Nearly Half Survive 2 Years With GBM Protocol

BY RICHARD HYER

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY

CHICAGO — A new protocol that adds temozolomide and radiation to bevacizumab and irinotecan for patients with newly diagnosed glioblastoma multiforme has resulted in median overall survival reaching 21.2 months, according to investigators from Duke University.

VITALS

Major Finding: For newly diagnosed GBM patients, median overall survival reached 21.2 months with a regimen incorporating bevacizumab, temozolomide, irinotecan, and radiation.

Data Source: First 75 patients treated with bevacizumab, temozolomide, and radiation followed by bevacizumab, temozolomide, and irinotecan in a phase II trial.

Disclosures: The investigator-sponsored study received support from Genentech Inc. and Schering-Plough. Dr. Vredenburgh said he consults for Genentech.

At 16 months, 65.3% of the first 75 patients in the up-front, phase II trial were still alive, they reported. The 2-year overall survival rate was 45%.

"We were not surprised by the findings. … We had shown that bevacizumab plus irinotecan had good efficacy in glioblastoma," said principal investigator Dr. James Vredenburgh, a professor of medicine and the medical director of adult clinical services at Duke University Medical Center.

He suggested that the findings will encourage investigators to enroll patients in phase III studies now underway. "I think the phase III studies will change clinical practice," Dr. Vredenburgh said.

In May 2009, the Food and Drug Administration approved bevacizumab (Avastin) monotherapy second-line for treatment of glioblastoma that had progressed after first-line treatment. Temozolomide (Temodar) was approved in March 2005 as a first-line treatment with radiation and as a maintenance therapy.

The new experimental protocol uses bevacizumab in combination with temozolomide and radiation therapy, followed by bevacizumab, temozolomide, and irinotecan (Camptosar) for newly diagnosed glioblastoma multiforme and gliosarcoma.

The study rationale was that VEGF (vascular endothelial growth factor) is an essential part of glioblastoma biology, and the anti-VEGF monoclonal antibody bevacizumab has demonstrated synergy with radiation and chemotherapy. Irinotecan was thought possibly to have synergy with temozolomide. Bevacizumab with or without irinotecan had shown activity in recurrent disease, and it was thought that using bevacizumab with chemotherapy in newly diagnosed patients might improve survival.

Using previously reported median survival of 15.8 months in resected patients (N. Engl. J. Med. 2005;352:987-96) as a benchmark, the investigators set the primary end point of this trial as the proportion of patients who were alive 16 months after initiation of combination chemoradiotherapy, with a target of more than 60%.

Findings should encourage patient enrollment in potentially practice-changing phase III trials.

DR. VREDENBURGH

The study was opened on August 15, 2007, and 75 patients were accrued through September 4, 2008, with a median follow-up of 25 months (range, 19-31 months). A second cohort of 50 patients was enrolled from October 30, 2008, to March 26, 2009. These 50 patients are included in the toxicity data, but not in the survival analysis.

The protocol called for all patients to start receiving radiation therapy and temozolomide at 75 mg/m^2 per day at 2-6 weeks post craniotomy. They began bevacizumab 10 mg/kg every 14 days at least 4 weeks after surgery.

After radiation therapy, patients received 6-12 monthly cycles of temozolomide at 200 mg/m^2 per day on days 1-5, bevacizumab at 10 mg/kg, and irinotecan (340 mg/m^2 for patients on enzyme-inducing antiepileptic drugs [EIAEDs] and at 125 mg/m^2 for patients not on EIAEDs) on days 1 and 15.

Median progression-free survival reached 14.2 months, and the 2-year progression-free survival rate was 13.3% for the first 75 patients, Dr. Vredenburgh reported.

Median overall survival from progression, which was measured in 62 patients, was 5 months; the 2-year overall survival from progression was 8.8%.

Grade 4 hematologic toxicity occurred in 17 of 125 patients, and deep vein thrombosis/pulmonary embolism occurred in 9 patients.

All other toxicities occurred in not more than two patients. There were four toxic deaths (one each from myocardial infarction, DVT/PE, sepsis, and pneumocystis pneumonia). ■

Bevacizumab-Irinotecan Data Hold Up in Recurrent GBM

BY SUSAN LONDON

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY

CHICAGO — Bevacizumab, alone or in combination with irinotecan, is generally safe and active in patients with relapsed glioblastoma, according to updated results of the phase II BRAIN trial.

We think the majority of the effect that we are seeing with the two drugs in this trial comes from bevacizumab.

DR. CLOUGHESY

"Up to 16% of patients who received bevacizumab-based therapy remained alive at 30 months," lead investigator Dr. Timothy Cloughesy reported. "The incidence of selected [adverse events] in the updated safety data was consistent with what was previously reported—there were no new safety signals that were identified."

The Study to Evaluate Bevacizumab Alone or in Combination With Irinotecan for Treatment of Glioblastoma Multiforme (BRAIN) trial's efficacy results compare favorably with those of similar trials testing other regimens, Dr. Cloughesy said: the 12-month survival rate was 38% whereas it has been 14%-27% with cytotoxic agents such as temozolomide (Temodar) or lomustine (CCNU).

Sorting out the specific contributions of bevacizumab (Avastin) and irinotecan (Camptosar) to the observed outcomes is difficult because of the trial's design, he said. However, "when we look at what is providing the majority of the effect that we are seeing, I think it is coming from bevacizumab."

The multicenter trial, sponsored by Genentech (manufacturer of bevacizumab), opened in July 2006 to patients with glioblastoma in first or second relapse who had previously received radiation therapy and temozolomide.

They were randomly assigned in nearly equal numbers to open-label treatment with bevacizumab alone or bevacizumab plus irinotecan.

Updated results were based on data cutoffs of July 2008 (treatment exposure, safety, and median survival) and July 2009 (survival rates), according to Dr. Cloughesy. The 167 enrolled patients had a median age of about 55 years. The majority were male (68%) and white (90%), and experiencing a first relapse (81%). Progression occurred in 59% of the patients in the bevacizumab arm, and these patients went on to receive the combination therapy.

VITALS

Major Finding: The 12-month rate of survival was 38% with both bevacizumab alone and bevacizumab plus irinotecan in updated analyses, and no new adverse effects were noted.

Data Source: A randomized, noncomparative, open-label phase II trial among 167 patients with relapsed glioblastoma multiforme (the BRAIN trial).

Disclosures: Genentech sponsored the trial. Some of the investigators are employees of or consultants to Genentech, or have received honoraria or research funding from the company. Dr. Brandes disclosed having a consultant or advisory role with and receiving honoraria from Roche, which owns Genentech.

The median number of bevacizumab doses received was 9 in the bevacizumab group and 11 in the bevacizumab-irinotecan group during the main phase of the trial, reported Dr. Cloughesy, director of the neuro-oncology program and a clinical professor at the Ronald Reagan UCLA Medical Center in Los Angeles. The median number was three during the post-progression phase.

The updated safety data showed little change from the initial results, he said. Some 51% of patients in the bevacizumab group and 71% in the bevacizumab-irinotecan group had adverse events of grade 3 or higher. Hypertension was the predominant event with monotherapy (11%), whereas venous thromboembolism was the predominant event with combination therapy (10%).

"The things that… we are concerned about with regard to patients who are taking anti-VEGF [vascular endothelial growth factor] therapy—cerebral hemorrhage, wound healing, arterial thrombotic embolism, and gastrointestinal perforation—these all stayed fairly low," he commented. These events occurred at a severity of grade 3 or higher in only 0%-3.6% of patients.

Median overall survival was 9.3 months with bevacizumab alone and 8.9 months with both drugs. The proportion of patients still alive was 38% in each arm at 12 months; 24% and 18%, respectively, at 18 months; 16% and 17%, at 24 months; and 11% and 16%, at 30 months.

Dr. Alba A. Brandes, a medical oncologist at Azienda USL in Bologna, Italy, noted that the trial's size and promising results were strengths, but said its evaluation criteria and lack of a standard control arm and biomarker studies were weaknesses.

"Bevacizumab has brought light into the treatment of recurrent GBM, a setting with scarce options and dismal results," she commented. "The advantage of bevacizumab over classical cytotoxics seems to be in the range of 2 to 3 months. That represents a prolongation of 30% in survival at recurrence," said Dr. Brandes. "However, this advantage should be proven in phase III trials." ■