

Head and Neck Cancers



Articles by Sarah Pressman Lovinger, Fran Lowry, and Jane Salodof MacNeil

Commentary by Marshall R. Posner, M.D.

Associate Professor of Medicine
Harvard Medical School
Medical Director, Head and Neck Oncology Program
Dana-Farber Cancer Institute
Boston

HPV Confers 79% Lower Risk of Death in Prospective Trial

A prospective analysis of a phase II Eastern Cooperative Oncology Group study confirms what has up to now been reported only in retrospective, single-institution studies—that head and neck squamous cell cancer patients infected with the human papilloma virus have significantly better survival than do their counterparts without the virus.

Human papilloma virus (HPV) positivity conferred a 79% lower risk of death in the multicenter ECOG 2399 study, Dr. Carole Fakhry reported. She said HPV status should now be considered a biomarker for prognosis in head and neck squamous cell cancer (HNSCC).

Moreover, these results may necessitate a reinterpretation of survival rates in previous trials to determine whether survival differences were in fact due to HPV status, rather than to the actual therapy that was used, according to Dr. Fakhry of the Johns Hopkins Medical Institutions in Baltimore.

The primary objective of ECOG 2399 was to assess organ preservation with taxane-based induction chemotherapy followed by taxane-based concurrent chemoradiation in resectable stage III and IV larynx and oropharyngeal cancer patients.

The trial also sought to estimate disease-free survival and patterns of failure.

Dr. Fakhry and associates evaluated pathologic tissue samples from 96 study participants for the presence of HPV infection, and then went on to determine prognostic factors, treatment response, and survival outcomes in terms of HPV status.

HPV status—in particular HPV-16, which is the dominant viral isolate known to be responsible for a subset of HNSCC—was assessed with in situ hybridization, polymerase chain reaction, and line blot tests.

These tests also screened for HPV-31, 33, and 35, which are the other isolates that have been linked to HNSCC.

A total of 40% of patients (38) were found to be HPV-positive, and all had oropharyngeal tumors. They were more likely to have a better ECOG performance status, and lower cumulative lifetime exposure to smoking than were HPV-negative patients.

They were also more likely to be

male, have less weight loss on presentation, and present with a stage T2 tumor, Dr. Fakhry reported.

HPV-positive patients had a higher response to induction and chemoradiation therapy. Response rates after induction chemotherapy were 82% for

HPV-positive patients vs. 55% for HPV-negative patients ($P = 0.01$). After chemoradiotherapy, they were 84% vs. 57%, respectively, ($P = 0.07$).

At a median follow-up of 39 months, the risk of progression was 72% lower and risk of death was 79% lower in

HPV-positive patients, compared with HPV-negative patients. These figures were derived from a Cox proportional hazards model, Dr. Fakhry said.

Discussant Thomas F. Pajak, Ph.D., of the Radiation Therapy Oncology Group in Philadelphia said these results are impressive at first glance, but that he was troubled by the Cox analysis in the trial.

He proposed that the investigators generate a new Cox model, restrict it only to oropharyngeal patients, and compare HPV status to no more than three other factors in order to obtain a new, and more reliable, estimate of the risk of death.

“A Cox model with too many variables in it is unreliable,” Dr. Pajak remarked.

In another presentation that looked at HPV-associated HNSCC, Dr. Anil K. Chaturvedi, of the National Cancer Institute in Rockville, Md., reported that HPV-related HNSCC has increased in the United States during the last 3 decades, particularly among white men between the ages of 40 and 59 years.

Using data from the Surveillance, Epidemiology, and End Results (SEER) registry for the period 1973-2003, Dr. Chaturvedi and co-investigators also found that HPV-related HNSCCs were being diagnosed at more advanced stages and at significantly younger ages. These trends became apparent in the early 1990s. Meanwhile, the incidence of cancers not related to HPV decreased in both men and women, especially in those over the age of 40.

He concluded that the increasing incidence of HPV-linked HNSCC could be due to changes in sexual behavior, and that the decreasing incidence of cancers not related to HPV could be due to the decreased prevalence of smoking. ■

Commentary

These studies on HPV represent a critically important topic, since HPV-related oropharynx carcinoma is beginning to constitute a significant portion of the oncologist's practice in head and neck cancer.

In our experience at the Dana-Farber Cancer Institute, HPV is a factor in almost 50% of the patients we see. As many as 25% of patients in the community are HPV-positive, young, nonsmoking, and nondrinking individuals. Their life expectancy is higher, but they often present with more advanced disease.

I believe this “epidemic” of HPV-related disease is going to change the demographic and the urgency of treatment in this cancer. The fact that HPV-positive tumors have a better prognosis than oropharynx cancer caused by smoking is extremely important. Curing these patients will mean dealing with long-term sequelae in a young population living longer after treatment—living with scarring and fibrosis, as well as other complications from radiation, including a risk for second cancers.

The prevalence of HPV-related oropharynx cancer also raises other issues. Because this is a sexually transmitted disease in which sexual practices increase risk, we must ask whether the patient's significant other or sexual partners should be vaccinated or tested. Do they need surveillance? And what about children? It is possible that HPV is transmitted by saliva. We don't have these answers yet.

ECOG 2399, which showed survival to be better in patients with HPV-positive tumors, involved a very aggressive sequential treatment plan of induction chemotherapy fol-

lowed by chemoradiotherapy. We do not have data showing that we can reduce aggressive curative treatment with these patients; i.e., use less intensive chemotherapy or radiotherapy and achieve the same effect.

At Dana-Farber, we have seen distant metastases in patients presenting initially with HPV-related oropharynx cancers and in those treated with chemoradiotherapy without systemic therapy. Our experience suggests we must take this report with a grain of salt. The HPV-positive patients had better overall survival, but they also had better performance status, were less likely to smoke, were healthier, and were better able to tolerate treatment. We need to know more about these factors, particularly, treatment tolerability. These are prognostic factors that significantly affect outcome.

Looking at future treatments, HPV-induced oropharynx carcinoma is a poster child for targeted therapy. The HPV E6 and E7 viral gene products are necessary for tumor cell survival, and they can serve as specific targets for gene therapy, immunotherapy, siRNA, antisense, and other targeted approaches. We should look intensively at these possibilities; hopefully, there will be new funding for research in these novel approaches.

As we move into the next decade, this should be a major effort on the part of our colleagues in translational research.

Using targeted agents, I believe that within 5 years we can cure this group of patients without resorting to chemotherapy or radiation therapy.

— Marshall R. Posner, M.D.

Fakhry C. et al. Prognostic significance of human papillomavirus (HPV) tumor status for patients with head and neck squamous cell carcinoma (HNSCC) in a prospective, multi-center phase II clinical trial. Abstract 6000.

Chaturvedi A. et al. Incidence trends for human papillomavirus-related (HPV-R) and unrelated (HPV-U) head and neck squamous cell carcinomas (HNSCC) in the United States (US). Abstract 6001.

Cetuximab Prolongs Survival in Squamous Cell Cancers

Cetuximab in combination with standard chemotherapy offers a significant survival advantage, compared with standard chemotherapy alone, as a first-line treatment in patients with recurrent or metastatic squamous cell cancer of the head and neck, according to the results of the phase III European-based EXTREME trial.

Median overall survival was 10.1 months in the study's experimental arm



'It is a unique observation to see the first systemic treatment in 25 years that shows a survival benefit.'

Dr. Vermorken

versus 7.4 months with standard treatment ($P = .036$). Survival at 1 year was 39% with cetuximab (Erbix) vs. 31% with standard therapy, Dr. Jan Baptist Vermorken reported.

"It is a unique observation to see the first systemic treatment in 25 years that shows a survival benefit over platinum-based chemotherapy in recurrent or metastatic squamous cell carcinoma of the head and neck," said Dr. Ver-

morken of the University of Antwerp, in Belgium.

"Head and neck cancer is a very difficult disease to treat," he said. Median survival is only 6 to 7 months for recurrent or metastatic patients receiving standard chemotherapy with carboplatin or cisplatin plus 5-fluorouracil (5-FU). This statistic has not changed much in the past 25 years, he noted.

Most squamous cell head and neck tumors express the epidermal growth factor receptor (EGFR). It is an independent and unfavorable prognostic factor. Cetuximab, an IgG1 monoclonal antibody, targets EGFR.

The EXTREME trial enrolled patients at 80 centers in 17 European countries, randomizing 442 patients with recurrent (54%) or metastatic (46%) squamous cell cancer of the head and neck and no prior chemotherapy in this setting. The primary tumor site was oral cavity/hypopharynx in approximately 35% of the population and other head and neck sites in 65%.

Patients were randomized to six cycles of standard treatment with carboplatin (AUC = 5) or cisplatin 100 mg/m² on day 1 plus 5-FU 1000 mg/m² on days 1-4, or to the same chemotherapy plus cetuximab 400 mg/m² loading dose on day 1 followed

by 250 mg/m² weekly. After the end of chemotherapy, patients in the experimental arm could continue cetuximab.

Hematologic and nonhematologic toxicity was similar between the arms. Skin rash and a slight increase in vomiting and diarrhea were the only significant adverse effects attributed to cetuximab. Analysis of progression-free survival has not been completed.

Discussant Dr. Marshall R. Posner of the Dana-Farber Cancer Institute in

Boston called the results extremely important, noting, "This is the first demonstration of a survival improvement in the palliative setting ever shown for any treatment in head and neck cancer." ■

Vermorken J. et al. Cetuximab extends survival of patients with recurrent or metastatic SCCHN when added to first line platinum based therapy - Results of a randomized phase III (Extreme) study. Abstract 6091.

Commentary

Based on this study, it is reasonable to expect that all patients with head and neck cancer will at some point receive an anti-EGFR agent. Within this class, cetuximab is the most active and well studied.

It remains unclear whether patients should receive cetuximab combined with standard cisplatin or carboplatin plus 5-fluorouracil (PF) chemotherapy—or as sequential treatment after PF. The study did not include a crossover protocol in which patients treated with PF got cetuximab upon progression.

This trial has implications for curative therapy. The three-drug com-

bination was more effective than the two-drug regimen. This suggests the three-drug combination may be more effective and reasonable in the induction setting. It will also be important to assess toxicity and dose reductions more fully.

That being said, this study is the first demonstration of improved survival with combination chemotherapy in recurrent head and neck cancer. It will never be repeated because cetuximab should soon be approved in Europe, at least in the second-line setting for recurrent disease.

— Marshall R. Posner, M.D.

Larynx Preservation Protocol Does Not Improve Survival

An experimental strategy alternating radiotherapy and chemotherapy as a means of larynx preservation in advanced head and neck cancer failed to show a benefit over a more conventional induction approach in a phase III trial conducted by the European Organisation for Research and Treatment of Cancer's Head and Neck Group and Radiotherapy Group.

"Despite a 6.7% difference in larynx function preservation at 3 years favoring the alternating arm, this did not translate into a significant difference in survival with a functional larynx," said investigator Dr. Jean-Louis Lefebvre.

Dr. Lefebvre of the Centre Oscar Lambret in Lille, France, reported the results of EORTC 24954. At 5 years the difference still was not significant. Likewise, 5-year survival with a functional larynx, progression-free survival, and overall survival in the two arms were similar at a median follow-up of 6.5 years.

This study included 450 previously untreated patients with T2-T4 tumors of the larynx or hypopharynx requiring total laryngectomy. Men comprised about 90% of the population, which had a median age of 55 years.

Investigators randomized 226 patients to an experimental arm of cis-

platin 20 mg/m² plus 5-fluorouracil 200 mg/m² on days 1-5, followed by radiation therapy 20 Gy, in alternating cycles; patients received chemotherapy in weeks 1, 4, 7, and 10, alternating with radiation therapy given in intervals lasting 2 weeks. The other 224 patients were randomized to a control arm that included a sequential induction regimen of two cycles of cisplatin 100 mg/m² plus 5-fluorouracil 1000 mg/m² (PF) on days 1-5, followed in patients who responded by two additional cycles of PF, followed by radiation therapy (70 Gy).

Responses were assessed at 6 weeks. Nonresponders in either arm received surgery and postoperative radiation.

Survival with a functional larynx (defined as not requiring laryngectomy, tracheostomy tube, or feeding tube), which was the primary end point, was not significantly different at 3 or 5 years. Also, the rates of local-regional failure were similar between the groups.

Patients in the control group reported slightly more grade 3/4 mucositis (32%) than those in the alternating group (21%), and more functional mucosal reactions (33% vs. 21%), but they received a higher radiation dose (70 Gy vs. 60 Gy total). There were few late effects

of radiotherapy, with severe fibrosis/sclerosis limited to 10% with sequential and 7% with alternating treatment.

Discussant Dr. Merrill S. Kies of M.D. Anderson Cancer Center, Houston, said the data don't support a shift to alternating radiotherapy and chemotherapy. However, the investigators combined the data for tumors in the glottis, the supraglottis, and the hypopharynx. These

tumors can behave differently from each other and a reexamination of the data may shed more light on outcomes. ■

Lefebvre J. et al. Phase III study on larynx preservation comparing induction chemotherapy and radiotherapy versus alternating chemoradiotherapy in resectable hypopharynx and larynx cancers. EORTC protocol 24954-22950. Abstract LBA6016.

Commentary

This trial is one of the few randomized phase III comparisons we have of induction chemotherapy and chemoradiotherapy. The cisplatin/5-fluorouracil (PF) regimen given with the radiotherapy was quite robust. The radiation dose in the alternating chemoradiotherapy group was somewhat lower than might be given compared to radiotherapy delivered in a nonalternating manner. It is doubtful that higher doses would have been deliverable, however; hence this is an adequate test of the treatment. The vigorous chemotherapy between radiation weeks produced overall results that were consistent

with and better than those seen in similar trials involving the Merlano regimen (N. Engl. J. Med. 1992; 327:1115-21) (J. Natl. Cancer Inst. 1996;88:583-9).

It is important to recognize the induction chemotherapy was state of the art, but today PF would be replaced by the more effective docetaxel-PF (TPF) regimens reported by Calais et al. last year (Proc. Am. Soc. Clin. Oncol. 2006;24:281s. Abstract 5506). Nonetheless, the equivalence of PF induction and chemoradiotherapy makes this an important study supporting induction and chemoradiotherapy.

— Marshall R. Posner, M.D.

Axitinib Shrinks Advanced Thyroid Cancer in Phase II Trial

Axitinib, an investigational drug, shrank tumors and stabilized advanced thyroid cancers in a small but groundbreaking phase II trial.

Median progression-free survival had reached 18.6 months as of May 2007. Of 60 patients who started the single-arm trial, 24 were still on axitinib, an oral antiangiogenesis agent that inhibits vascular endothelial growth factor (VEGF) receptors 1, 2, and 3. Duration of treatment ranged from 6 to 744 days by the data cutoff point.

"This is a disease where literally in a span of months I went from offering patients almost nothing to being able to offer them a treatment [that] I believe is efficacious," Dr. Ezra E.W. Cohen, the study's lead author, said at a press briefing before his presentation.

No new drug has been approved for thyroid cancer in at least 30 years, according to Dr. Cohen, of the University of Chicago. Doxorubicin, the only chemotherapy drug indicated for refractory thyroid cancer, is highly toxic and its effect on survival has not been tested in a randomized trial. Only 30% of people who fail standard therapy with surgery and/or radioactive iodine live 5 years.

Pfizer Oncology, developer of axitinib, provided research support, and its employees participated in the study. The company has already started a second phase II trial in thyroid cancer patients who do not respond to doxorubicin. Other companies also have begun to test their VEGF inhibitors in thyroid cancer studies.

"I can't tell you that the other ones won't work. They probably will work," Dr. Cohen said, envisioning "a day when clinicians will have more than one agent that is active in this disease, and that we probably will ... have to compare them head to head."

All histologic subtypes of thyroid cancer were allowed in the multicenter trial reported by Dr. Cohen, and every subtype appeared to respond. The patients enrolled had a median age of 59 years; slightly more than half were men. Most had prior surgery and/or io-

dine treatment. Nearly half had had external beam radiation. Nine patients had tried chemotherapy. The protocol called for a starting dosage of one 5-mg axitinib pill twice a day with the option to escalate.

No patient had a complete response, but 18 patients (30%) had a partial response (defined as tumor shrinkage by 31%-68%). Duration of these responses ranged from 1 to 26 months.

Another 25 patients (42%) had stable disease that remained stable for 16 weeks or more. All but two of these patients had some tumor shrinkage as well.

Among 17 patients (28%) who did not respond to axitinib, seven patients had disease progression. Disease course was described as "indeterminate/unknown" in 10 nonresponders.

As of May, 36 patients in the trial had discontinued treatment with axitinib. Five dropped out because of treatment-related adverse events (one each for proteinuria, hypertension, fatigue, cerebral vascular accident, and unspecified toxicities). Nine stopped because of adverse events (including three deaths) that were not treatment related. Another 18 patients discontinued when their disease progressed; four others broke off for unspecified reasons.

At the time of data cutoff, Dr. Cohen reported that 37 patients (62%) were "alive and without evidence of progressive disease." No deaths were treatment related.

Axitinib was well tolerated with manageable side effects, according to Dr. Cohen. Hypertension was the most common grade 3 or higher toxicity (seven patients, 12%), followed by proteinuria (four patients, 7%), fatigue (three patients, 5%), and diarrhea (two patients, 3%).

A telling finding for drug developers was that blood tests showed reduced levels of VEGF receptor 2 in nearly all patients, regardless of response. "It does appear that patients who had the greatest degree of tumor shrinkage had the greatest decrease in soluble VEGF R2," Dr. Cohen said.

In a discussion of the trial, Dr. Bar-



At the data cutoff, Dr. Ezra E.W. Cohen reported that 37 patients (62%) were "alive and without evidence of progressive disease." No deaths were treatment related.

bara A. Burtness, of Fox Chase Cancer Center in Philadelphia, said it gave clear evidence that axitinib is active in thyroid cancer and "more than supports" further research. Although the investigators presented "pretty good results for iodine-refractory thyroid cancer," she noted that information on postprogression outcomes was limited because patients had remained enrolled in the study.

"Although posttherapy vascular growth may not be an issue when a patient is on an agent 744 days ... this has not been explored in the clinic and is something we should pay attention

to," she said, citing a preclinical study that reported mice revascularized after axitinib was withdrawn.

Dr. Burtness also foresaw a need for future research to address whether antiangiogenesis agents can be used earlier in the course of thyroid cancer, what the risks and benefits of multi-targeted kinase inhibitors are in thyroid cancer, and which of these agents "will be best for which histology." ■

Cohen E.E. et al. A phase II study of axitinib (AG-013736 {AG}) in patients (pts) with advanced thyroid cancers. Abstract 6008.

Commentary

This study of the experimental agent axitinib—along with associated trials evaluating other anti-VEGF agents, such as sorafenib, sunitinib, and vandetanib (ZD6474)—has demonstrated that there is a major role for angiogenesis inhibitors in thyroid cancer. They are the first class of agents shown to be effective in this disease. The response rates in this tumor type appear to be relatively low, however, especially compared with combination therapy in colon cancer and single-agent treatment in renal cell cancer.

Among the studies evaluating vascular endothelial growth factor (VEGF) receptor inhibitors in a variety of thyroid cancers, this particular trial showed axitinib to be the most effective. Vandetanib has demonstrated considerable efficacy as well in medullary thyroid cancer.

In general, it appears that the VEGF receptor inhibitors and related small molecule tyrosine kinase inhibitors are effective in this disease, and, we hope, will improve outcomes for patients with aggressive thyroid carcinoma.

Whether we will be able to cure any of the many types of thyroid cancers with these agents remains to be seen, however.

Combination regimens with other cytotoxic agents may show enhanced results. It is likely that we will see genetic instability emerge, and tumors will find ways of escaping treatment.

We know that we can rescue some patients with other cancers using bevacizumab, so it will be interesting to see how these agents can be combined, and whether they might be synergistic.

— Marshall Posner, M.D.

Response by Histologic Subtype

	Partial Response	Stable Disease	Progressive Disease
Papillary (n = 30)	7	13	2
Follicular/Hurthle cell variant (n = 15*)	7	7	1
Medullary (n = 12)	3	4	3
Anaplastic (n = 2)	1	0	1
Other/unknown (n = 1)	0	1	0

*Of the 15 patients with follicular cancer, 11 had the Hurthle cell variant.
Note: Excludes nine indeterminate assessments and one ineligible patient.
Source: Dr. Cohen

Erlotinib Boosts Response to Standard Chemotherapy

The addition of erlotinib to standard chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck produced a 66% response rate in a phase III trial.

“This is the first study to report on erlotinib combined with chemotherapy in incurable head and neck cancer,” the lead author, Dr. Edward S. Kim of the University of Texas M.D. Anderson Cancer Center in Houston, announced.

Acknowledging that historical data show that chemotherapy is not very effective in head and neck cancer, Dr. Kim proposed that epidermal growth factor receptor (EGFR) inhibitors such as erlotinib (Tarceva) might improve outcome. “EGFR inhibitors do have activity in head and neck cancer,” he said.

Prior research has suggested that EGFR inhibitors work synergistically with chemotherapy to enhance cell cycle arrest. A phase I trial showed efficacy with chemotherapy and erlotinib (Clin. Cancer Res. 2006;12:7406-13).

Dr. Kim and his colleagues conducted the open-label study of 50 patients (48 evaluable) with previously untreated recurrent or metastatic disease. Near-

ly two-thirds had locoregional disease; over one-third had metastatic disease.

Patients received docetaxel 75 mg/m² and cisplatin 75 mg/m² every 3 weeks along with erlotinib 150 mg daily for up to six cycles. After six cycles of chemotherapy, they could continue on erlotinib until disease progression. Most also received growth factor support.

The overall response included complete response in 4 patients and partial response in 28. Also, 13 patients had stable disease. Following two treatment cycles, only three patients progressed. After 19 months of follow-up, median overall survival was 11 months and median progression-free survival was 6 months. One-year survival was 48%.

In the subgroup of 25 patients with recurrent disease in a prior radiated field, the response rate was 56%, including complete responses in 3, partial responses in 11, and stable disease in 8.

“We were encouraged when we saw the response rates,” Dr. Kim remarked.

Neutropenia was the most common grade 3-4 toxicity, reported by 64% of patients. Only 10% experienced grade 3-4 febrile neutropenia, however. Grade

3-4 anemia, dehydration, diarrhea, and nausea were each reported by 14%.

The discussant, Dr. Marshall Posner of Dana Farber Cancer Institute in Boston, commented that the study showed “a low” 8% complete response rate but an “impressive” 66% overall response rate, and a “fairly impressive” 1-year survival

of 48%. He noted that, except for neutropenia, toxicity was mild for an every-3-week regimen. ■

Kim E.S. et al. Final results of a phase III study of erlotinib, docetaxel, and cisplatin in patients with recurrent/metastatic head and neck cancer. Abstract 6013.

Commentary

This study is interesting because the response rates with erlotinib as a single agent in head and neck disease are a disappointing 4%-5%.

That being said, Kim et al. report excellent response and survival rates by combining erlotinib with docetaxel and cisplatin for 6 months, and then continuing the erlotinib until disease progression. The triple therapy produced a 66% response rate, and then continued to keep the disease in check for a 1-year survival of 48%. That is a big victory for patients who cannot tolerate long periods of toxic combination chemotherapy.

It needs to be pointed out that single-agent docetaxel produced a 40% response rate in phase II studies, and this rate may be even higher when docetaxel is combined with cisplatin. Investigators at M.D. Anderson showed prolonged survival with this combination years ago (J. Clin. Oncol. 2002;20:1593). Thus, it is unclear what role erlotinib actually played in the long-term survival of these patients. We need a randomized trial to determine whether this triple therapy improves progression-free and overall survival over docetaxel/cisplatin alone.

— Marshall R. Posner, M.D.

Cetuximab Enhances Chemoradiation Results in Advanced Disease

Most patients who stayed on a new regimen of cetuximab, standard chemotherapy, and radiation for advanced squamous cell carcinoma of the head and neck responded in an Eastern Cooperative Oncology Group study.

The phase II trial (ECOG E2303) has not yet yielded a report on its primary end point of 1-year event-free survival. About two-thirds of patients had a complete pathologic response at the primary site with induction therapy alone. The proportion rose to 98% after chemoradiotherapy.

“These results suggest a substantial biologic tumor effect by the combining of C225 [cetuximab (Erbix)] with chemotherapy and chemoradiation,” said lead investigator, Dr. Harold J. Wanebo.

The trial enrolled 74 patients with potentially operable stage III/IV squamous cell cancer of the head and neck. Patients with cancer of the nasopharynx, nodal metastases, and multisite invasion were excluded. Most participants were white (91%), and most were men (78%) with a history of smoking. The most common tumor site was the tonsils (33%), followed by the oropharynx (15%), the tongue (14%), the larynx (10%), the hypopharynx (4.6%), and the pyriform sinus (4.2%).

Dr. Wanebo of Landmark Medical Center in Woonsocket, R.I., presented data on 66 patients, who began induction therapy with 400 mg/m² of ce-

tuximab over 2 hours the first week followed by weekly intravenous cetuximab doses of 250 mg/m² for the next 5 weeks. They also received weekly paclitaxel (90 mg/m²) and carboplatin (AUC=2) for 6 weeks.

At the end of induction therapy, clinical responders underwent a restaging biopsy of the primary site. If the biopsy was negative, they received 3 more weeks of chemotherapy and radiation for a total of 68-72 Gy of radiation.

Patients with positive restaging biopsies or not responsive to induction therapy resumed treatment with weekly cetuximab (250 mg/m² over 1 hour), paclitaxel (30 mg/m² over 1 hour) and carboplatin (AUC=1 over 15 minutes) for 5 weeks plus 50 Gy of radiation therapy in 25 fractions over 5 weeks.

After 14 weeks, another primary site biopsy was done. If it was positive, the patient had salvage surgery. Patients who had a negative biopsy at 14 weeks also were scheduled to receive 3 more weeks of chemotherapy and radiation for a total of 68-72 Gy of radiation.

Patients still in the study received maintenance therapy with cetuximab (250 mg/m²) weekly for 6 months.

Dr. Wanebo reported 40 patients were clinical responders and had a primary site repeat biopsy at week 8. Of these, 25 (63%) had no residual tumor. Some patients dropped out of the trial at this point, but 56 went on to chemoradia-

tion. One of 31 patients with a restaging biopsy at week 14 had a positive biopsy. Overall, 55 of 56 patients had a negative biopsy during the study.

Adverse events forced 7 patients out of the trial. One patient died on study, and three progressed. Fourteen withdrew or ended treatment for other reasons. Only 23 patients completed 6 months of maintenance therapy.

Despite the strong pathologic responses, discussant Dr. Merrill S. Kies of the M.D. Anderson Cancer Center in Houston urged caution in interpreting

the results. “We only have evidence that approximately 44% of patients completed the treatment sequence,” he said, adding, “We can’t really make any assessment of whether this treatment is something we should move to.” ■

Wanebo H.J. et al. Phase II evaluation of cetuximab (C225) combined with induction paclitaxel and carboplatin followed by C225, paclitaxel, carboplatin, and radiation for stage III/IV operable squamous cancer of the head and neck (ECOG, E2303). Abstract 6015.

Commentary

This is a very interesting trial of an extremely aggressive sequential treatment plan using a triple-drug induction regimen of weekly chemotherapy followed by a three-drug chemoradiotherapy approach in operable cancer. The acute and long-term toxicity of this approach has not been fully addressed and may impact survival. More than one-third of patients withdrew, suggesting the regimen is acutely toxic and may need to be reconfigured for best results. One also has to question the utility of a highly aggressive approach in resectable tumors, when this might be more appropriate for patients with unresectable disease

who lack a salvage therapy. Since no other induction regimens combine chemotherapy with cetuximab in a less toxic manner, the approach by Wanebo et al and ECOG may fall by the wayside in favor of user-friendly and potentially less damaging treatments. That being said, the overall negative biopsy results (55 of 56 patients) and short-term data suggest efficacy. We need to know how many patients will develop distant metastases and the long-term toxicities and ultimate survival rate. Until we see the full data, I would be hard pressed to recommend this therapy for my patients at this time.

— Marshall R. Posner, M.D.