Commentary (Cohen/Glod): Current Management of Childhood Ependymoma

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Ependymoma is a rare central nervous system (CNS) tumor in children, and our progress in treating this disease has been hampered by its rarity as well as by a nonuniform approach to treatment among practitioners. Dr. Merchant’s comprehensive review provides a framework for plotting a course of further progress in treating children with ependymoma.

Optimal Local Control
As the author points out, optimal local control has been repeatedly shown to be the single most important prognostic factor in the treatment of this disease, and achieving this goal begins with maximal surgical resection. Failure to perform a gross total or near total resection substantially decreases the likelihood of long-term disease control.

To that end, one goal of the next Children’s Oncology Group trial is emphasis on increasing the number of patients whose tumors are gross totally or near totally resected. Second surgery is recommended for patients who undergo an initial subtotal resection. In an attempt to facilitate the second surgery, chemotherapy is administered between the first and second resections in the hopes of rendering the tumor more amenable to complete removal and, perhaps, reducing the likelihood of disease dissemination in the interim.

Following surgery, postoperative conformal radiation therapy is administered to all patients, with the exception of those with supratentorial, differentiated ependymomas whose tumors have been completely resected. Notably, and in contrast to other contemporary trials, children will receive irradiation if they are 1 year of age or older at the time of planned irradiation. Merchant argues, based on his own institutional experience, that in light of newer radiation techniques, irradiation in young children will likely result in fewer long-term neurologic sequelae than have been seen in the past, while improving long-term survival. To date, disease control in his series has been excellent, but the follow-up period is still relatively short.

Long-Term Neurologic Outcome
Aggressive attempts at local control appear to be a reasonable strategy to improve the treatment of patients with ependymoma. However, we must be careful to follow-up on the possible consequences of this approach. Although there is reason to hope that the use of more modern radiation technology and neurosurgical techniques will improve the long-term neurologic outcome of survivors, this is by no means assured.

Surgical procedures need to be performed by practitioners specifically skilled in pediatric neurosurgery. As Merchant points out, a variety of abnormalities (eg, neuroendocrine, cranial nerve dysfunction requiring G-tubes, or tracheostomies) manifest prior to the implementation of irradiation, suggesting a major impact of the primary tumor and the subsequent surgical intervention on outcome in these patients. The neurocognitive sequelae in patients receiving radiation therapy, particularly those under age 3, are still a major concern. Recent studies have shown that exposure to as low as 20 Gy can cause white matter changes evident on magnetic resonance imaging.[1]

It is also clear that the posterior fossa, a frequent location of ependymoma in the pediatric population, is vulnerable to injury. In addition to its traditional role in motor processes, a growing body of evidence shows that the cerebellum plays a critical role in many cognitive functions.[2] A cerebellar cognitive affective syndrome has been described in adults[3] and children with damage to the cerebellum from tumor growth and surgery. These patients exhibit long-term sequelae such as behavioral problems and deficits in language processing and spatial memory,[4,5] as well as the frequently described phenomenon of postsurgical mutism. These findings suggest that injury to the
cerebellum might be anticipated to have wide-ranging neurodevelopmental effects. It is imperative, therefore, that long-term neuropsychological outcome be monitored in patients, particularly the very young, who receive upfront irradiation following definitive surgery. This follow-up is particularly critical because if it is determined that the youngest children (eg, less than 2 years old) are disproportionately affected by irradiation, then perhaps an interval of delay might be recommended in future treatment trials. Study findings suggest that irradiation might be safely postponed for a period not to exceed 1 year.

Conclusions
Dr. Merchant has nicely summarized the chemotherapeutic literature related to ependymoma. The role of chemotherapy is evolving, with several agents demonstrating activity in this tumor, albeit with unclear evidence of the impact on event-free survival. Additional approaches are certainly needed, particularly for patients with distant spread of tumor, which is uniformly lethal. The author does not discuss the role of molecular diagnostics in the treatment of this tumor. There is a growing body of literature regarding the genetic abnormalities seen in these tumors. Ideally, the evolution of this knowledge might allow for more molecularly rational approaches to treatment, such as those that are being evaluated for other pediatric CNS tumors, most notably medulloblastoma.

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