Attempts to Decrease Toxicity of Chemoradiotherapy: Cetuximab, Immuno-Radiation, and De-Intensification

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TRANSCRIPT

(JW) Hello, I'm Jared Weiss, Vice President of Cancer GRACE and a Medical Oncologist at the University of North Carolina Chapel Hill and I'm here with my colleague. (JB) I'm Josh Bauml, I am a Medical Oncologist at the University of Pennsylvania.

(JW) One of the most common problems I think that we see in our head and neck practice is the Cisplatin ineligible patient. Cisplatin radiation or of course one of our standards of care for cure in locally advanced head and neck cancer probably varies a little bit by practice location, but over a third of my patients have an absolute or relative Cisplatin contraindication. I think a lot of us have struggled for years on what to do with these patients. We have an FDA approved drug, Cetuximab. Based on the modern data I think we've spoken about on Cancer GRACE before, but for everyone else it was a study randomizing patients with stage three or four head and neck cancer to radiation alone or radiation plus the addition of Cetuximab which is not a chemo, but is a drug active against cancer. The combination arm did better. So, for many of us I think this was a way out for awhile and then there was some doubts introduced into just how effective Cetuximab was. We got some new data informing this controversy at this ASCO.

(JW) So, the first was SEER-Medicare data. SEER-Medicare analysis, so a big data analysis, a lot of flaws and caveats perhaps to it. But, it pointed in a direction of concern. (JB) Yes, I think that was looking at SEER-Medicare. So, SEER is a database which pulls all the patients who have Medicare. A lot of their medical information is brought into that. But, there's a couple of problems with this database.

(JB) First, is that it doesn't actually have very much information on what chemo is given and it also doesn't have a lot of information about what radiation is given. In my opinion as a database to answer the question of chemoradiation, if you don't know about the chemo and you don't know about the radiation it can be a little bit problematic. We actually did a separate analysis using data from the Veterans Administration. (JW) Which is more complete? (JB) Well, it has more comprehensive chemo information because the Veterans Administration is a uniform health system where all of the data is within under one roof. We have how much chemo is given. (JW) And you have a population enriched for the problem questioned, right? (JB) Right, so there's a lot of tobacco and alcohol exposure amongst veterans. (JW) And noise exposure. (JB) And noise exposure, yes. And so, the noise exposure is relevant of course because Cisplatin is associated with hearing loss, so we can't give Cisplatin to persons who have hearing loss as easily. So, as you were mentioning there are a couple of ways that we deal with patients who are ineligible or relatively ineligible for Cisplatin. The first question is what do we call the Cisplatin or what's the Cisplatin dose we're even giving. The standard dose is a very high dose given once every three weeks and I would agree with you, many of my patients cannot tolerate that. It's very nauseating, it causes hearing loss, and it's quite difficult to administer. The options that we have are either giving Cetuximab for which there is phase three data, so robust clinical data, or giving Cisplatin at a lower dose once a week. These were the comparisons that were in our heads as we did this VA analysis. What we did was, we looked at about 4,000 patients who had undergone definitive chemo or bio radiotherapy, so radiation with curative intent without surgery for either Cisplatin or Cetuximab. We had to do a special analysis called propensity score matching. What that means is patients who are ineligible for Cisplatin might be weaker, sicker, older, and their outcomes might be worse in general. So, what propensity score adjustment does is it tries to adjust for that so that you can compare these groups accordingly. In an unadjusted analysis, we found that Cetuximab was significantly worse in terms of overall survival than Cisplatin. It didn't matter which primary site was involved whether the oral cavity, the oral pharynx, or the larynx and hypopharynx; all of them are associated with worse outcomes. That persisted after we matched for propensity score. What I think was particularly interesting about our analysis was because the VA database has chemo information, we were able to compare Cetuximab to low-dose Cisplatin as well. When we did that analysis still Cetuximab was much much worse. So, the conclusion that we reached in our analysis was that if you have a patient who is even vaguely eligible for Cisplatin, they should probably receive Cisplatin with radiation instead of Cetuximab. Though, based on our prior work I would argue that a patient who is relatively unfit could get weekly Cisplatin with similar outcomes. (JW) So, not very satisfying? (JB) Well, I mean I think that Cisplatin has a lot of problems, but it's good to know what is a more effective approach. It would be better though, if we had other regimens that would have better outcomes for these patients with less toxicity. While the toxicity of weekly Cisplatin is relatively manageable, there's still a lot of nausea, there can be renal failure, hearing disfunction, mucositis; these are not appealing options for patients. It would be great if we could improve outcomes for them.

(JW) Now, I think what a lot of us were waiting for were data on the combination of immunotherapy and radiation. It's all the rage in incurable disease. I think we covered a lot of that data last year. I think the hope was that this could combine with radiation and be perhaps more effective and perhaps more tolerable. We saw data on that this year. (JB) Yes, we did. In the locally advanced setting we saw a number of trails that tried to combine Cetuximab, which we've just been speaking the limitations of, but combining Cetuximab with immunotherapy. Now, we don't have any efficacy data really at this point. (JW) None, four or five studies and no efficacy data. (JB) What we have is, it looks safe. And that's good, that's a good sign, but efficacy data is really what we need to move it forward and actually start using it outside the confines of a trial.

(JB) You did a trial on this space, didn't you? (JW) Yes, so mine was Pembrolizumab combined with standard dose radiation. Like all the other abstracts that we saw, I showed it to be safe. We showed some pretty detailed toxicity data. One way we presented a little differently than some of the others was that we included the total toxicity of the regimen not just attributable to the drug. It really looked like radiation alone. Other groups showed more rash with Cetuximab than with Pembrolizumab although there was some Pembrolizumab rash in there, but quite a bit worse dermatitis and rash in general this year looked worse with Cetuximab. Actually, Cetuximab didn't look so gentle at all when comparing it to these regimens. The combination looked fine as well, Cetuximab with one of these agents looked acceptably toxic. For mine and all the others, I think we now need wait and see how well it actually works which will take some time. (JB) But, I think it's really important the phrase you use I think is completely appropriate "acceptably toxic." We're still in a phase where unfortunately our treatment for locally advanced head and neck cancer are quite toxic so, I think we do have a long way to go to really have our patients being cured at the rates that we want with improved toxicity profiles. (JW) Well, you know seven weeks of radiation is pretty toxic to start with. (JB) Yes, it is. (JW) We maybe say, celebrating I didn't make it worse, but no immunotherapy protects against those side effects.

(JB) Right, and so one of the things I've thought about, and this is something that people are trying to do is to de-intensify these approaches. There's a lot of ways you can de-intensify treatment whether it's less radiation, whether its different systemic therapy agents, I'm hopeful that in the future we'll be able to do this. However, I do want to say that it's important that we not pull back completely. These are cancers that aren't always cured despite the fact that with HPV positive cancers we have pretty high cure rates, they're not always cured. I would hate to miss an opportunity to cure a patient out of a desire to just de-intensify the treatment. Unlike lymphoma, where we've also done some de-intensification approaches, we really only have one shot to cure this cancer when we're doing these treatments. I think that's important to remember.

(JW) I commend you for that because that note of worry is pretty rare in our world. Everyone is in a rush.

(JW) So, just as a reminder for all of you, HPV positive, virally driven cancer has a much better prognosis than smoking driven, lots of experimental efforts to decrease the radiation dose, to decrease the chemo with the hope of preserving the cure rate. I think your point is very key. The HPV is not the be-all end-all. It's modified by smoking. Patients with HPV positive cancers who've smoked have some smoking biology and there that's highest risk modified by stage. We haven't really gotten very refined in figuring out who's truly low prognosis versus not.

(JW) I think it's actually beholden to us as oncologists to council people appropriately. Patients hear about the toxicity of the things we do, accurately by the way I'm not saying they're wrong, and they come in and what I've noted over the years of counseling people about options and trials is that they will always take the gentlest option in head and neck cancer. Maybe not in every cancer, but there's a definite theme that way where if you offer something more likely to cure versus something gentler, most people I've seen take the gentler. I think it's our job, maybe not to hit people over the head with it but to explain what happens when you don't cure and reinforce that that's real and that's why we sometimes push for aggression.

(JB) One of the things I always try to think about when we're talking HPV positive head and neck cancer is we often say that the cure rate for an HPV positive head and neck cancer in a never or rare smoker is around 90%. That's very very good. (JW) But, I know that 1/10 people. And if I see 100 in a year, I know 10 of them. (JB) Exactly, I take care of those 10 people and so to me it doesn't matter that it's a 90% cure rate because that means that there is 10 people who are not and that means that we have to figure out how to identify those persons and not de-intensify their care unnecessarily. (JW) Yes. The cancer causes a lot of suffering and the things we do at the second shot of cure are frankly brutal. (JB) Yes, they can be.

(JW) So, some promise here. We now have more data to make us a little nervous about Cetuximab; to push the Cisplatin when we can. And we have numerous therapeutic strategies and trials that'll hopefully give us immune radiation as a less toxic maybe even more effective option.

http://cancergrace.org/lung/2018/07/17/asco-2018-roundtable-head-and-neck-cancer-attempts-to-decrease-toxicity-of-chemoradiotherapy/