Induction Chemotherapy for Head and Neck Cancer, Part 1: New Concepts Moving Forward
by Dr. Jared Weiss, University of North Carolina-Chapel Hill

Let’s talk about what features we desire in chemo. We want chemo to be active, otherwise there’s no point of doing it at all - so licorice would be awful chemo. We want our chemo to have an acceptable side effect profile - so poison, even if it were active against cancer, would be bad chemo. Good chemo should have low side effects.

Patients shouldn’t have to suffer too much to get cured. These low side effects shouldn’t just result in comfort during treatment. They should also lead to high feasibility so that you could actually get through all of the therapy. Tolerability is worthless unless it’s accompanied by efficacy. The chemo should have a high response rate. You should actually shrink the tumors and it should be active. That shrinkage shouldn’t just be so doctors and patients can give each other high fives. The high rate of response should lead to an actual improvement and cure it. I’ve broken down TPF, why in my opinion it’s insufficiently active and excessively toxic. Is there something better out there? In my opinion there is. The phase two Haraf study made two substitutions of drugs. It substituted carboplatin for cisplatin. Cisplatin causes a lot of nausea and vomiting, a lot of damage to nerves, a lot of damage to kidneys, a lot of hearing damage. In contrast carboplatin is a much more tolerable drug. Its only side effect that’s worse than cisplatin is that it does suppress blood counts a bit more.

Docetaxel causes a lot of fatigue and a lot of count suppression. Taxol, in contrast, is a gentler agent. It does cause more neuropathy when used for long-term use but we’re not talking about long-term use here. Also importantly, TPF was given as an atomic bomb of chemotherapy every three weeks.

In contrast, in the Haraf regimen, not only were we using gentler chemo but we were breaking up the dose. We were giving lower, gentler doses weekly and it turns out that even if you get the same total cumulative amount of chemo in, when you give it broken up as weekly it can be gentler and easier to tolerate so this phase two study treated very advanced patients with six weeks of gentle chemotherapy.

Response rates of the induction was high, at 82 percent and survival was very good for an advanced population but can we do better?

Before we go onto whether we can do better let me share with you the data that it was feasible and safe. At left you can see the toxicity was acceptable and at right that this resulted in a high dose intensity. Now onto the question of whether we can do better.

What about adding on the drug cetuximab? For those of you who aren't familiar with cetuximab let’s review it. Cetuximab is a targeted agent and antibody that is active against head and neck cancer. At left you had the data from the EXTREME trial. This was a palliative trial so incurable patients showing that when you add cetuximab onto standard chemotherapy patients live longer. At right you have a curative intent trial that randomized patients to radiation or radiation plus cetuximab, again improving survival.
Cetuximab causes a lot of rash. It can lower your magnesium a bit and in some parts of the country, has some allergic reactions but overall is a very tolerable, and as you can see here, active drug. The key study grafted cetuximab onto the Haraf regimen of weekly carbo/taxol. You had to be very advanced to get on to this study and you had to be treatment naïve. You can see at right that toxicity was low and at left that this resulted in high feasibility of the regimen.

Here are the treatment results. At top left on the blue curve you can see the progression-free survival with the confidence intervals in gold. These are very good results for such an advanced population. At right you can see the survival, similarly favorable. In a modern era the breakdown by HPV is of interest. We haven’t done a podcast on HPV yet but HPV is a virus that can cause head and neck cancer and it seems that the prognosis is better for these patients. The biology is certainly different and it may be that some treatments are particularly effective for this population while others may work less so there are only 12 HPV positive patients in this study shown in blue but their progression-free survival curves out to a bit over two years of maturity are hugging the 100 percent line.

This regimen that I am personally excited about, weekly carboplatin/paclitaxel and cetuximab, has not been proven in a phase III study. There are three ongoing studies that explore this paradigm of weekly gentle chemotherapy with cetuximab that I’m particularly excited about and would like to share with you.

The first is a collaboration between MD Anderson and the Dana-Farber Cancer Institute. It’s a four-arm study that has two randomizations.

The first is choice of induction regimen. One is the carbo/taxol/cetuximab regimen that I’ve shared with you, and the other is the TPF regimen with cetuximab grafted on. That’s the first randomization -- which one of these inductions you get. After effective induction, it’s unclear how much the addition of chemo to radiation helps versus radiation alone and so the second randomization is to radiation alone versus chemo-radiation. This generates a four-arm trial. The next study is for very advanced patients. They have to have at least N2b nodal disease, meaning multiple nodes in the same side of the neck or strictly surgically unresectable cancer. Such patients are treated with weekly carboplatin/nano albumin bound paclitaxel and cetuximab, followed by standard of care chemo-radiation therapy. The study is looking for a response rate of 80 percent. At the moment it’s open at UNC and at the University of Washington.

Why make this substitution of nab-paclitaxel for paclitaxel? Well, it gets rid of the cremophor solvent. Believe it or not, a lot of the side effects of Taxol aren’t the active chemotherapeutic drug. A lot of them come from the solvent. It’s less infusion time so patients can spend less time getting their treatment and more time in their normal life, and there’s data from other cancers to suggest that it’s a more active agent.

In breast cancer the response rate has increased and more recently we’ve discussed the results of the lung study here on CancerGRACE. There are multiple histologies to lung cancer, often broken down to squamous and non-squamous. Head and neck cancer is almost all squamous and so the squamous subset is very relevant to us. In the squamous subset of lung patients response rate went from 24 to 41 percent in a very large study. There’s also head and neck cancer specific literature on nano albumin-bound paclitaxel, otherwise known as Abraxane. Both
the phase one and phase two study of intra-arterial nab paclitaxel showed a 75 percent response rate with just one drug.

The other study makes a different substitution, substituting out cetuximab and putting in lapatinib. This study gives six weeks of weekly chemotherapy followed by transoral surgery, followed by risk-adaptive chemo-radiation. This study seeks to exploit all of the advances of chemo, surgery and radiation, but not blindly dial therapy up for high-risk patients or blindly dial it down for low-risk patients rather to dial it intelligently. The induction chemo here is hopefully a more effective, less toxic, non-bridge-burning chemo so at the end of the chemo patients should be in good shape to go on to surgery.

Similarly, newer surgeries are less toxic than old surgeries. Old surgeries had high blood loss, high disfigurement and long recovery times. Transoral surgeries are a dramatic improvement upon this and so you have non-bridge-burning chemo after which you can easily do surgery. After non-bridge-burning surgery, you can easily do whatever you need to do next. Here the surgery serves not only to take out the cancer but also to define a post-induction risk level. This is more important than it might seem at first glance.

Most of the study of induction chemo has been followed by radiation. Because of limitations of modern imaging you can’t totally trust the imaging to show you where the cancer is and where it is not after induction. Because of this if you do induction and cancer shrinks your radiation field is exactly the same as it was before you started.

This is really important because most of the long-term speech and swallowing deficits that happen with radiation are related to field size so in this medium risk group here who have close margins or other pathologic medium risk features patients get chemo-radiation, however the radiation here can be tailored to where the cancer actually is as defined by pathologists.

In low-risk patients who either have a complete response or get their nodes down to no nodes or just one node radiation is omitted. This is really important. The hope here is that by omitting radiotherapy for these lowest risk patients that we can allow our cured patients to live with normal quality of life, more normal speech, more normal swallowing, no radiation burn for life.

In contrast to the severe long-term side effects we sometimes see, however this is also the major risk of the trial. If we’re wrong and these people really need the radiation then we may delay or even fail to cure. I’m hoping that we don’t have any patients in the highest risk group. If despite induction chemotherapy and surgery you’re still high-risk by our criteria then the only driver of your long-term quality of life will be cure of the cancer and in this case we use a very aggressive chemo-radiation regimen.

Why the substitution of lapatinib for cetuximab? Cetuximab’s target, EGFR, is otherwise known as HER-1 or ERBB-1. This is a target present on most head and neck cancer but what’s less recognized is that it often is co-expressed with HER-2, a famous target for breast cancer with their preferred dimerization partner and so we’re hoping that by taking out both of these receptors that we might improve treatment outcomes. The drug is oral unlike cetuximab so there’s no infusion time and cetuximab has a risk of allergic reactions. In the Southeast of the United States this reaches as high as 20 percent. Lapatinib doesn’t have that problem.
Can chemo alone cure? If our induction chemo keeps getting good enough and more and more active could it cure some patients without surgery or radiation? This would actually be a very laudable goal because the long-term morbidity of therapy would be expected to be much lower.

You’re looking at an older study here, a regimen that’s no longer under investigation, TIP, but the reason I show you these results is that there were a few patients on this study who were actually cured with chemotherapy alone. Should we be studying this at this point and trying to do this in a larger scale trial?

I actually think we need to hold our horses. I think we can improve our induction regimens. We can improve them better but I am excited that we will go here one day and improve care.

I thank you for your kind attention. I’ve decided to do this content as a podcast and not as a webinar but I would like to give you the opportunity to leave comments or questions if you have any so feel free to do so online on the online forums and I’d be happy to answer. Have a good day.