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

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tbd

Dr. Sands:

NUT carcinoma is an aggressive form of cancer that is extremely rare and highly resistant to therapy and is not as familiar to physicians and oncologists as other tumor types. With a disease this rare that has a low survival rate, no defined standard treatment, and limited data, how can we ensure the best diagnostic strategies and treatment plans for patients?

Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands. And joining me to help answer these questions is Dr. Jia Luo, a medical oncologist at Dana-Farber Cancer Institute and an Instructor of Medicine at Harvard Medical School in Boston.

Dr. Luo, thanks for being here today.

Dr. Luo:

Thank you so much for having me, Dr. Sands.

Dr. Sands:

To start us off, Dr. Luo, can you tell us a little bit about the prevalence and epidemiology of NUT carcinoma?

Dr. Luo:

Absolutely. So just like you said, Dr. Sands, this is an uncommon cancer, and I think part of it is that the cancer was only defined in 2003 and is driven by a fusion oncoprotein, and so it's actually difficult to pick up, and it's a fairly new disease. In terms of the prevalence, it's actually not a hundred percent defined, but based on how many patients we've been getting referrals about, I would suspect that there's at least 300 cases alone in the US. And I think that that is an underestimate per year. I think it's probably higher if we look for it more. And in terms of the epidemiology of NUT carcinoma, just like you said, it's very aggressive. The median overall survival—so not just even progression-free survival—overall survival is 6.7 months, so it is a very aggressive disease. And a little more about it includes that it's generally a thoracic primary, so it looks like a non-small cell lung cancer or a head and neck primary, and those are the most common presentations. We generally see it in adolescent and young adult populations. The median age of presentation in most of the cohorts that we have are between 20 and 30, but I would say that don't let these diagnostic or illness scripts bias you because NUT carcinoma can actually present in any organ that has squamous histology, and we've seen it in not just midline structures—and so I know that some of you may have learned this disease is one involving the midline—but we've seen it, for instance, as GI primaries and as GU primaries, and so that's one thing to be aware of. And we're actually trying to remove the term midline from the name. Additionally, the age of diagnosis, although mostly adolescent and young adults, we've seen it as young as age 1 or 2 and as old as in the 80s.

Dr. Sands:

So you've mentioned that we're likely underdiagnosing, which highlights the fact that there are some diagnostic challenges. What would you say are some of the diagnostic pitfalls for NUT carcinoma? And what makes it look like other cancers or aspects we should be aware of when trying to decipher which patients have NUT carcinoma?

Dr. Luo:

Absolutely. So I think the reason this diagnosis is underdiagnosed is because there's actually no defined histology or organ system at the end of the day, and the ultimate biology that drives NUT carcinoma is actually molecular. So because it's a fusion oncogene that

individuals don't tend to look for, it's a diagnosis that could be missed.

And so the most common presentation of NUT carcinoma is generally a young person with a squamous or poorly differentiated cancer, and thinking through the non-small cell algorithm, a lot of times next-generation sequencing is not sent, or sometimes it is sent but no one is looking for the NUT fusion, and oftentimes it's diagnosed using RNA-based sequencing because fusions are quite difficult to detect in DNA-based sequencing.

The other thing that really helps with diagnosing this disease is partnering with your pathology colleagues. I think at this point, pathologists are very attuned to making the diagnosis of NUT carcinoma, and it can be done easily by just staining for NUT via immunohistochemistry, but sometimes it could be forgotten; and so if you're suspecting a young individual who really doesn't have much of a smoking history or the picture doesn't fit and they're coming with an aggressive, poorly differentiated cancer, I would urge you to consider testing for NUT.

Dr. Sands:

So as a follow-up to that then just to confirm, it sounds like there is an IHC stain that can be done to make the diagnosis, although maybe more specifically, there's genomic sequencing that can define it. So related to that, is the IHC stain sufficient to make the diagnosis, or is the genomic testing required? Or is the genomic testing really something to consider when the IHC stain doesn't show up but your suspicion is high?

Dr. Luo:

Great question, Dr. Sands. There's been several studies validating the IHC test, and it's 87 percent sensitive and 100 percent specific, so at this point, I think if anyone is concerned about a poorly differentiated cancer, NUT IHC really should be performed, especially if it's a presentation of the thoracic or head and neck area. And you're right that technically, sequencing is ultimately what would make the diagnosis, but oftentimes these cancers are so rapidly growing that a NUT IHC that's done by your pathology department is just going to make the diagnosis faster and potentially get people on trials and treatment faster.

Dr. Sands:

So we've mentioned that there really aren't defined standard of care treatment options for NUT carcinoma, so what are the existing therapies that are utilized? And what's driving those being the more commonly used drugs, as well as, are there scenarios where radiation or surgery end up being a part of the treatment?

Dr. Luo:

Absolutely. So right now, because this is often presenting as a poorly differentiated or squamous thoracic or head and neck cancer, most individuals are treated as if this is a squamous non-small cell or a squamous head and neck, and I think that those principles are generally great. We are going to be presenting some upcoming data. It's going to be over a hundred cases of NUT carcinoma with known treatment outcomes at the upcoming World Lung Conference. And hopefully, this paper will be published soon as well. But what we found is that we looked at different regimens, including platinum-based regimens that are typical for head and neck and thoracic cancers, and then we compared them to ifosfamide-based treatments. Based on the data we know so far, it looks like there may be a role for ifosfamide-based treatment in the nonmetastatic, locally advanced setting, but we haven't really seen durable results in other disease settings.

In terms of locally directed therapies, I think it's absolutely key for NUT carcinoma. Within this cohort, we have a series of about a dozen individuals who have been alive with NUT carcinoma for three years or longer, which is quite remarkable for this disease, and all of them actually presented with operable resectable disease, and so I think really going after this disease in an earlier setting if it's presenting like that is key to long-term outcomes. I think the other thing about this cancer is now that it's being more recognized and diagnosed, participation in a clinical trial is going to be key to advancing this field. And so I think because we don't get such great outcomes with ifosfamide or platinum-based treatments and the objective response rate is around 25–30 percent, we really should be thinking about clinical trials, and we have them both in the first-line and beyond in other lines. We should really be thinking about these clinical trials in everyone who has a diagnosis of NUT carcinoma.

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. Jia Luo about a rare and aggressive form of cancer called NUT carcinoma.

Dr. Luo, you just highlighted the importance of clinical trials in therapy, and we've talked about the very poor prognosis generally in patients. Are there subpopulations within NUT carcinoma? And which trials would you really highlight as treatment options for all or

some of those patients?

Dr. Luo:

I think the subpopulation of individuals with NUT carcinoma who do better are those who have it diagnosed early. And so going back to what we had discussed before, early recognition, you know, young person, poorly differentiated, squamous, those people should be tested, and then really up-front kitchen sink approach, you know, with consideration of locally directed treatment, surgery, and radiation; those are the people who are going to be doing better.

In terms of the promising clinical trials, we currently have four trials that are enrolling at Dana-Farber Cancer Institute here in Boston. We have a first-line clinical trial of a targeted therapy known as a BET bromo-domain inhibitor combined with chemotherapy, and then in the second-line metastatic setting, we have three clinical trials open. There is one that is combining the BET bromo-domain inhibitor, which is a targeted pill option for NUT carcinoma, with CDK4/6 inhibition. We also have a CDK9 inhibitor, so that's a drug that also targets epigenetic readers, and then a dual p300 BET bromo-domain inhibitor.

Dr. Sands:

And as a follow-up to that, if one of our listeners has a patient that they want to enroll in one of these studies, how best can they identify these studies or where they might be open to be able to get a patient enrolled?

Dr. Luo:

You are always welcome to reach out to the investigators here in Boston. We're pretty aware, I think, of all the options that are currently available. Also, just going on to clinicaltrials.gov, if you type in NUT carcinoma, you'll get a pretty good sense of the trials that are available.

Dr. Sands:

Well, with those final thoughts in mind, I want to thank my guest, Dr. Luo, for joining me to discuss how we can increase diagnosis and improve treatment of NUT carcinoma. Dr. Luo, it was wonderful having you on the program.

Dr. Luo:

It was absolutely wonderful to speak with you, Dr. Sands. Thank you so much for having me.

Dr. Sands:

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