Glioblastoma: two studies herald a new start

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Surprise results of a temozolomide trial, and a new marker predicting who will benefit, offer hope for progress in the treatment of a highly aggressive brain tumour.

An international clinical trial has revealed that the addition of the chemotherapy agent temozolomide to radiation therapy increases survival in patients suffering from glioblastoma. And a companion laboratory study has offered hope of even greater improvements in survival in the future through identification of a molecular change in the tumour that allows prediction of benefit from the new treatment.

The combined work, published this March in the *New England Journal of Medicine* (vol 352, pp 987-996; 997-1003), is being seen as a significant breakthrough in medical research for patients with glioblastoma. In an accompanying editorial (pp 1036-1038), Lisa DeAngelis, Chair of Neurology at the Memorial Sloan-Kettering Cancer Center in New York City, hailed it as 'a new beginning' in chemotherapy for brain tumours.

Glioblastoma is the most common type of primary malignant brain tumour. It tends to occur in younger men and women, with around 20,000 new patients being diagnosed each year in the European Union. Patients have an average life expectancy of one year with the standard treatment of surgical resection followed by radiotherapy. The trial aimed to find out whether this could be extended without deleterious impact on quality of life through adding temozolomide to radiotherapy, both concomitantly and as an adjuvant treatment.

The clinical trial was performed for the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumour and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group. Almost 600 patients from 85 centres who had newly diagnosed, histologically confirmed glioblastoma were randomly assigned to receive radiotherapy alone or radiotherapy plus temozolomide (see box).

Results showed 26.5% survival at two years in those treated with the new combined therapy, compared to only 10.4% in those receiving radiotherapy alone.

The dramatic improvement in median survival at two years has surprised even the investigators.

Martin van den Bent, a member of the research team based at the Daniel den Hoed Oncology Centre in Rotterdam, the Netherlands, said: "Temozolomide is a new drug increasingly being used with patients undergoing radiotherapy, and this makes it an interesting candidate to

THE TRIAL

A total of 573 patients were randomly assigned to receive one of the following treatment options:

- Radiotherapy alone: focal irradiation in daily fractions of 2 Gy given five days per week for six weeks, to a total of 60 Gy
- Radiotherapy plus continuous daily temozolomide: 75 mg/m^2 body-surface area per day, seven days per week from the first to the last day of radiotherapy, followed by six cycles of adjuvant temozolomide at a dose of 150–200 mg/m^2 for five days during each 28-day cycle.

The median age of the patients was 56 years, and 84% had undergone debulking surgery.

Martin van den Bent: The combined treatment has become accepted as standard in glioblastoma in a very short space of time

investigate, but we had assumed that the study would be negative – the outcome was a surprise for us."

An earlier meta-analysis of around 3,000 patients had shown only small benefits from adjuvant chemotherapy, raising controversy about its use. The new trial seems to have cast such doubts aside and is changing practice in a dramatic fashion in van den Bent's home country.

Improved access

"Prior to the publication of this study," van den Bent says, "access to adjuvant chemotherapy for patients with glioblastoma depended on which country they were treated in. Those in the Netherlands or UK wouldn't get it, while those in Germany, France and the US would.

"Since the study, most patients in the Netherlands with glioblastoma who are candidates for treatment have been getting the combined modality treatment. It has become accepted as the standard for these patients in a very short space of time."

A key concern of any new chemotherapy treatment is that it should not significantly worsen patients' quality of life. The trial has found no such effects with the addition of temozolomide.

"Analysis of the seven most important quality-of-life domains, such as social functioning, shows no difference with the combined modality treatment," van den Bent explains. "This was also the reported experience of participating physicians – we were really amazed by the ease with which patients tolerated the treatment. Many of the side-effects suffered, like fatigue, occurred as a result of the radiotherapy, not the temozolomide."

Cost is another important element, and while van den Bent concedes that the combined modality treatment is more expensive, it may be the case that costs are shifted within the treatment programme rather than dramatically increased overall.

"Some patients will now have chemotherapy early in their disease process rather than later, so there may be a shift of costs from late to early," he says.

A health economic analysis is currently being undertaken to establish the impact of the new intervention on total treatment costs.

Predictive marker

The companion laboratory study, led by Monika Hegi of the Laboratory of Tumour Biology and Genetics at University Hospital, Lausanne, offers the promise of even greater impact of the combined modality treatment in the future.

The study found that patients who had glioblastoma that contained a methylated MGMT (O^6-methylguanine-DNA methyltransferase) promoter benefited from temozolomide, while those who didn't showed less benefit.

Identifying this specific molecular change is a complicated process, and no simple test is currently available. Van den Bent is hopeful, however, that following further trials, a test will be ready for the market in late 2005 or early 2006.

In the meantime, he and his colleagues are continuing their investigations, with the aim of further refining the combined modality treatment to improve survival even more.

"We are launching three new trials that will look to improve this now-standard treatment in several ways," he says. "One is intensifying the adjuvant part of the treatment, another is prolonging it, and the last is to add other drugs to the combination. These trials are being initiated right now."

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