NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

Drug Combo May Prevent Glioblastoma Recurrence

amma-secretase inhibitors could play an important role in augmenting the effectiveness of temozolomide chemotherapy for glioblastoma multiforme if the results obtained in recent in vitro, ex vivo, and in vivo experiments are supported in future studies.

Although temozolomide (TMZ) has increased the 2-year survival rate of patients with glioblastoma multiforme (GBM) when it is used in combination with surgical resection and radiotherapy, some cells still escape treatment in most patients and contribute to local tumor recurrence. Gamma-secretase inhibitors (GSIs) are an attractive therapeutic option because they have been found in previous studies to stop both glioblastoma cell growth and the formation of glioblastoma neurospheres by blocking the Notch

signaling pathway, which is commonly overexpressed in glioblastoma cells, wrote Candace A. Gilbert and her colleagues at the University of Massachusetts, Worcester (Cancer Res. 2010 Aug. 10 [doi:10. 1158/0008-5472.CAN-10-1378]).

Before Ms. Gilbert and her associates tested the combination of TMZ and a GSI in vivo, they tested TMZ alone, a GSI alone, and both together on neurosphere cultures derived from patients' GBMs. Although GSI treatment alone decreased Notch pathway signaling and reduced neurosphere formation, it could not stop the proliferation of GBM cells and the formation of secondary neurospheres. And although treatment with TMZ alone and combined treatment with TMZ and a GSI yielded similar decreases in initial neurosphere formation, cultures treated with the combination recovered to a smaller size, and there were fewer of them than was the case for those treated with TMZ alone. When these neurosphere cultures were dissociated to single cells and replated, the cells that underwent combination treatment formed far fewer secondary neurospheres than did those treated with only TMZ. Treatment with both drugs also led to significantly fewer cells in each neurosphere that were capable of self-renewal.

Further in vitro experiments of the combination of drugs showed that a single dose of a GSI could reduce neurosphere recovery and the formation of secondary neurospheres only when the GSI was administered 24 hours after TMZ, in comparison with TMZ alone.

When the tumor cells were treated and then injected subcutaneously into immunocompromised mice, the researchers observed palpable tumor growth in very few mice that received cells treated with TMZ and a GSI (tumor latencies, 43-96 days), compared with tumor growth in all mice that received cells treated with a GSI alone (latencies, 3-16 days) and growth in nearly all mice that received cells treated with TMZ alone (latencies, 25-43 days).

In another group of immunocompromised mice, tumor cells that were injected subcutaneously were allowed to grow to 150 mm³. Ms. Gilbert and her associates found that the xenografts were completely eliminated in half of immunocompromised mice by an intraperitoneal injection of TMZ followed by ingestion of a GSI mixed into their food supply. The mice also survived free of a palpable tumor until they were euthanized at 150 days. The remaining half of the mice that received the combination treatment showed tumor progression at a mean of 26 days.

All tumor masses progressed (doubled in size) in mice that received only TMZ.

"Because Notch activity is associated with GBM stem cell function and survival, and the cells that survive TMZonly treatment are capable of self-renewal and tumor initiation, it is probable that the cells targeted by TMZ plus GSI treatment possess a cancer stem cell phenotype," the researchers wrote.

They suggested that the variability of response to combined treatment in the in vivo studies could have been due to a TMZ concentration that was not "high enough to induce a cell cycle arrest in all the cells capable of recovery, which could hinder GSI enhancement," or a "slight variability" in food consumption.

The need for only a single dose of a GSI to enhance TMZ therapy is beneficial, the researchers noted, because GSIs can cause cytotoxicity in the gastrointestinal tract. They found no change in the weight of the mice during combined treatment.

'These studies suggest a role for TMZ plus GSI therapy to reduce recurrences in patients with low tumor burden after surgical resection of the bulk tumor," wrote the investigators, who acknowledged that they ultimately need to include radiation in their treatment schedule to see how it contributes to combination therapy with TMZ and

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Research report by Managing Editor, Jeff

A Springboard to Future Treatments

Since 2005, the treatment standard for GBM has been concomitant TMZ with radiotherapy followed by adjuvant TMZ. This treatment showed slightly increased overall survival, compared with radiotherapy alone. However, the most striking finding in support of this treatment was the 2-year survival rate of 26.5%, which was higher than any prior

treatment regimen had shown. The time to progression on the aforementioned regimen is about 6 months, which points to the refractory and aggressive nature of this tumor. Despite the progress made with up-front therapy, researchers in the field con-

tinue to struggle with how to prevent tumor recurrence, and we remain limited in our treatment options for recurrent disease.

Thus far, bevacizumab has been the only agent approved by the Food and Drug Administration for use in the setting of recurrent GBM. Studies are currently underway to assess the up-front efficacy of using bevacizumab with radiotherapy and TMZ. Given the dismal prognosis for this patient population, novel agents are needed not only to augment upfront therapy to prevent recurrence but also to provide further treatment options in the recurrent setting.

Ms. Gilbert and colleagues conducted an eloquent study using a

novel GSI to assess influence on neurosphere replication in the pre-, adjunct, and post-TMZ treatment periods. The remarkable in vitro and in vivo data suggest that GSI and TMZ act together to halt neurosphere replication, and that administering a GSI after TMZ may have the maximum impact in affecting neurosphere repopulation. These data sug-

gest that GSIs may indeed have an impact on glioblastoma recurrence and time to progression.

As the authors point out, future studies to assess the total impact of the GSI in the GBM population will need to incorporate irradiation in addition to TMZ

to reflect a more accurate sense of the full effect and toxicity of the GSI. Toxicity was measured in this study by rodent weight; according to the data provided, it seemed well tolerated with TMZ. The authors suggest that GSIs may also improve the impact of irradiation, which may further reduce treatment toxicity. This study certainly provides a springboard for considering future directions in the use of GSIs and may indeed provide further treatment options for this patient population, in whom options are greatly needed.

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standardized international criteria for eligibility and response for phase II studies in neuroblastoma, he said.

In multivariable analysis, factors at diagnosis that were independently predictive of overall survival post relapse were stage 4 (hazard ratio, 6.9); stage 3 (HR, 4.3); stage 4S (HR, 3.5); MYCN amplification (HR, 2.4); age less than 18 months (HR, 1.6); and time to relapse less than 12 months (HR, 2.0) – all with a P value less than 0.0001, Dr. London said.

Time to relapse was predictive of survival post relapse in patients with stage 1, stage 2, or no MYCN amplification, but it was not independently predictive,

Time to Relapse Useful for Determining Trial Eligibility

lapse predicts survival in neuro-

available for investigation in this dis-

ease and especially when nontradi-

blastoma is made possible by the analysis of a large international collaborative database. Given the unique biology of neuroblastoma and the extreme clinical heterogeneity that impacts its natural history despite therapy and initial response to therapy, this finding will be important as new agents become

The observation that time to retional end points such as time to progression and progression-free survival are considered.

In addition, refining and enriching patient populations for some degree of biological homogeneity is important, not only for the purpose of accurately defining activity of a specific investigational agent in this specific disease, but

also for potentially identifying a group of patients with relapsed disease who may be candidates for more conventional or standard salvage therapy approaches. This will also aid in defining eligibility criteria and estimating accrual requirements for investigational approaches.

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