Cetuximab Yields Benefits in Colorectal Cancer

BY ROBERT FINN
San Francisco Bureau

LOS ANGELES — Cetuximab (Erbitux) prolonged overall survival of patients with metastatic colorectal cancer in one large clinical study and extended progression-free survival for patients in another investigation, according to the results of two large phase III trials presented for the first time at the annual meeting of the American Association for Cancer Research.

In a study conducted by the National Cancer Institute of Canada (NCIC) and the Australasian Gastro-Intestinal Trials Group, 572 patients who had failed two previous rounds of chemotherapy were randomized to receive either best supportive care alone or best supportive care plus cetuximab.

According to Dr. Derek J. Jonker of the University of Ottawa, overall survival increased from a median of 4.6 months to 6.1 months with cetuximab, a monoclonal antibody that inhibits cell growth by binding to the epidermal growth factor receptor. Among patients on cetuximab, 19 (6.6%) had complete or partial responses; none of the patients on best supportive care alone had such improvements. Cetuximab also was associated with a 32% decrease in the risk of progression. These results were statistically significant.

In the Erbitux Plus Irinotecan in Colorectal Cancer (EPIC) trial, 1,298 patients who had failed one previous round of chemotherapy were randomized to receive either irinotecan alone or irinotecan plus cetuximab. According to Dr. Alberto F. Sobrero of Hospital San Marino in Genoa, Italy, the combination resulted in an increase in progression-free survival from 2.6 months to 4.0 months and an increase in the response rate from 4% to 16%, with both differences being statistically significant. There was no statistically significant increase in overall survival, but Dr. Sobrero said this might be because half of the patients in the irinotecan-alone arm crossed over and received cetuximab following the end of the trial.

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DR. JONKER

These studies "give us the preponderance of evidence that we need to conclude that cetuximab is a real drug of use in patients with colorectal cancer," said Dr. Richard M. Goldberg, of the University of North Carolina at Chapel Hill, at a press briefing. Dr. Goldberg was not directly involved in either trial.

He noted that although these trials present evidence for the use of cetuximab as a second-line or third-line therapy, the drug might also find a use as a first-line therapy. He expects some results from one of the two trials of cetuximab as first-line therapy to be presented at the meeting of the American Society for Clinical Oncology in June. And two additional trials are investigating cetuximab as adjuvant therapy for colorectal cancer.

In the NCIC and EPIC trials, patients received cetuximab at an initial dose of 400 mg/m^2 followed by a weekly infusion of 250 mg/m^2. The dose of irinotecan in the EPIC trial was 350 mg/m^2 per week for 3 weeks.

Cetuximab is not without side effects. The most common are diarrhea, fatigue, and an acneiform rash, and severe infusion reactions are also possible. The rash, which can be quite troublesome, appears to correlate with treatment effectiveness. Patients who did not experience a skin reaction had a response rate of 4%-5%, while those with severe skin reactions had a 55% response rate, Dr. Sobrero said.

Describing the results of the NCIC trial as "clear and unambiguous," Dr. Jonker said, "The study is significant because it is the first time that a biologically targeted therapy given on its own has improved survival in colorectal cancer. … There are now five effective types of therapy for the treatment of colorectal cancer. … It's going to be a complex issue to sort out how to best give these drugs in an appropriate sequence."

In considering the clinical impact of these trials, Dr. Sobrero said, "One thing is running scientific experiments; the other is taking this into the battleground of everyday patient management. That is really tough. …If the patient has indolent disease, he's not heavily symptomatic, why should I bother in going for a combination? I have data showing that if I give [cetuximab] later in the course, I will attain the same survival. So that would be the condition for going for sequential treatment. If I have an aggressive disease, a symptomatic condition, as we very often encounter in our practice, I will be very much tempted to go with the combination."

Dr. Goldberg noted that "a minority of patients responds to these drugs, but those patients who respond have a very meaningful response in most cases."

Cetuximab has already received Food and Drug Administration approval for use in colorectal cancer and head and neck cancer. The NCIC trial was supported by ImClone and Bristol-Myers Squibb, which manufacture and distribute the drug. The EPIC trial was supported in part by Bristol-Myers Squibb and Merck. ■

Increased Cetuximab Improves Response in Colorectal Cancer

BY FRAN LOWRY
Orlando Bureau

ORLANDO — Patients with metastatic colorectal cancer who have mild skin reactions or no reactions at all when treated with standard doses of cetuximab can be safely treated with escalated doses of cetuximab to achieve an improved tumor response, according to a randomized trial presented at a symposium on gastrointestinal cancers sponsored by the American Society of Clinical Oncology.

Cetuximab dose escalation in patients with no or mild skin reaction on standard dose treatment may improve response.

DR. VAN CUTSEM

Increasing the cetuximab dose boosted the response rate in these patients, Dr. Eric Van Cutsem, professor of medicine at University Hospital Gasthuisberg, Leuven, Belgium, said at the symposium, also sponsored by the AGA Institute, the American Society for Therapeutic Radiology and Oncology, and the Society of Surgical Oncology. Positive responses to cetuximab, an epidermal growth factor receptor blocker that inhibits the growth of EGFR-expressing tumors, correlate with the intensity of the associated skin reaction.

The EVEREST trial sought to determine whether escalating the dose in EGFR-expressing patients with metastatic colorectal cancer who had no or slight skin reactions when treated with a standard dose would cause them to develop the acnelike rash that indicates they are benefiting from the drug, said Dr. Van Cutsem, speaking on behalf of the EVEREST investigators.

The study randomized 45 patients who had failed to exhibit a skin reaction greater than grade 1 to continue a cetuximab dose of 250 mg/m^2 per week (arm A) and 44 similar patients to receive escalating doses, starting at 250 mg/m^2 and increasing 50 mg every 2 weeks until a tumor response, severe toxicity, or the maximum dose of 500 mg/m^2 was reached (arm B).

Outcomes in these two arms were compared with those of 77 patients who were ineligible for randomization because they had demonstrated more severe skin reactions when treated with the standard regimen. This group, arm C, continued to receive their standard treatment.

After 24 weeks of treatment, arm B patients had a higher complete response rate than those in arm A (30% vs. 13%, respectively), while patients in arm C had a 34% complete response rate.

Dr. Van Cutsem disclosed that he is a consultant or adviser for Sanofi-Aventis, Roche, Pfizer, and Merck. ■

Chemotherapy for Colorectal Ca May Be Misunderstood by Patients

BY FRAN LOWRY
Orlando Bureau

ORLANDO — Many patients with colorectal cancer are willing to undergo adjuvant chemotherapy in the hopes of warding off a recurrence, even though the likelihood of recurrence is slight.

In a survey of 150 patients, just over one-third of those who had received adjuvant chemotherapy with 5-fluorouracil and oxaliplatin said they would go through chemotherapy again to reduce their chance of cancer relapse by 1%, and 57% said they would be treated again for a 3% reduction, said Dr. Neil Love, president of Research to Practice, an oncology education company in Miami, at a symposium on gastrointestinal cancers sponsored by the American Society of Clinical Oncology.

'Patients may be far more willing to receive cytotoxic therapy for what others might view as modest ... benefits.'

DR. LOVE

At the other end of the spectrum, even when chemotherapy would result in a 1 in 10 chance that they would avoid relapse, about 10% of patients said they would forgo treatment, he said at the symposium, also sponsored by the AGA Institute, the American Society for Therapeutic Radiology and Oncology, and the Society of Surgical Oncology.

These responses came after the patients were given educational CDs and videos, and had the opportunity to talk with oncologists about adjuvant chemotherapy.

Dr. Love and his associates did a parallel survey of 150 oncologists and clinical investigators who specialized in gastrointestinal cancers, asking them to predict what their patients would choose. The oncologists and investigators thought that far fewer patients, just 19%, would choose to undergo chemotherapy for a 1% reduction in cancer recurrence risk.

More than half the patients in the survey expected to have severe nausea and vomiting and lose their hair as a result of their chemotherapy, despite being told otherwise by their doctors. "Patients seem to be getting a lot of misinformation from friends and relatives about the chemotherapy that is used for colorectal cancer, which usually doesn't cause those side effects because of the medications we have today," Dr. Love said.

These results suggest that "doctors are not getting the right information across to their patients [and] that patients may be far more willing to receive cytotoxic therapy for what others might view as modest potential treatment benefits," he said. ■