are under investigation?

Dr. Daver:
This is very important. So there are various therapies that are now being used to target CD123. I'll put them in different buckets. One of them is what we call antibody-drug conjugates. These have actually done really well in various heme malignancies for various targets.

Basically, the idea here is that you targeted particular antigens like CD123. But after targeting, there is a toxic agent or what we call a toxin that is released into the surface of the leukemia cell, causing death of the leukemic cell. You can think of it as a heat-seeking missile where the missile is guided specifically to the leukemia cell, it latches onto the leukemia cell, swoops through the CD123 receptor, and then delivers the payload more specifically into the leukemic cell, causing death of the leukemic cell.

The other approaches are using what we call bi-specific antibodies, where we have a construct that has two different receptors. One is CD3 for the T-cell; the other is CD123 for the leukemic cell, and when the bi-specific antibody engages it, it brings the CD123-expressing AML cell in proximity to the CD3-expressing immune T-cell, resulting in T-cell-mediated killing of the acute myeloid leukemia cell.

And then the third form is what we call CAR T, which is a cell-based therapy that is very potent, where we actually generate T-cells that have a receptor called a CAR receptor inserted onto them that, again, makes them home into the CD123 in circulation, causing T-cell-related death.

So all three of these are being evaluated, but the CD123 antibody-drug conjugates are the ones that are most advanced in the clinical setting at this time.

Dr. Caudle:
Excellent. And we've certainly covered a lot of information today, but before we close, Dr. Daver, do you have any final thoughts on the significance of CD123 in AML?

Dr. Daver:
We have looked at various different treatment approaches in acute myeloid leukemia. So these include target therapies that have had a lot of impact and improved responses, outcomes, and survival in AML patients in various settings. These are the FLT3 inhibitors. We

have three of them that are FDA-approved. Three IDH inhibitors are also FDA-approved, as well as now, very recently, menin inhibitors.

It's important to note that tagraxofusp is a CD123-directed cytotoxin. This is a fusion protein composed of a recombinant interleukin-3 with a diphtheria toxin as the payload. And the diphtheria toxin is the cytotoxic moiety in this treatment regimen.

And through such targeted therapies, there has definitely been progress in the last eight to 10 years. And among these, we have, over the last seven to eight years, worked with various therapies that target different surface antigens. It appears that CD123 may be the best-suited antigen target for acute myeloid leukemia and for related myeloid diseases based on its restricted expression, more predominantly on the leukemic blast, and limited expression in normal liver, kidney, coronary, and cardiac tissue, as well as the ability to have CD123 targeting in about 90 to 95 percent of AML. This is probably one of the most frequent and prevalent antigens expressed on AML.

So that is why there is a number of different approaches that have entered in the clinic to target CD123, and I do think, in the very near future, we are going to see ADC or bi-specific antibody approaches. And maybe then, even more into the future, CAR T approaches that can effectively target CD123 will actually become part of the standard treatment approach for acute myeloid leukemia.

To that point, we have started front-line studies that are adding CD123 such as tagraxofusp. Now, we're looking at this in the front-line setting in acute myeloid leukemia in combination with standard therapy for acute myeloid leukemia, such as azacitidine and venetoclax. And we're also looking at other, newer CD123 antibody-drug conjugates, such as pivekimab, also called IMGN632, which is being evaluated both in BPDCN and acute myeloid leukemia. Both of these we have presented data in various subsets of BPDCN AML, showing very good activity.

So I do think that this is a next frontier of clinical development for acute myeloid leukemia. And then we will have to see how to best optimally sequence this or combine this with existing standard cytotoxic chemotherapies, targeted therapies, and maintenance approaches, potentially post-chemotherapy or post-transplant. But this is a very important area for drug development in AML in the next few years, in my opinion.

Dr. Caudle:
As those final comments bring us to the end of today's program, I'd like to thank my guest, Dr. Naval Daver, for joining me to discuss CD123 as a therapeutic target in acute myeloid leukemia. Dr. Daver, it was great having you on the program today.

Dr. Daver:
Thank you very much, Dr. Caudle. It was a pleasure to be here.

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