



## **Adjuvant Therapy for Head/Neck Cancer: Focus on Chemotherapy, by Dr. Ezra Cohen**

### **Dr. Weiss:**

Hello, my name is Dr. Jared Weiss; I'm a Medical Oncologist at the University of Pennsylvania and faculty member for GRACE, The Global Resource for Advancing Cancer Education.

Today I'm happy to introduce Dr. Ezra Cohen; Associate Professor in the Department of Medical Oncology at the University of Chicago, who will be speaking on adjuvant therapy and locally advanced head and neck cancer.

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Dr. Cohen has received honoraria from Bristol Myers Squibb and sanofi-aventis. He has consulted for Amgen. And with that I will turn the talk over to Dr. Cohen.

### **Dr. Cohen:**

Thanks and thanks for inviting me to participate in this program. What we'll cover for the next little while is an overview of this disease of head and neck cancer; primarily squamous cell carcinoma of the head and neck. And concentrate of post operative or adjuvant therapies for patients with advanced disease and then we'll finish off with some of the new directions that people are taking especially with respect to trying to prevent recurrence of disease in patients who have already been diagnosed and treated.

The first slide reminds me to tell you that we're dealing with a fairly heterogeneous population. We know that squamous cell carcinoma of the head and neck, at different sites really is treated differently and comprises different entities with different clinical behaviors, different biology and ultimately different treatment approaches. So whereas the approach to a patient with oral cavity cancer is going to be markedly different than a patient with larynx cancer, many of the comments that I'll make, at least at the beginning of this talk apply to all patients with squamous cell carcinoma of the head and neck. And then, when we're talking about the patient who undergoes surgery first we are really talking about patients primarily with oral cavity cancer, some patients with oral pharynx cancer and some patients with paranasal sinus cancer.

The other thing to keep in mind about head and neck cancers is that the great majority, 95% are squamous cell carcinoma. And again I'll confine the discussion today to squamous cell carcinomas of the head and neck.

When we talk about this disease in the United States, these are numbers from 2008 but they haven't changed very much in 2009. and we don't expect them to change very much this year; we're talking about a disease that affects about 40,000 new patients in this country with about 7600 deaths. So certainly not the most common cancer diagnosed in the US, but if you think about what we do on a daily basis and how important things like speaking, eating, swallowing are to normal human contact you begin to realize that this disease has much broader

implications for the patients and for their care givers than the pure incidence numbers would suggest.

Moreover, squamous cell carcinoma of the head and neck is truly a worldwide public health issue. There are at least half a million new cases diagnose per year and that number is likely very conservative and a low estimate because many of the countries where this disease is prevalent do not have rigorous [inaudible 0:29:05] or case reporting. It is, in fact, the 6<sup>th</sup> leading cause of cancer mortality in the world and the 6<sup>th</sup> leading cancer by incidence in the world. There is a male predominance to this disease related to what we'll talk about in just a minute and that is the risk factors, but about a 2:1 ratio of males to females with head and neck cancer.

In terms of survival, despite the fact that, as I'll show you in a minute, most patients can be treated with curative intent; in truth only about 50% of patients will have long term survival and that number gets a little bit lower when we talk about patients who have far advanced disease. That survival is impacted by 3 major factors; recurrent disease, second malignancies again related to the risk factors and we'll talk about those in just a minute, and then co morbidity so diseases affecting other organs primarily cardio vascular or respiratory diseases, again relating to the co morbidities.

When we look at presentation and how patients come to our clinics in terms of their stage they can be split up into really 3 groups. There are patients who present with localized disease and what I mean by that is patients essentially with a primary tumor and very minimal lymph node involvement and a very localized or confined primary tumor. These are patients that are usually treated with a single modality, surgery or radiation therapy and for the most part we expect to cure these patients at high rates; 80 to 90%.

The other group and as you can see the biggest group in this pie is the patients who present with regional disease and here I include patients who have either large tumors that are invading secondary structures or who have significant lymph node involvement. And for these patients we need to treat with multi modality therapy that is surgery, radiation therapy and chemotherapy; the sequencing of those depends on many factors including where the primary tumor is, what the patient's wishes are, the treating institution expertise and so on.

And then you can see the smallest wedge in this pie is patients that actually present with distant disease. So unlike non small cell lung cancer or small cell lung cancer, unlike breast cancer or some other diseases or other cancers; actually there are only a small number of patients 10% of head and neck cancer that present with metastatic lesions at their initial diagnosis. So when we take that into account what we actually end up seeing and here you see the stages of these patients with stage 4C being distant, when we take all this into account we see the majority of patients or those with localized and with regional disease are actually going to be treated with curative intent. These are patients that we are going to design therapies with the goal of cure. And remember despite that intent only about 50% of these unfortunately will actually be cured.

Now how do patients get head and neck cancer, what are the risk factors? Well the truth is we have a lot more to learn in this area but we do know that patients who are older are at greater risk. The majority of patients with squamous cell carcinoma of the head and neck are greater than 50 years old. Certainly the most well recognized risk factor is tobacco exposure usually in the form of cigarettes. Secondary to that and synergistic with that, so there's an interaction between tobacco and alcohol, we're talking now about significant alcohol intake, not the individual who will have a drink every once in a while or even one drink a day but we're talking about an individual who really is having several alcoholic beverages per day on a regular basis.

What have begun to emerge recently are viral agents that appear to underlie the etiology of at least a couple of specific types of head and neck cancers. Epstein-Barr virus is now widely recognized as the causal agent for some patients with nasopharynx cancer especially nasal pharynx cancer that is endemic in certain parts of the world like Asia, the Mediterranean, and Northern Africa. We don't see a lot of EBV or Epstein-Barr virus related nasopharynx cancer in the United States. In the US, the nasopharynx cancers we see tend to be Epstein-Barr virus negative.

The other viral agent that now we've recognized as important is HPV, or Human Papillomavirus, this is the same HPV that's been implicated in cervical cancer and indeed it appears now that about at least 50% of the patients with oral pharynx squamous cell carcinoma of the head and neck, oral pharynx begin tonsil and the base of tongue the back of the tongue where it attaches to the throat; that 50% of those patients will actually be HPV positive. And we believe that HPV is actually responsible, is the causal agent for this disease.

There are rare hereditary syndromes that are associated with head and neck cancer. A family history does increase your risk by about 3 ½ times and then syndromes like Fanconi anemia increase the risk for head and neck cancer tremendously in fact about 200 fold, but those again are very rare and account for a very small minority of patients with squamous cell carcinoma of the head and neck.

Now one thing to consider when we're talking about treatment decisions, and I like to put this slide up because I think although it's intuitive, it's important to keep in mind; and what this slide represents is a questionnaire given to patients prior to starting therapy asking them to rank their priority for each of these factors in terms of what's most important to them. The factors you see at the bottom of the graph so for instance activity would mean that their activity level on a daily basis was the most important thing to them. At the other end, appearance: so patients who felt that appearance was the most important would rank that #1. And the greater the number of patients that ranked each item #1 that is most important to them, the larger the pie in that row.

And what you can see quite clearly in the #1 row, or the #1 priority, the biggest pie is *cure*. So clearly, when patients are asked what is most important to them, they will respond that they want to be cured. And this is a study that we performed at our institution, but others have found exactly the same data in similar analysis.

So cure is paramount to both the patient and for most physicians. Not to ignore quality of life -- quality of life is important -- but the priority for patients is to be cured of the disease.

Today we'll focus on a specific set of patients, and those are patients who have undergone surgery for their disease, and now for one reason or another are being treated with adjuvant therapy, or post-operative therapy. The reasons to consider post-operative therapy in squamous cell carcinoma of the head and neck are really based on high risk features in either the pathological specimen or the stage of the patient prior to surgery. We'll talk about what high risk features are especially important, but for now, suffice it to say that any patient with stage III disease and any patients with stage IV disease who has undergone therapy would certainly be considered for adjuvant treatment. And even some patients with stage II disease should be considered for adjuvant/post-operative therapy.

But what about the specific question of post-operative chemotherapy radiation? Well this really stems from the work in other settings of squamous cell carcinoma of the head and neck, where

we've come to realize that the addition of chemotherapy to radiation improves cure rates. For patients who don't undergo surgery that is certainly true, and what investigators began to ask is, "Well, can we add chemotherapy to radiation in patients who have had surgery and further improve our ability to cure this disease?"

So two large randomized studies were undertaken, one in Europe, called EORTC 22931, and one in North America, run by the Radiation Therapy Oncology Group, called RTOG 9501.

With both studies being similarly designed and asking the same questions, patients who had resectable squamous cell carcinoma of either the oral cavity, oropharynx, hypopharynx, or larynx who had undergone surgery, were no candidates to participate in these studies. They could not have had other treatments other than surgery, and they were randomized to either radiation therapy alone with some slight nuance differences between what the Europeans and North Americans did, or a chemotherapy drug called cisplatin added to radiation therapy, and there you can see that the cisplatin was given on days 1, 22 and 43 of radiation.

There were some slight differences between the two studies. In the European trial, the primary end point was progression-free survival, and in the North American study, it was loco-regional control. Here you'll also see some differences between the patient populations enrolled. The Europeans enrolled more patients with positive margins, which clearly are a risk factor that is associated with a high risk of recurrence; they also enrolled more patients with two or more lymph nodes, but fewer patients with extra-capsular invasion.

Let's take this opportunity to talk about what some of the high risk features are, and in what patients' one would consider a more aggressive approach adding chemotherapy. Clearly, if a patient has positive margins, so implying that there's microscopic disease left behind after surgery, there is a high risk of local tumor recurrence, and in older studies that risk approaches 90% in patients with positive margins. The other important pathologic feature to look at is the lymph nodes and what the lymph node invasion looks like. If the cancer has grown beyond the capsule of the lymph node, we call that extra-capsular invasion or extra-capsular spread. Again, clearly that represents a high risk feature, and the chance of recurrence if nothing is done in those patients is quite high, probably exceeding 50 or 60%.

Other features that are likely associated with a higher risk of recurrence, but less so, include that presence of more than one lymph node, so two or more lymph nodes involved with cancer, the presence of peri-neural invasion, and the presence lympho-vascular invasion. Those are all features that now should be routinely reported in a pathology report in a patient with squamous cell carcinoma of the head and neck; and all factors that should weigh in on the decision of whether to treat the patient with adjuvant therapy and whether to add chemotherapy.

Well, these two studies as I said were undertaken and completed, and here you see a summary of the results. What you can see here is that actually both studies were positive. The incidence of local regional failure was higher in patients who did not receive chemotherapy, so patients did better with chemotherapy. Progression-free survival was higher in patients who received chemotherapy, and overall survival was higher in patients who had the added chemotherapy. The primary endpoints in both studies were indeed met: here you see progression-free survival for the EORTC trial; and I am circling the local regional control rate in the RTOG trial; so both positive trials, with some differences between the two results, but both trials, in my opinion, supporting the addition of chemotherapy for these high risk patients.

The investigators on both these studies decided to take one extra step and combine their data to ask a slightly different question; that being what the most significant factors for poor outcome were in a pooled analysis. So what the investigators did here was. they put all the data together, they looked at the high risk features that patients were enrolled for, and they asked what were the most significant high risk features that could predict the poor outcome. or another way to put it, "what could predict which patients benefitted most from the addition of chemotherapy?"

And it turned out that two high risk features were the most significant: extra-capsular invasion and positive margins. In fact, subjects with two or more lymph nodes without extra-capsular invasion did not seem to benefit from the addition of chemotherapy to radiation. Let's keep in mind that this was an unplanned pooled analysis, and it's certainly hypothesis-generating, so I don't think it would be inappropriate to treat certain patients with two or more lymph nodes with the addition of chemotherapy to radiation, but the data at least from the pooled analysis would support extra-capsular invasion and positive margins as two definitive features that I think mandate the addition of chemotherapy for a patient who can tolerate it.

Well, we've certainly entered the era of targeted therapy in cancer, and head and neck cancer is no exception, with epidermal growth factor receptor (EGFR) being the target that's been most commonly exploited. The EGFR is universally expressed in squamous cell carcinoma of the head and neck. That expression has been linked to poor prognosis, so the higher the EGFR expression, the worse the prognosis of the patient; and these are patients treated with surgery, with radiation or with chemotherapy. We know that inhibition of the function of this protein EGFR by either antibodies or small molecule inhibitors work very well in experimental models, and in patients with a recurrent metastatic disease do demonstrate single agent activity.

So with all that in mind, the next step was to integrate the use of an EGFR inhibitor into the post-operative setting as adjuvant therapy. And a trial was presented recently by Dr. Kies on behalf of the Radiation Therapy Oncology Group that did just that.

In this study, patients were randomized to receive chemotherapy/radiation with cetuximab in combination with either cisplatin or docetaxel.

And here you see the schema; In arm 1, patients received cisplatin on a weekly basis with cetuximab and radiation, and in arm 2, patients received docetaxel with cetuximab and radiation, and the primary endpoint of the study was progression-free survival to see if one regimen was worthwhile taking forward and testing in a larger trial.

These are patients, again, who had surgical resection, and now the risk factors were positive margins, more than two lymph nodes, or extra-capsular lymph node spread. So getting back to the same high risk features that were mentioned in the pooled analysis; and patients had to have a good performance status of 0 or 1.

The big difference in this study was with respect to toxicity, and here you see that the circled bone marrow toxicity that was evidence in the cisplatin arm and not seen in the docetaxel arm. Other than that, the toxicities were fairly even across the board, but patients who received cisplatin had a higher incidence of bone marrow toxicity, mostly myelosuppression and thrombocytopenia.

In terms of disease-free survival -- remember that was the primary endpoint -- there was really no difference between the two arms: this curve separate a little bit in terms of docetaxel and

cisplatin, but they really don't separate markedly. Both arms were compared to a historical control of radiation/cisplatin: that's the white line.

If we go back a slide, this is the yellow, is the cisplatin/cetuximab used in this study versus a historical control, and again the yellow here is docetaxel/cetuximab compared to a historical control. Really not a major difference between the two arms in terms of efficacy, but definitely a difference between the two arms in terms of toxicity; and now the RTOG is considering taking this regimen of docetaxel/cetuximab forward into further clinical trials.

Let's shift gears a little bit for the last few slides of the talk and discuss a form of adjuvant therapy, and that is really chemoprevention. We can treat patients with chemotherapy and radiation after they have surgery, but we are still very aware that despite that treatment, the majority of patients unfortunately will still recur and are still at high risk for a disease relapse. There have been now reinvigorated efforts to try an added agent based on the biology that we know in this disease or are beginning to understand, that may help to further prevent recurrence.

One effort is we're using a drug called erlotinib. Again, erlotinib is a drug that targets the same protein that we were talking about before -- the EGFR -- but it's an oral compound that is relatively well tolerated, and so in the so-called EPOC study (Erlotinib Prevention of Oral Cancer), patients with certain chromosomal abnormalities, that is, something called loss of heterozygosity in specific genetic foci -- that is 3P and 9P -- are eligible to participate. We believe that these genetic losses confer a higher risk of recurrence, and that's why the eligibility criteria includes those patients. And these patients are then stratified according to their cancer history and then randomized to either receive this drug erlotinib or a placebo for a total of 1 year.

The placebo of course is quite appropriate in this setting because the standard of care is observation alone. This study is ongoing, it's nearly completed accrual and we hope to see results in the next 1 to 2 years.

The other effort that's about to initiate is one targeting a completely different protein. A protein called mammalian target of rapamycin (mTOR); in fact the mTOR inhibitors have actually been approved now in renal cell carcinoma (kidney cancer), and there is a feeling that they may be effective in several other cancers. There is work emerging from several groups that, at least in experimental models, the use of mTOR inhibitors can prevent a recurrence of squamous cell carcinoma of the head and neck.

With that in mind, there is now a large multi-institutional trial about to be undertaken in the United States that looks at one of these drugs, called everolimus, and again compares it to placebo in patients who have completed treatment for locally advanced head and neck cancer who are disease-free as far as we can tell, but are still at significant risk for disease recurrence.

This schema is, as you see it here, patients had to have completed treatments, they have no evidence of disease as far as we can tell from CT scanning or PET scanning, and then are randomized to receive this drug called everolimus versus placebo for a total of 1 year, with a primary end point of two-year progression-free survival.

In conclusion, clearly there are high risk post operative patients who benefit from the addition of chemotherapy to radiation therapy, and we have now two very well conducted, large, randomized studies demonstrating the same thing. Now what we didn't talk about in detail is

the decision to undergo surgery first: we did say that it's appropriate for some patients with locally advanced head and neck cancer, but in truth it does not represent the standard of care for most patients with head and neck cancer, and for those patients, a non surgical approach using chemotherapy/radiation is often more appropriate. Again, that decision needs to be individualized on patient to patient basis.

And then we also talked about new therapies that are beginning to enter this arena, such as EGFR, and now even newer therapies such as ,TOR inhibitors that we hope will further improve outcomes and further improve cure rates in patients especially at high risk.

Thank you.