Bevacizumab Effective in Glioblastoma Trials

BY KATE JOHNSON

FROM THE ANNUAL MEETING OF THE SOCIETY FOR NEURO-ONCOLOGY

MONTREAL – Bevacizumab-containing regimens continued to show efficacy against glioblastoma in recent reports of phase II trial results, but the trials' designs have come under fire by some neuro-oncologists.

Investigators from Duke University, Durham, N.C., reported at the meeting that adding bevacizumab (Avastin) and irinotecan (Camptosar) to a standard temozolomide (Temodar)–based chemoradiation regimen for newly diagnosed glioblastoma increased progression-free and overall survival by about 6 months, compared with historical controls.

In a separate RTOG (Radiation Therapy Oncology Group) study, investigators defined efficacy as a progression-free survival rate of 35% at 6 months in patients with recurrent glioblastoma. Both regimens in the noncomparative trial – bevacizumab with dose-dense temozolomide and bevacizumab with irinotecan – cleared the mark at 40% and 39%, respectively. Median overall survival was longer with the temozolomide partnership (9.4 months vs. 7.7 months with irinotecan), but the difference was not significant.

In 2009, the Food and Drug Administration approved bevacizumab as a single agent for the second-line treatment of glioblastoma, based on objective response rates in two single-arm trials.

Newly Diagnosed in Duke Study

The Genentech-sponsored study from Duke began with 125 patients (mean age, 56 years; 59% male) with newly diagnosed grade IV malignant glioblastoma multiforme (GBM), reported Dr. Annick Desjardins of the university's brain tumor center. Most (70%) had Karnofsky performance scores greater than 90%.

Between 2 and 4 weeks after resection, patients started 6 weeks of radiotherapy and daily temozolomide at 75 mg/m^2. At a minimum of 28 days post craniotomy, bevacizumab was added at a dose of 10 mg/kg once every 2 weeks.

In the second phase of the trial, 113 patients went on to receive 6-12 more weeks of bevacizumab at the same dosage, combined with temozolomide at 200 mg/m^2 on days 1-5 of each month, and irinotecan dosed according to whether patients were or were not taking enzyme-inducing antiepileptic drugs (340 mg/m^2 or 125 mg/m^2, respectively, on days 1 and 15 of each month).

The first phase of treatment was associated with minimal toxicity, the investigators recently reported (Int. J. Radiat. Oncol. Biol. Phys. 2010 Oct 30 [doi: 10.1016/j.ijrobp.2010.08.058]). Grade 4 thrombocytopenia occurred in 2.4%, neutropenia in 0.8%, central nervous system hemorrhage in 0.8%, and deep vein thrombosis and pulmonary embolism in 1.6%, said Dr. Desjardins.

Five patients did not complete the first phase (one patient with grade 2 CNS hemorrhage, two with pulmonary emboli, one with grade 4 pancytopenia, and one with wound dehiscence). Seven other patients did not go on to the second phase (three with tumor progression, two withdrawing because of fatigue, and one each with a bowel perforation and a rectal abscess). Patients in the second phase have been followed for a median of 28 months, said Dr. Desjardins.

A final analysis for the original cohort of 125 shows that median progression-free survival reached 14.2 months and median overall survival was 21.3 months. This compares with medians of 6.9 months and 15.9 months, respectively, that had been reported in the literature, she said.

Additionally, progression-free survival rates were 88% at 6 months, 64% at 1 year, and 16% at 2 years in the Duke cohort; overall survival rates were 94%, 82%, and 44%, respectively.

For all 125 patients enrolled, the overall serious toxicities included 1 CNS hemorrhage, 9 VTEs, 2 wound dehiscences, 1 bowel perforation, 17 grade 4 hematologic toxicities, 1 secondary malignancy, and 2 cases of pneumocystis pneumonia. There were four toxicity-related deaths.

RTOG Trial in Recurrent GBM

The noncomparative RTOG study enrolled patients with recurrent glioblas-

Continued on following page

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toma who had failed previous chemoradiation with temozolomide. In all, 57 patients were assigned to bevacizumab 10 mg/kg IV plus irinotecan 200 mg/kg every 2 weeks, and 58 were assigned to the same bevacizumab dose plus dose-dense temozolomide 75-100 mg/m^2 daily on the first 3 weeks of a 28-day cycle (Neuro. Oncol. 2010;12[suppl. 4; abstract NO-14, RTOG 0625]:iv36-57 [doi:10.1093/neuonc/noq116.s6]).

The two arms had different end points: safety with temozolomide and efficacy in the irinotecan arm, noted the presenter, Dr. Mark Gilbert, a professor of neuro-oncology at the University of Texas M.D. Anderson Cancer Center in Houston.

Hematologic toxicities were seen more in the temozolomide arm, whereas gastrointestinal toxicities predominated in the irinotecan arm, said Dr. Gilbert. One case of gastrointestinal perforation resulted in death.

"The primary objectives were met," he reported. "We found that administering bevacizumab regimens in a cooperative group setting was feasible. We had acceptable toxicity with the combination of bevacizumab and dose-dense temozolomide, and it supported our use of this type of regimen in the up-front setting. And, in fact, the efficacy of both arms reached our target."

Trials' Protocols Criticized

Both study designs were challenged at the meeting.

Session moderator Dr. Martin van den Bent contended that exposing all patients to the bevacizumab/irinotecan regimen in the Duke study – rather than randomizing patients to one agent or the other – makes it impossible to know which drug is preferable.

"It's flatly outrageous. It should not have been done," Dr. van den Bent elaborated in an interview after the session. "What I find very disturbing is they did a very big study of 120 patients … but by doing it in an uncontrolled fashion, they ended up with an impossible interpretation of whether the irinotecan added to the bevacizumab made any difference."

Dr. van den Bent, professor of neuro-oncology at the cancer center of Erasmus University in Rotterdam, the Netherlands, charged that Duke has a history of doing uncontrolled trials, but he also criticized the field's eagerness to embrace bevacizumab based on such trials.

"The use of bevacizumab at present is based on uncontrolled studies; it's been FDA approved on a scientifically not valid end point," said Dr. van den Bent, a past chair of the EORTC (European Organisation for Research and Treatment of Cancer) Brain Tumor Group.

Study design also triggered a complaint with the RTOG trial. Dr. Gilbert cautioned that randomization was not consistent because of safety concerns with the temozolomide regimen. Until these were resolved, the initial 90 patients were randomized 2:1 favoring irinotecan. Consequently, the final 30 temozolomide patients were assigned to that arm without randomization.

For these reasons, "we cannot on the basis of this study tell which of the two treatments" is better, "or in fact whether a combination of chemotherapy with bevacizumab is better than bevacizumab alone," he said, stressing that the study was not powered for comparison.

A member of the audience asked whether this wasn't "kind of a charade," since comparisons were being made anyway.

"It's not a charade," Dr. Gilbert replied, reiterating that the investigators had two separate goals: safety with temozolomide and efficacy with irinotecan. "It is what it is," he said. "We certainly weren't going to power it, because we weren't interested particularly in the question of which was the better regimen."

Genentech sponsored the study from Duke University. Dr. Desjardins reported no conflicts of interest. Dr. Gilbert disclosed research support from Merck and Genentech, and honoraria/advisory board participation with Merck and Genentech. Dr. van den Bent said he is a consultant for eight companies, including F. Hoffmann-La Roche, parent company of Genentech. ■

Device for Glioblastoma May Offer Advantage Over Chemo

BY KATE JOHNSON

FROM THE ANNUAL MEETING OF THE SOCIETY FOR NEURO-ONCOLOGY

MONTREAL – An investigational treatment for recurrent glioblastoma that delivers alternating electric fields through scalp electrodes has shown signs of improved survival in a post hoc analysis of results in particular subgroups of patients in a phase III trial.

Quality of life outcomes also favored patients who used the device, known as NovoTTF-100A, compared with those who received chemotherapy.

To date, reports about the device have elicited both antagonistic and enthusiastic reaction from oncologists, with "neither the enthusiasts nor the antagonists having significant basis for either kind of acute reaction," Dr. Zvi Ram said in an interview after presenting the subgroup analyses at the meeting. "I think it is exciting that we're getting something completely new – a different, noninvasive modality with no side effects. I think we should be exhilarated."

The device delivers low-amplitude "tumor treatment fields" of 100-300 kHz that have been shown in vitro to slow and reverse tumor cell proliferation by inhibiting mitosis, according to NovoCure Ltd., the manufacturer of the device and sponsor of the trial.

The portable device weighs about 6 pounds and connects to a battery pack. It is designed to be worn almost constantly, with a target of at least 20 hours of use each day.

In a phase III clinical trial presented earlier this year at the American Society of Clinical Oncology, an intent-to-treat analysis comparing NovoTTF vs. best-available chemotherapy found no statistical difference in 1-year overall survival (OS) among 237 recurrent glioblastoma patients randomized to either treatment.

However, a per-protocol analysis (which included only those patients who wore the device for at least 70% of the recommended time during the first month) showed a statistically significant benefit to NovoTTF in 1-year survival, compared with chemotherapy (29.5% vs. 19.1%, respectively; hazard ratio, 0.64; $P = .01$).

In the new post hoc analysis, a subgroup of 110 patients with a "good prognosis" (aged younger than 60 years, and with a Karnofsky performance status score greater than 80%) showed a "more robust" survival benefit than that seen in the overall intent-to-treat analysis, he said.

In this subgroup, patients treated with NovoTTF had a median survival of 9.2 months, vs. 6.6 months in those treated with chemotherapy (*P* less than .01). However, in the overall intent-to-treat group, median survival was 6.6 months and 6.0 months, respectively, he explained. Moreover, the 1-year OS in this subgroup was significantly higher in the NovoTTF group than in the chemotherapy group (35.2% vs. 20.8%, respectively; *P* less than .01), whereas the difference was nonsignificant in the larger analysis (23.6% vs. 20.7%).

VITALS

Major Finding: 1-year overall survival in a subgroup of patients was significantly higher among those treated with NovoTTF-100A than it was in those who received chemotherapy (35.2% vs. 20.8%).

Data Source: Post hoc subgroup analysis of 237 patients with recurrent glioblastoma.

Disclosures: Dr. Zvi Ram disclosed that he is a consultant for NovoCure, which sponsored the trial and manufactures the device. Dr. Brandes said that she had no relevant financial disclosures.

Another subgroup analysis looked at patients who had previously failed treatment with bevacizumab (about 20% of the entire cohort). Both an intent-to-treat analysis and a per-protocol analysis showed significant OS advantages to NovoTTF, said Dr. Ram, chair of neurosurgery at Tel Aviv (Israel) Medical Center.

The median OS in 44 patients in the intent-to-treat group was 4 months with NovoTTF vs. 3.1 months with chemotherapy (HR, 0.43; *P* less than .02). NovoTTF also gave a significantly better median OS among 29 patients in the per-protocol analysis for this subgroup (6.3 months vs. 3.3 months; HR, 0.21; $P = .02$).

"You don't see this anywhere," he said. "There's no drug in the world that could produce such response in patients who had already failed" bevacizumab.

The investigators also analyzed a surgery-naive group. "You know these are going to be poor responders, almost identical to [those with] bevacizumab failure," Dr. Ram commented.

In this group of 38 patients, an intent-to-treat analysis showed that overall survival was 9.8 months with NovoTTF vs. 5.5 months with chemotherapy.

Patients also reported significantly better quality of life with NovoTTF than with chemotherapy. On the Quality of Life Symptom Scale, NovoTTF patients scored –34 and –35 on constipation and diarrhea, compared with scores of +77 and +50 for the chemotherapy group. Nausea and vomiting scores were 15 for the NovoTTF group and 61 for the chemotherapy group, and pain scores were –1 for the NovoTTF group and +63 for the chemotherapy group.

A quality of life analysis using the EORTC (European Organisation for Research and Treatment of Cancer) QLQ-C30 instrument showed scores of 14 vs. –7 in favor of NovoTTF for cognitive functioning, and scores of 7 vs. 1 in favor of NovoTTF for emotional functioning.

"We do this to all our patients. We intoxicate them," Dr. Ram said. "So even if NovoTTF did not extend survival, if it was equivalent to chemotherapy [for survival], it may still improve quality of life."

Dr. Ram did not know the median length of time that the NovoTTF cohort wore the device, but an earlier phase II study followed some patients up to 59 months. He noted that "70% are still alive; that's unheard of."

"There were concerns that patients might have more headaches or seizures, but there were none," he added.

In the current study, the rate of adverse events related to the central nervous system was similar (66% for NovoTTF and 67% for chemotherapy). Seizures occurred in 15% of the NovoTTF group and 12% of the chemotherapy group, and headaches occurred in 18% and 13%, respectively.

"It's very interesting and exciting, even if we do not yet have enough definitive data," commented Dr. Alba B. Brandes, moderator of the session and the chair of medical oncology at Azienda USL, a group of nine hospitals in and around Bologna, Italy.

The investigators have been criticized for repackaging their nonsignificant intent-to-treat results into per-protocol results that show significance, she said. "An intention-to-treat population and per-protocol population are two different things, and from a statistical point of view, it is sometimes difficult for the oncologic community to accept." Despite those reservations, she said that the per-protocol observations should not be dismissed, because when they are analyzed in this way the results are highly significant.

Dr. Ram acknowledged that per-protocol analysis is unconventional, but "there is no precedent for this kind of therapy and I think we may need to redesign the way we assess results in the future. We cannot use the same guidelines and definitions we were traditionally using." ■