Should Cetuximab Replace Cisplatin in Head and Neck Cancer?

By Karen Rowan

In September, researchers at the European Society for Medical Oncology (ESMO) meeting in Berlin debated whether patients with head and neck cancer should receive cetuximab (Erbitux) instead of conventional chemotherapy, usually cisplatin, with radiation therapy.

The case for cetuximab rests mainly on one phase III trial, published in 2006 in the New England Journal of Medicine. Led by James Bonner, M.D., at the University of Alabama at Birmingham, the trial showed a survival benefit for cetuximab with radiation, compared to radiation alone.

On the other side of the debate, critics point to the limitations of this study, which did not directly compare cetuximab to cisplatin, and the lack of any further phase III studies. They conclude that the data are insufficient to warrant changing the standard of care.

Arguments are stacked up on both sides of this debate. Cisplatin commonly has toxic effects during treatment that can continue for years, whereas cetuximab, a monoclonal antibody that targets the epidermal growth factor receptor (EGFR), has not so far been shown to have such problems. But scores of randomized trials have shown survival benefits when conventional chemotherapy is added to radiation treatments, robust results that are lacking for cetuximab.

“It’s a very interesting question...there is a big difference in the power of the data.”

Cetuximab Data

The Bonner trial, as many in the field refer to it, compared the effect of giving weekly cetuximab with radiation to radiation alone in 424 patients. When the trial was undertaken, Vermorken said, chemotherapy given with radiation had not yet become standard. The investigators found that, after a median follow-up of 54 months, patients given cetuximab along with radiation had a median overall survival of 49 months, compared to 29.3 months for patients given only radiotherapy—a statistically significant difference. In an update, published in November in Lancet Oncology, the investigators reported that, of the patients who received cetuximab, 45.6% survived to 5 years, compared to 36.4% of the patients in the control arm—another statistically significant finding.

But the fact that the control arm of the Bonner trial used radiotherapy alone was problematic by the time the results were published, because many studies had shown increased survival when cisplatin was added to radiotherapy. Vermorken, who was chair of the Head and Neck Cancer Group of the European Organisation for Research and Treatment of Cancer when the Bonner results were published, said he tried to set up a trial that he thought was needed: one that would directly compare cetuximab and radiation to standard chemotherapy and radiation. Today, such a trial still has not been done.

“The company making cetuximab was not really keen to support this,” said Vermorken, who has served as a consultant and speaker for Merck, which distributes cetuximab outside North America. The benefits of cetuximab in the Bonner trial were comparable to those seen when cisplatin was added to radiation, he said. But comparing cisplatin to cetuximab required considering the results of separate studies together. “It was a good indirect comparison, but working in the medical profession, we would like to see scientifically stronger evidence.”

Another criticism of the Bonner trial is that some patients received different radiotherapy regimens. Some received once-daily radiation, 5 days a week for 7 weeks; some received doses that were higher and were given twice daily for about 6 weeks; and some received a concomitant boost regimen, in which even higher doses were given over about 3.5 weeks.

“In a subset analysis, there was no benefit from cetuximab seen in patients on the concomitant boost,” said Johannes A. Langendijk, M.D., Ph.D., at University Medical Center Groningen in The Netherlands. Concomitant boost regimens have been shown to improve survival, compared to the standard, once-daily regimens, so interpreting these data is difficult, said Langendijk, who has received support from Merck.

But many experts say that the Bonner data are sound. “After the first report and now after the update, the data are really convincing,” said Lisa Licitra, M.D., of Istituto Nazionale Tumori in Milan, who moderated the ESMO debate.

But she and others are not ready to abandon conventional chemotherapy. Licitra said that she would “stick with chemoradiation because the results are so solid.” She pointed to a recent meta-analysis, led by Jean-Pierre Pignon, M.D., Ph.D., a biostatistician at Institut Gustave-Roussy in France, published in Radiotherapy and Oncology in July. Pignon’s work examined...
data from about 17,000 patients in 87 randomized trials comparing radiation alone to radiation plus chemotherapy, finding a statistically significant survival benefit for those receiving chemotherapy. That number of patients is compelling, said Licitra. “We would like to see more studies on cetuximab.”

Cetuximab has also been shown to be effective in patients with non–small-cell lung cancer and colorectal cancer, said Kian Ang, at the University of Texas M. D. Anderson Cancer Center in Houston, who worked on the Bonner trial and presented the cetuximab side of the debate at the ESMO meeting. “Although there is only one positive trial in head and neck cancer,” he argued, “cetuximab has been shown to be beneficial in many settings.” Even so, only about one-third of patients in the U.S. with locoregionally advanced head and neck cancer are treated with cetuximab, he said, according to data from the Longitudinal Oncology Registry of Head and Neck Carcinoma. That registry, however, may not completely represent nationwide practices, said Ang, who is a member of the advisory boards of Imclone and Bristol-Myers Squibb, the maker of cetuximab in the U.S.

**Toxic Effects**

Cisplatin’s toxic effects are a key point driving the debate. The longer it has been used, Ang said, the more apparent its late toxic effects have become. He cited the results of a recent study he worked on that analyzed the late toxic effects, such as severe difficulty in swallowing or feeding tube dependency. The study was led by Mitchell Machtay, M.D., at...
Case Western Reserve University School of Medicine in Cleveland, and published in 2008 in the *Journal of Clinical Oncology*. The researchers found that severe late toxic effects occurred in 43% of the 230 patients available for the analysis. The study was based on a group of 479 patients who received chemoradiation as part of several phase III trials begun as long as 15 years ago.

“The problems with the late toxicities in chemo pave the way to go back to bench experiments with monoclonal antibodies and small molecules that inhibit EGFR,” said Jacques Bernier, M.D., Ph.D., at the Swiss Genolier Medical Network, in Geneva, who serves on the advisory board for Imclone and for Merck. After the data reported by Machtay, he said, it is clear that cetuximab and other EGFR inhibitors will be more widely investigated.

In addition to the long-term effects, high-dose cisplatin’s acute toxic effects can be so severe that some patients cannot complete their planned treatment regimens, Bernier said. “The acute toxicity is so much higher when high-dose cisplatin is added to radiation,” he said, “two-thirds of patients are only able to receive two cycles of treatment” instead of the recommended three.

On the other hand, the possible late toxic effects of cetuximab are not known, said Licitra, who has served as a consultant and speaker for Merck. “We know that chemoradiation is toxic, but whether these late effects can be reduced with biological therapy is not clear,” she said. She pointed out that the Bonner trial reported severe late effects related to radiation in about 20% of the patients in each group, and the 2009 update did not report data for late toxic effects.

Less clear is exactly which patients are benefiting most from cetuximab. “We do not have biological markers that can predict anti-EGFR efficacy,” said Licitra. “For a targeted therapy, that is quite counterintuitive.” However, the skin toxic effects seen in patients on cetuximab may provide a clue, she said. Acneiform rash is a common side effect (see StatBite) and may be important in indicating the patients who are benefiting most from cetuximab. It may even be possible for physicians to consider switching continued on page 78
patients on cetuximab to a different treatment if the patients do not develop toxic effects on the skin within about 15–20 days, she said. “Although this evidence has yet to be validated, it is presently a useful tool.”

Meanwhile, cetuximab is usually not given to high-risk patients because chemotherapy is needed to combat the metastases of systemic disease, said Bernier. Combining the two agents may be a possibility. A phase II study found that combining cetuximab and chemotherapy with radiation was safe and feasible for high-risk patients. And an upcoming phase III trial will examine whether adding cetuximab to cisplatin during radiation improves disease-free survival. The trial, led for the Radiation Therapy Oncology Group by M. D. Anderson’s Ang, completed accrual in April, with 942 patients.

**HPV Status**

The latest wrinkle in research in this field has been the increasing recognition that the presence of human papillomavirus (HPV) in head and neck tumors must be taken into account; patients with HPV-positive tumors tend to respond more strongly to treatments and have better outcomes than those with HPV-negative tumors.

“The question of using cetuximab instead of chemotherapy has become much more germane in light of HPV,” said Barbara Burtness, M.D., chief of head and neck oncology at the Fox Chase Cancer Center in Philadelphia. Many in the field have begun to look at how treatments may be de-escalated for HPV-positive tumors because they are so much more responsive to treatments, said Burtness, who has received funding from and served as a paid consultant for Bristol-Myers Squibb. These patients could be candidates for cetuximab instead of cisplatin, she said.

Increasing data on HPV also raise the possibility of new targeted treatments, she said. “Beyond de-escalation, treatments that interfere with the biology of HPV would be an important advance.”

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