Research Highlight

Pediatric high-grade gliomas: survival at what cost?

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Survival of children with tumors of the central nervous system has improved over the past three decades with more than 70% of patients now expected to survive at least five years (1). However, pediatric CNS tumors are histologically heterogeneous, affect children over a wide span of developmental stages, and have vastly different treatment approaches. Five-year survival ranges from <10% for those with diffuse intrinsic pontine gliomas to >90% for those with focal pilocytic astrocytomas. Treatment approaches for those with intractable, poor prognosis tumors now include aggressive, combined modality therapy involving surgery, radiation and chemotherapy. Unfortunately, experience has shown that survival of these children comes at a price, with the majority demonstrating significant treatment-related sequelae (2). Rather than resign ourselves to the notion of survival at any cost, it is our responsibility to define these treatment effects in order for parents to make more informed decisions, and to investigate the etiology of late effects with the hope of ultimately preventing or diminishing them.

There are several published and ongoing studies involving long-term outcome of children with cancer, but few, if any, specifically addressing the long-term outcome of children treated for high-grade gliomas due to the relatively small numbers of patients and survivors. The recently published article by Sands *et al*., (3) "Long-Term Follow-Up of Children Treated for High-Grade Gliomas: Children's Oncology Group L991 Final Study Report" is a key study as it is the first to systematically investigate and define neuropsychological outcome specifically in this population. Previous studies of children with acute lymphoblastic leukemia who received CNS prophylaxis with radiation and/or chemotherapy, and studies of children with brain tumors (which primarily include good prognosis tumors such as medulloblastoma and low-grade glioma) have attributed neurosensory impairments, cognitive deficits, problems with memory and attention, slower processing speed and decreased visual-spatial skills to these treatment modalities (4,5). It is not surprising that children treated for high-grade gliomas have similar deficits as those treated for other diseases for which therapy is directed at the developing nervous system. However, in addition to radiation and chemotherapy, children with high-grade gliomas suffer from the added detrimental effects of the tumor itself and of surgery. Attempting to identify cause and effect of neurotoxicity is compounded by the fact that the source of neurologic insults and neurocognitive decline in this population are multifactorial.

This study by Sands *et al*. demonstrates the difficulties in performing long-term studies in children with brain tumors. Patient numbers are small and the population is heterogeneous with respect to age, assessment instruments, tumor location, treatment and time from treatment. Individual patient results were compared to normative test means for each measure rather than using baseline pre-testing with each patient as their own control. Relapsed patients who were retreated and who therefore presumably have a greater risk of neurotoxicity due to additional therapies were included. Histopathologic classification of pediatric brain tumors is variable. Notably, 44% of patients on this study were subsequently found to have a tumor other than high-grade glioma. Lastly, while quality of life did not appear dramatically impacted overall, 13 survivors declined participation for unknown reasons suggesting potential bias in the population willing to undergo evaluation.

Despite these limitations, several risk factors that place

patients at higher risk for neuropsychological, social-emotional and behavior dysfunction and lower quality of life were identified. This suggests that a subpopulation of patients (younger age at treatment, midline tumor location and female gender) can be targeted for closer follow up and early intervention, and ultimately avoidance of the inciting factor. However, although reasonable suppositions can be made in associating young age and tumor location with increased risk of neurotoxic effects, the relationship with female gender is unclear. Until our understanding of cause and effect increases, specific preventive measures or treatment alterations are difficult to employ.

The study by Sands *et al*. is an important study in pediatric neuro-oncology as it evaluated a number of long-term survivors treated for high-grade gliomas in several domains. Despite its limitations, it confirms that there is a significant lasting impact on neuropsychological function, as well as social-emotional and behavioral functioning, from the tumor and its treatment. It has been suggested that children who receive therapy directed to the CNS have baseline neuropsychological evaluation following diagnosis and annual reassessment (6). However, limited resources and clinical status limit our ability to obtain extensive accurate baseline assessments. Development and incorporation of a brief neurobehavioral screen administered shortly following diagnosis has been shown to be both feasible and informative (7). Until we prioritize up-front and follow-up testing of these patients, our ability to define risk, understand the pathophysiology, and alter treatment to prevent significant sequelae will be hindered.

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Footnote

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