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From Medscape Medical News > Oncology

Bevacizumab Beneficial in Newly Diagnosed Glioblastoma?

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December 1, 2010 (Montreal, Quebec) — A large study of patients with newly diagnosed glioblastoma multiforme suggests that the addition of 2 agents — bevacizumab and irinotecan — to standard chemoradiation can extend survival, compared with historic controls.

The addition of bevacizumab, an inhibitor of vascular endothelial growth factor, and irinotecan, a topoisomerase inhibitor that prevents DNA replication, appears to boost progression-free survival and overall survival by about 6 months, compared with rates reported for patients receiving temozolomide-based chemotherapy and radiation alone, reported Annick Desjardins, MD, from Duke University Medical Center in Durham, North Carolina.

But the study design was harshly criticized by Martin van den Bent, MD, PhD, who chaired the session in which it was presented here at the Society for Neuro-Oncology 15th Annual Scientific Meeting.

"It's flatly outrageous. It should not have been done," he said in an interview with *Medscape Medical News* after the session. Dr. van den Bent is past chair of the European Organization of Research and Treatment Brain Tumor Group, and professor of neuro-oncology at the Daniel den Hoed Cancer Center, Erasmus University, in Rotterdam, the Netherlands.

"What I find very disturbing is that they did a very big study of 120 patients — which is a lot; it's really a big study — 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."

The study, which was supported by Genentech, began with 125 patients (mean age, 56 years; 59% male) with newly diagnosed grade 4 malignant glioblastoma multiforme. The majority of patients (70%) had Karnofsky Performance Status scores above 90.

Two to 4 weeks after surgical resection, patients received the standard of care — 6 weeks of radiation and daily temozolomide 75 mg/m^2. Added to this regimen, starting a minimum of 28 days after craniotomy, bevacizumab 10 mg/kg was administered once every 2 weeks.

In the second phase of treatment, patients received 6 to 12 more weeks of bevacizumab at the same dose, combined with temozolomide at 200 mg/m^2 on days 1 to 5 of each month, plus 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 authors report in their study published online October 30 in the *International Journal of Radiation Oncology, Biology, Physics*.

At the meeting, Dr. Desjardins reported that grade 4 thrombocytopenia occurred in 2.4% of patients, neutropenia in 0.8%, central nervous system (CNS) hemorrhage in 0.8%, and deep vein thrombosis and pulmonary embolism in 1.6%. Five patients did not complete the first phase of the treatment (1 with grade 2 CNS hemorrhage, 2 with pulmonary emboli, 1 with grade 4 pancytopenia, and 1 with wound dehiscence), and 7 others did not go on to the second phase (3 had tumor progression, 2 withdrew because of fatigue, 1 had a bowel perforation, and 1 had a rectal abscess).

A total of 113 patients went on to the second phase of treatment and have been followed for a median of 28 months, said

Dr. Desjardins.

Better Results Than Historic Controls

A final analysis of the original cohort of 125 shows a median progression-free survival of 14.2 months and a median overall survival of 21.3 months, she reported. A median progression-free survival of 6.9 months and a median overall survival of 15.9 months have been reported in the literature, she noted.

Additionally, progression-free survival at 6 months, 1 year, and 2 years in her cohort was 88%, 64%, and 16%, respectively, and overall survival at was 94%, 82%, and 44%, respectively.

There were 4 toxic deaths in the entire cohort: 1 from pulmonary embolism, 1 from sepsis, 1 from myocardial infarction, and 1 from *Pneumocystis jiroveci*.

For all 125 patients, overall serious toxicities included 1 CNS hemorrhage, 9 venous thromboembolisms, 2 wound dehiscences, 1 bowel perforation, 17 grade 4 hematologic toxicities, 1 secondary malignancy, and 2 pneumocystis pneumonias.

The regimen appears safe and tolerable, and appears to improve survival, compared with historic controls, concluded Dr. Desjardins.

But historic controls are not a valid comparison, said the moderator, Dr. van den Bent.

In addition, he challenged Dr. Desjardins on the podium about the design of the study, pointing out that exposing all patients to the bevacizumab/irinotecan regimen rather than randomizing them to one or the other makes it impossible to know which drug is preferable.

Wasting Resources and Opportunities

Asked in an interview about his public criticisms, Dr. van den Bent was adamant.

"Duke has been accused repeatedly of not doing the right studies, doing studies that don't make reasonable interpretation possible. By doing that, they are wasting resources, wasting progress, and wasting opportunities to carry the field forward. This is a very serious thing," he said.

> **Doing studies in this way is not the way to go.**

"Doing studies in this way is not the way to go. . . . If you have an uncontrolled study, you basically have no way of telling if the addition of a novel compound makes any difference or not. So all the patients were exposed to the toxicity of the combination regimen and we don't know if it works or not."

Dr. van den Bent was also critical of the field's eagerness to embrace bevacizumab on the basis of questionable science. "The use of bevacizumab at present is based on uncontrolled studies, it's been [approved by the US Food and Drug Administration] on a scientifically nonvalid end point. There are ongoing, properly controlled, randomized studies looking at adding bevacizumab to radiation and temozolomide, but . . . Duke takes the next step and adds another compound before we even know if there is benefit to adding bevacizumab. They're taking 2 steps at a time and we can't evaluate. We haven't learned anything."

Medscape Medical News has previously reported on the widely different viewpoints in Europe and the United States about the use of bevacizumab in glioblastoma. This is an indication that has been approved in the United States but not in Europe — decisions that were made on the basis of the same data.

The study was supported by Genentech. Dr. Desjardins has disclosed no relevant financial relationships. Dr. van den Bent is a consultant for MSD, Hoffman-La Roche, BMS, Ark Therapeutics, Siena Biotech, Novartis, Merck, and Eli Lilly.

Int J Radiat Oncol Biol Phys. Published online October 30, 2010. Abstract

Society for Neuro-Oncology 15th Annual Scientific Meeting: Abstract OT-34. Presented November 21, 2010.

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