Relapse Speed Predicted Neuroblastoma Survival

VITALS

Major Finding: INSS stage 4 patients had a 5-year survival of 8%, compared with 52% for those who were stage 1, 2, 3, or 4S.

Data Source: A retrospective analysis of children in the International Neuroblastoma Risk Group database.

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BY PATRICE WENDLING

FROM THE ANNUAL MEETING OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY

CHICAGO – Time to relapse is highly predictive of overall survival post relapse in children with neuroblastoma, according to an analysis of 2,266 children in the International Neuroblastoma Risk Group database.

The analysis identified other factors prognostic of overall survival post relapse as well as a small proportion of relapsed patients who are salvageable, Wendy B. London, Ph.D., reported at the meeting.

Currently, clinicians do not know how to identify which patients are more likely to respond to postrelapse therapy and have difficulty in interpreting time to relapse because neuroblastoma is a heterogeneous disease, she said.

The median time to relapse among the 2,266 children was 13.2 months, with a wide range from 1 day to 11.4 years.

All told, 73% of children who relapsed were aged 18 months or older, 72% were International Neuroblastoma Staging System (INSS) stage 4, and 33% had amplified MYCN oncogene expression.

Overall survival at 5 years was 20%.

It was not possible to categorize time to relapse using a simple 1-year cutoff, said Dr. London, director of biostatistics at Children's Hospital Boston.

The risk of death was about the same for children who relapsed within the first 6 months as it was for those who relapsed at 18-24 months. The risk of death was highest in those who relapsed between 6 and 18 months.

All three groups had a significantly higher risk of death, compared with patients who relapsed after 36 months (*P* less than .001).

The association between time to relapse and overall survival appears to be driven by stage 3, 4, and MYCN-amplified patients, Dr. London said.

In a survival tree regression analysis that adjusted for time to relapse, disease stage was identified as the most highly significant variable for survival post relapse. INSS stage 4 patients had a 5-year survival of 8%, compared with 52% for those who were stage 1, 2, 3, or 4S.

"Aggressive disease that advances unhindered by treatment has a highly predictable time course and ultimate death; we already knew this, but now we're able to describe it quantitatively," she said.

Upon further analysis, three cohorts emerged as salvageable after relapse:

- Patients who are stage 4, with nonamplified MYCN, and less than 18 months of age.
- Patients who are stage 1, 2, 3, or 4S with MYCN amplification.
- Patients who are stage 1, 2, 3, or 4S with nonamplified MYCN and undifferentiated grade histology.

Patients who had stage 4 disease and MYCN amplification had a 5-year survival of 4%, compared with 12% for stage 4 patients with nonamplified MYCN.

Time to first relapse as a predictor of survival is important for two reasons, said Dr. Andrew Pearson, chair of pediatric oncology at the Institute of Cancer Research and the Royal Marsden Hospital in London, who was invited to discuss the findings. It can be used to stratify and/or describe patients in early clinical trials and to identify a salvageable population post relapse.

"In the past, I'm sure that some agents have had a negative response in early clinical studies because a group of very poor prognosis patients were included," he said.

The study findings will also be utilized by the International Neuroblastoma Risk Group, which is nearing completion of

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NEUROSCIENCE TODAY, NEUROLOGY TOMORROW

Drug Combo May Prevent Glioblastoma Recurrence

Gamma-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 mm^3. 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 TMZ-only 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 GSIs.

The National Institutes of Health and the CVIP Technology Development Fund funded the research. The investigators had no conflicts of interest to disclose. ■

Research report by Managing Editor, Jeff Evans.

ADVISER'S VIEWPOINT

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 continue 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 up-front 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 suggest 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, she said. ■

MY TAKE

Time to Relapse Useful for Determining Trial Eligibility

The observation that time to relapse predicts survival in neuroblastoma 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 available for investigation in this disease and especially when nontraditional 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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