CHICAGO – Time to relapse is highly predictable of survival post relapse in patients with multiple sclerosis, according to an analysis of 2,266 children in the International Multiple Sclerosis Risk Group database.

The analysis identified other factors prognostic of overall survival post relapse as well as a proportion of relapsed patients who are salvageable, says primarily B. London, PhD, re- ported at the meeting.

Currently, clinicians do not have enough information to identify which patients are likely to require post tospodrel therapy and have difficulty in interpreting time to relapse because neuroblastoma is a heteroge- neous disease, she said.

The median time to relapse among the 2,266 children was 13.2 months, with a wide range of 1 day to 14.1 years.

All told, 73% of children who relapsed were aged 18 months or older, 72% were International Neuroblastoma staging (INSS) stage 4, and 33% had ampli- fied 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 relapse was the same for children who relapsed within the first 2 years and those who re- lapsed at 18-24 months. The risk of death was highest in those who relapsed between 8 and 18 months.

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

The association between time to relapse and overall survival appears to be driven by stage 4, and MYCN-ampli- fied 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, or 4.

“Aggressive disease that advances un- hindered by treatment has a highly predict- able 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 were stage 1, 2, or 3 with non- MYCN amplified, and less than 18 months of age.
• Patients who were stage 1, 2, or 3 with MYCN amplified and under 18 months of age.
• Patients who had stage 4 disease and MYCN amplification had a 4-year survival of 4%, compared with 12% for stage 4 pa- tients with non-MYCN amplified.

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 Hospi- tal in London, who was invited to discuss the findings. It can be used to stratify and design clinical trials and to identify a salvageable popu- lation post relapse.

“This is clearly a significant finding,” he added.
Drug Combo May Prevent Glioblastoma Recurrence

Glia-omega-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, its impact on overall survival post relapse has been limited. Researchers now report a finding in support of this treatment 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-, ad-, 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 a role in 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.

Alux B. Porter, M.D., is a neuro-oncologist at the Mayo Clinic in Arizona. She has no relevant disclosures.

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.

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Time to Relapse Useful for Determining Trial Eligibility

The observation that time to relapse predicts survival in glioblastoma is made possible by the analysis of a large international clinical trial database. Given the unique biology of glioblastoma 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 setting, 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.

Gregory H. Reaman, M.D., is chair of the United States–based Children’s Oncology Group. He is also a professor of pediatrics at George Washington University School of Medicine and Health Sciences and the head of the Division of Hematology-Oncology at the Children’s National Medical Center, both in Washington.