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A Step-by-Step Approach to Managing Mesothelioma

Dr. Sands:
Today, the topic is a complicated one: a cancer with limited treatment options. Mesothelioma has been a challenging cancer to treat, but some recent FDA approvals increase the options. What those developments are and what they could mean for patients and clinicians alike is what we'll be exploring today. Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and joining me to discuss updates in mesothelioma is Dr. Aaron Mansfield, Associate Professor of Oncology and Co-director of Precision Cancer Therapeutics at Mayo Clinic in Rochester. Dr. Mansfield, welcome to the program.

Dr. Mansfield:
Thank you for the invitation.

Dr. Sands:
Let's start briefly with diagnostics of pleural mesothelioma. We'll get into some of the specifics about treatment later, but can you provide us with an overview of diagnostics and the significance of subtypes and staging?

Dr. Mansfield:
Yeah, so, when you see someone with pleural disease, there's a handful of things you need to consider. I know the topic is mesothelioma, but you always want to step back and think, "is this actually mesothelioma?" So, a lot of tumors spread to the pleura. There are some other primary tumors there, like a solitary fibrous tumor, there's also plaques that can result from asbestos exposure that are not malignant, per se. So, the first thing you want to do is just take your patient's history and put that in a context of what you're seeing. Once you've done that, you need tissue to figure out what's what, of course, and our pathologists are our best friends, there. I would say it's sometimes difficult to make a diagnosis from pleural effusion cytology alone. There's a lot of mesothelial reactive cells and that's probably where I see a lot of misdiagnoses being made. Now that we're using molecular techniques on those cells, though, it's a little easier to determine whether someone has mesothelioma or not from cytology. But if you're a purist, you'll probably want to get a biopsy and prove that these malignant cells are invading tissue planes to make a diagnosis. Not everyone does that, some people argue about what to do there.

Then, once you've confirmed this is mesothelioma, there's three main sub-types and one's really a mix of the two – someone described this as having vanilla, chocolate or swirl – but you have epithelioid, you have sarcomatoid, and then you have biphasic, which represents both. And, as you sample more areas of disease, the more commonly you find someone has biphasic mesothelioma. It's not always the case, but the more you poke or the more you resect, the more you may find that there is a subcomponent that you may have missed on your initial sampling.

The reason the histologic subtypes are so important is that sarcomatoid disease typically is a very bad actor. Our surgeons typically will not operate on patients with sarcomatoid disease, and now that we have a new immunotherapy approval – the approval was for all comers – but the larger benefit was seen in a sarcomatoid or non-epithelioid subsets. So, all those factors are important as we're considering our therapeutic options for our patients.

Dr. Sands:
And then, the chemotherapy that you're using just systemic therapy, in early-stage disease, can you take us through that a little bit, what you're considering, and what you're utilizing?

Dr. Mansfield:
So, for meso, it's rare that we use a single modality in isolation. And this is where, for us, our tumor boards are so important. We pretty

much present every case to our multi-disciplinary tumor board, with your radiation oncologists, your surgeons, your pulmonary team, etc. And we've been doing a variety of protocols, ones that smart protocol that was developed in Toronto with Dr. De Perrot, where you do a hemi-thoracic radiotherapy then an EPP. We've been doing something that Andreas Rimner and the Sloan Kettering team have been working on with some neoadjuvant chemotherapy surgery and then postoperative radiotherapy. It's rare we would just do surgery and then nothing, for what that's worth. It usually combined with another modality, albeit on one of these therapeutic pathways or surgery followed by adjuvant chemotherapy. I think the jury's still out as to what the best approach is given the low response rates to chemotherapy. I'm not entirely enthusiastic about a neoadjuvant Platinum doublet. I think we need to be trying to do more than that, but I do think looking forward, window of opportunity, these studies are very important to try to improve upon that and also inform tumor biology.

Dr. Sands:
Yeah, and you're bringing up some of those complexities of the later stage first line therapy, so let's jump into that a little bit. Take us through your thought process on first line treatment, for somebody who's got extensive, widespread mesothelioma, where you're not going to be able to treat this with surgery or radiation, and you're going to systemic therapies. What's your thought process and what are you choosing?

Dr. Mansfield:
Yeah I would say the majority of our patients fall into that camp, for what it's worth, at least the ones that we see in the upper Midwest, for whatever reason. As we're seeing them you wanna do your typical assessment of age, performance status, comorbidities and then that histologic subtype – "is this epithelioid disease or not?" And with a few months ago, with the approval received, now the conversation is, "do you start with a dual immunotherapy or not?" And for the patients we've seen since that approval with non-epithelioid disease, be it biphasic or sarcomatoid, I think the CheckMate 743 data are definitive for that subset that immunotherapy is your preferred treatment regimen, assuming they don't have an autoimmune condition or other things that immunotherapy may complicate.

When you're talking about someone with epithelioid disease, I then think you have to share that you've got a few options and then decide between them. The approval was for all comers, but when you do the subgroup analyses by histology, that immunotherapy curve does sit on top of the chemotherapy curve, but it didn't separate out when you look at the confidence interval of that hazard ratio. I think the upper end of it was 1.08. So, I don't know if there will be a tell, we'll do the extended overall survival outcomes as the data mature, but for now, I'm having a conversation with my patients where I'm talking about the chemotherapy-based regimen, the doublet with or without bevacizumab, or the Ipi-Nivo, and I think it's these drugs, as we know, from the lung cancer setting or other tumor types, that have different side effect profiles and I walk through them with that, and help them make an informed decision. At the same time as we have clinical trials we offer those, too, but just as we're talking about standard of care options, I am strongly considering immunotherapy for the epithelioid group, too, but I'm having a conversation about both options. Whereas for sarcomatoid, we know chemo really does not add a whole lot.

Dr. Sands:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands and today I'm speaking with Dr. Aaron Mansfield about the management of mesothelioma. Now, Dr. Mansfield, in the second line setting and beyond, things really get particularly interesting, I think; you've outlined how complex the first line has really become and the second line it's a bit more complex. Can you discuss what you're looking at, at progression and what your next line treatment option would be – and I assume that in some ways, that also relates back to first line that you just outlined as well.

Dr. Mansfield:
Yeah, the front line therapies complicated our whole thinking of the second line. First I'd like to add some of our patients have severe chest wall pain, so you want to ask, "is there anything you could do to palliate them with radiotherapy?" I'm not talking about hemi-thoracic IMRT, but just SBRT to an area with painful chest wall invasion, so you always wanna have that at the back of your mind, at new diagnoses or times of progression are the things you can palliate using local modalities or whatnot. After that you want to look back and see what did they start therapy with. So, since this Ipi-Nivo regimen was just recently approved, a lot of our patients who were not on clinical trials have had a platinum-based regimen. So, with that, I think for many years, we've been using pembrolizumab as a second line therapy, given its inclusion at the NCCN guidelines based on one of the keynote studies. But recently the ETOP study, the PROMISE study, which compare pembrolizumab to vinorelbine or gemcitabine, didn't really seem to differentiate immunotherapy from second line chemotherapy, and that second line chemotherapy is actually a pretty low bar to try to beat. So, those data were a little surprising, given the non-randomized data we had seen with pembrolizumab, where the median for second or third line therapy exceeded anything we had seen in the front line prior to it. So, one, those data didn't quite match. Two, when you look back, the patients in that trial had many patients with epithelioid disease and almost half the patients had no PD-L1 expression. So, as we've seemed to

learn that the non-epithelioid disease might be more responsive to immunotherapy, and PD-L1 expression may enrich for it, maybe that population for whatever reason just was geared towards not having one that's as responsive.

But just recently, Dean Fennell presented data from the CONFIRM trial, where in third line patients received nivolumab or placebo and it showed a definitive benefit of nivolumab. So, again, we're having a sort of a complicated picture as to what to do in second line, but I don't think immunotherapy is any worse than our gemcitabine or vinorelbine options. So, if a patient has received a Platinum-based doublet or with our without the bevacizumab in the front line, I am going to consider offering them immunotherapy or clinical trial with immunotherapy with the NCCN guidelines, including Ipi-Nivo. You may get more benefit with that than you might with pembro or nivo, but we now have data with both of those drugs as single agent, and then from the French group, we have data with Ipi-Nivo where it wasn't compared to nivo alone, but the curves sat on top of single-agent therapy. So, with what we know from the MAPS2 study and CheckMate 743, when I'm using immunotherapy, I'm much more inclined to use a doublet, whether I'm offering it in the front line or later in line.

Dr. Sands:
Now, it's exciting to hear about the things going on. I mean, you've mentioned some of the recent progress and a- and approvals that have come about and you've mentionedd th- uh, the um, the cryotherapy study that you guys are doing at Mayo, as well, and it's exciting to hear those things happening. Clearly there's a need in the space for more. So, when you're looking ahead, I mean, what are you watching, as far as the ongoing research within mesothelioma, what do you see coming down the line that will advance the field and maybe someday will become part of the standard of care?

Dr. Mansfield:
Right, so, unlike lung cancer, where we have so many subtypes, we have EGFR, ALK, and so on, all we have in mesothelioma is whether they have a BAP1 mutation or not, and whether it's germline or not. That's really been the focus of our discussion, and I would say that many people don't do molecular profiling routinely for this disease – we don't have targeted therapies for it – so I hope we can learn which subsets of disease are more responsive to immunotherapy versus those that are not. Can we improve upon what we know already from the histologic subsets as to who benefits? And then given the mutations we see, either in BAP1, or NF2, or CDKN2A, are there drugs that may benefit these patients? So, there's work looking at the germline mutations that some of these patients have and I think it's playing out to be about 10% of them, and the somatic ones – can we use that information to have a targeted approach? So, we're not there yet, this is forward-looking, but I hope to see data that, yeah, we can get there. Or also use that data to improve our selection of immuno-therapy, yet.

What our lab is doing a lot of work in is in mesothelioma, it's odd that a tumor which, in TCGA, every specimen but one had fewer than two mutations per mega base—why is it that immunotherapy beat chemotherapy in the front line? I have my own thoughts on that, and I hope I have data by the end of the year to share, but point mutations alone is probably not gonna give you the answer you need. So, I think we need to be more thoughtful about the genomics we are doing in this disease.

The other thing is cellular therapeutics. I know people are talking about that a lot in a variety of tumor types, but mesothelioma is one where this is being explored primarily targeting mesothelin, but that's a space I'm watching to see what happens. But trying to figure out targets for this disease, improving our predictors for who does benefit from immunotherapy and figuring out how to tune these cellular therapeutics to actually get into the tumors and kill 'em are all things that I think we'll see as the next steps.

Dr. Sands:
Well, you've outlined a lot for us to consider in the treatment of mesothelioma and I look forward to discussing some of these advances. I know you're involved in quite a bit going on within mesothelioma, so I look forward to those discussions in the future. But for now, I want to thank you, Dr. Mansfield. Absolutely wonderful having you on the program.

Dr. Mansfield:
Thank you for the invitation again. Nice to see you.

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.