Cetuximab Is Safe Addition to Induction Chemo

In small study, most patients with head and neck cancer show complete clinical response to regimen.

BY NEIL OSTERWEIL
Contributing Writer

CHICAGO — Cetuximab can be added safely and apparently to good effect when giving a standard induction regimen to patients with newly diagnosed, locally advanced head and neck cancer, reported investigators at the annual meeting of the American Society of Clinical Oncology.

In a phase I study looking at the addition of cetuximab (Erbitux) to induction chemotherapy with docetaxel (Taxotere), cisplatin, and 5-fluorouracil (the TPF regimen), 14 of 19 treated patients had a complete clinical response, 5 had a partial clinical response, and all 19 had a partial radiographic response, reported Dr. Robert I. Haddad, who is a clinical investigator in the Head and Neck Cancer Center at the Dana Farber Cancer Institute in Boston.

"The preliminary efficacy data [are] encouraging in this patient population with fairly advanced presentation," Dr. Haddad said.

The TPF regimen is both a new standard for induction chemotherapy in patients with previously untreated squamous cell carcinomas of the head and neck, and a platform for testing new agents such as cetuximab, which has been shown to have efficacy in head and neck cancer as a single agent and in combination with radiation therapy and cistplatin/5-fluorouracil (PF) chemotherapy, Dr. Haddad said.

He and his colleagues conducted a phase I study of the maximum tolerated dose of 5-fluorouracil (5-FU) in the TPF regimen when cetuximab was added. Secondary goals of the study included a toxicity assessment and response rates.

They enrolled 28 patients with biopsy-proven squamous cell carcinoma of the head and neck, with primary tumor sites in the oral cavity, oropharynx, nasopharynx, hypopharynx, or larynx. Patients with unknown primary site squamous cell carcinomas were also eligible.

The patients had to have stage III or IV disease with no evidence of distant metastases, and they had to have no prior chemotherapy, radiation therapy, or surgery, measurable disease by RECIST (Response Evaluation Criteria in Solid Tumors). In addition, patients needed to have good Eastern Cooperative Oncology Group performance status (0 or 1), and normal hematologic, renal, and liver function.

Patients received 400 mg/m^2 of cetuximab, 100 mg/m^2 of cisplatin, and 75 mg/m^2 of docetaxel on day 1, as well as a 5-FU at one of three dose levels on days 1-4. The three dose levels were 700, 850, and 1000 mg/m^2, with dose escalation continuing until maximum tolerated dose was achieved. The protocol called for enrolling 10 patients at the maximum tolerated dose, with patients added to the existing dose cohort for the purposes of analysis.

The treatment plan called for three cycles of induction chemotherapy, with TPF every 21 days, plus weekly cetuximab in doses of 250 mg/m^2 for the duration of induction, for a total of 9 weeks.

At the end of induction, restaging was performed and then patients underwent definitive chemoradiotherapy with a platinum-based regimen according to the institution's standard.

One of the patients withdrew consent before toxicity could be assessed, leaving 27 available for the analysis. Of these patients, 19 had completed chemoradiotherapy at the time Dr. Haddad presented the data.

There were no dose-limiting toxicities after the first cycle of cetuximab/TPF with 5-FU at 750 or 850 mg/m^2, but at the 1,000-mg/m^2 dose one of three patients had mucositis and febrile neutropenia. Three more patients with no dose-limiting toxicities were added to that cohort, and the 1,000-mg dose of 5-FU was chosen initially as the maximum tolerated dose.

But in that expanded cohort, there were two cases of gastrointestinal bleeding and one of febrile neutropenia, causing the investigators to reconsider 5-FU dosing, and they instead settled on 850 mg as the maximum tolerated dose. Of the 10 patients planned for enrollment in the expanded cohort at this dose, nine had enrolled at the time of the analysis. Only one dose-limiting toxicity was reported: mucositis.

Among the 12 patients in total enrolled at the 850-mg dose (3 from the original cohort, plus 9 additionally enrolled), there were four cases of grade 4 neutropenia and one of grade 4 diarrhea. Grade 3 events include three cases of neutropenia, two of febrile neutropenia, one mucositis (dose limiting), one fatigue, and one syncope. Skin toxicities included acneiform rash (seven grade 2 and one grade 3), and four cases of grade 2 nail fissuring and/or paronychial infection.

At the time of the data presentation, 19 of 27 patients had completed chemoradiotherapy with a platinum-based agent, and 8 remained on treatment. All but one of the patients received 70-Gy radiation over 7 weeks; the remaining patients received 59 Gy over 10 weeks.

An analysis of the best overall response showed a clinical complete response in 14 patients, and partial response in 5. Radiographic evaluation at the end of induction but before radiation showed a partial response in all 19 patients.

"All of these patients had still-persistent abnormalities on CT or PET," Dr. Haddad said. "Keep in mind these patients have fairly advanced nodal presentations, and often the CT scan or imaging is not normalized for these patients."

Among the 13 patients who underwent primary site biopsy after induction, 11 had pathologic complete response, and 2 had a partial response.

All patients were alive at 6-month follow-up; one patient with a stage T4 N2b cancer of the base of the tongue had local/regional recurrence and is currently on palliative chemotherapy. Two patients had neck dissections performed after chemoradiotherapy, and neither had pathologic evidence of residual cancer in the surgical specimen.

A randomized multicenter phase II study is being planned to compare the cetuximab and TPF combination with the M.D. Anderson Cancer Center induction regimen consisting of carboplatin, paclitaxel, and cetiuximab, Dr. Haddad said.

The study was supported by Bristol-Myers Squibb. Dr. Haddad disclosed receiving honoraria and research support from the company, and honoraria from Sanofi-Aventis and Imclone Systems. ■

Melanoma Survival Results Mixed With Pegylated Interferon

BY MARY ANN MOON
Contributing Writer

Prolonged therapy with pegylated interferon has been found to improve recurrence-free survival in patients with excised stage III melanoma in a randomized phase III trial.

In contrast, survival free of distant metastases was numerically but not statistically significantly better with adjuvant pegylated interferon, and the treatment had no apparent effect on overall survival, Dr. Alexander M. M. Eggermont and his associates reported in the European Organisation for Research and Treatment of Cancer (EORTC) trial 18991 (Lancet 2008;372:117-26).

In an editorial comment that accompanied the report, Dr. Vernon K. Sondak and Dr. Lawrence E. Flaherty wrote that "many patients with melanoma are willing to accept significant toxicity in exchange for a modest improvement in recurrence-free survival, even in the absence of an overall survival effect," (Lancet 2008;372:89-90).

It remains to be seen, however, whether such patients and their physicians will accept 5 years of pegylated interferon treatment "for an absolute benefit in recurrence-free survival of about 6% at 4 years," they noted.

Dr. Eggermont and his colleagues compared the therapy with observation alone in a randomized controlled trial involving 1,256 patients treated at 99 medical centers in 17 countries. All patients had undergone complete excision of stage III melanoma and complete regional lymphadenectomy.

The study was funded by Schering-Plough Research International.

The two study groups were well matched according to disease substage, number of involved lymph nodes, thickness of the primary tumor, and ulceration of the primary tumor. Patients who took interferon received high-dose induction therapy for 8 weeks, followed by once-weekly self-administered subcutaneous injections for an intended duration of 5 years, said Dr. Eggermont, of Erasmus University, Rotterdam, the Netherlands, and his associates.

After a median of 4 years of follow-up, significantly fewer recurrences had developed in the interferon group than in the observation group, with a 6.7% absolute difference in estimated rates of recurrence-free survival. The therapy's benefit was seen early in the course of treatment and remained at a consistent level throughout the study, the investigators said.

However, there was no difference in overall survival between patients who took pegylated interferon and those who did not.

The drug was most effective in patients who had microscopic rather than palpable nodal disease, patients whose involvement was limited to one lymph node, and in patients with ulcerated rather than nonulcerated tumors. These groups accounted for approximately 40% of the treated patients.

One-third of the study subjects who took interferon discontinued the drug because of toxicity. The most common adverse effects were fatigue and depression, which were reported in 25% and 16% of patients, respectively. Anorexia, liver function abnormalities, myalgia, headache, nausea, and fever also were reported.

In their editorial comment, Dr. Sondak of H. Lee Moffitt Cancer Center, Tampa, and Dr. Flaherty of Karmanos Cancer Institute, Detroit, said that a 4-year follow-up "is too short for final conclusions." Further follow-up and more clinical trials are needed. However, they added, "for the large group of patients with melanoma found in their sentinel node, we believe this regimen will be an attractive alternative to high-dose interferon."

Dr. Eggermont, Dr. Sondak, and Dr. Flaherty have all been paid consultants for Schering-Plough. ■

Brochure Describes Melanoma ABCDEs

The Skin Cancer Foundation's brochure entitled "The ABCDEs of Melanoma" is now available in both English and Spanish. The foldout helps patients to identify the most important differences between common moles and melanomas: Asymmetry, Border irregularity, Color variations, and large Diameter and Evolving. To order copies, contact the foundation at 800-754-6490. ■

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