Good evening and welcome to CancerGrace. My name is Jared Weiss and I’m a medical oncologist at the University of North Carolina, Lineberger Comprehensive Cancer Center. I’m also a faculty member here at GRACE, and it’s my pleasure to talk to you today about induction chemotherapy for head and neck cancer.

Let’s start by clarifying what is Induction Chemotherapy. Standard therapy to cure head and neck cancer consists of either surgery or radiation with the addition of chemotherapy for more advanced patients with the chemotherapy given at the same time as the radiation.

After surgery low-risk patients may be observed while higher risk patients require radiation after surgery or even chemotherapy and radiation at the same time. This is adjuvant therapy or additional therapy done to improve the rate of cure. Similarly, many patients who get radiation or chemotherapy will later need surgery, either right away for an incomplete response or later for a local relapse.

If adjuvant therapy is something that you can do after your main curative therapy, then neo-adjuvant is something that you can do before your main therapy to improve your rate of cure and in this case we’re talking about chemotherapy. For reasons completely unclear to me, when you give chemotherapy upfront in head and neck cancer you call it induction so we’re talking about giving chemo before surgery or chemo before radiation or chemo radiation. That’s our topic today.

Here’s the brief outline of what we’re going to talk about today. We’re going to start with brief historic data on induction. Next we’ll discuss a regimen called TPF that I credit with bringing induction chemotherapy back to the forefront of conversation. Then we’ll move on to a weekly regimen that is in my opinion, more promising. We’re going to conclude with my opinions on the future of induction focused on three studies that I’m particularly excited about, so let’s take a quick trip down memory lane.

This is MACH-NC, one of the most famous studies in all of oncology. It’s actually a meta analysis or a combination of other studies and the question that this meta-analysis was trying to answer was whether chemotherapy could improve treatment outcomes in head and neck cancer and so they pulled together studies that gave chemotherapy with radiation at the same time (concomitant therapy), studies that give chemo followed by radiation (induction) and finally, adjuvant studies that give chemotherapy after the radiation. Focusing on these top two groups you can see that the Induction Chemotherapy did seem to improve outcomes but the concomitant therapy did so more and this was one of the studies that led to our standard of care of giving chemotherapy and radiation at the same time for the primary cure of head and neck cancer.

Of note however (and an important note) is that the concomitant chemo used most of these studies was more modern themed chemo than that used in the induction context so it’s possible that concurrent therapy was better because that’s a better paradigm but it’s also possible that it related to the drugs used.
TPF is a three-drug regimen. The T is docetaxel (Taxotere), P is cisplatin, and F is 5FU. For a while before the two studies that I’m going to show you, the last two drugs PF or cisplatin/5-FU were a standard induction regimen when induction was used. These studies randomized patients to that standard regimen of cisplatin/5-FU or a third drug, the addition of docetaxel. One study was done in Europe. The other was done in the U.S. There were some design differences in them but fundamentally, they studied a very similar question.

Here’s the data from the second of these, TAX 324. You can see that the three-drug induction regimen had better survival and better progression-free survival than the two-drug regimen.

There are a number of caveats here. First and most importantly, neither of these compared to a standard of care or standard chemo radiotherapy. All they showed was that three-drug induction is better than two-drug induction. However many in my field extrapolated and said, “If three drugs can be so much better than two then surely induction may have some merit.”

There are more problems however. Here are the toxicity tables from these two studies. These are only the rates of severe toxicities, three or four toxicities, extremely high. Now if this were simply a case of short-term pain leading long-term gain many patients would accept this. Many patients for the six or nine weeks of induction would happily suffer through even extraordinary toxicity if it let them be cured for life, however that’s not quite what happened here.

Actually, the short-term pain led to a lack of long-term feasibility. Almost a quarter of patients in the control arm and 21 percent of patients in the three-drug arm could not be treated with the protocol to find subsequent therapy. It was too intense for them.

You might be scratching your head as to why three drugs could be less toxic than two. It’s because the 5FU dose was lower in the experimental arm. You might ask, “Well, what did they get if they didn’t get the study-defined therapy?” Well, seven percent in the three-drug arm and eleven percent in the two-drug arm actually got no attempt at cure at all.

Very recently results were published for a study that randomized oral cancer patients to surgery alone or surgery preceded by TPF induction therapy. You can see that survival was similar. It was not improved. At ASCO this year we saw the results of two studies that looked at TPF induction chemo before chemo/rads.

In terms of design of this first study the chemo/rads regimen, while it’s been properly field tested, is not one commonly used in the U.S. or in the world. It uses drugs that are less common, as well as a radiation schedule that is less common. The induction was only two cycles and actually the study was halted early due to inability to accrue all of the plan subjects. While it was supposed to have 400 subjects it only got 280 and so it was insufficiently powered from a statistical standpoint.

You’ve already heard my criticisms of the regimen that is insufficiently active and excessively toxic. Here are the treatment results. You can see that survival and disease-free survival were not statistically improved. Response rate was 73 percent.

Interestingly, there were decreased cancer deaths in this study but increased non-cancer deaths, suggesting that maybe the regimen did something for the cancer but that that was balanced by the harm that the toxicity of the drugs otherwise did and there were hints of benefit for the most advanced patients.
The other study gave three cycles of induction. Again, chemo/radiotherapy that, while reasonable, is not standard of care or at least commonly used outside the context of induction.

Again, treatment outcomes were not improved. Again, the study under-accrued. It didn’t get all of the planned patients, so in my opinion TPF is not optimal chemotherapy.

(continues with part 2)