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Unclear standard of care for pediatric high grade glioma patients

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To the Editor

Pediatric high grade gliomas (HGGs) are aggressive tumors with an unclear standard of care. However, there are many agreed upon treatment standards. The amount of surgical resection is one important clinical prognostic factor identified [1, 2]. The Children's Cancer Group (CCG) study945 revealed children who underwent a surgical resection of 90 % or greater had 5-year progression-free survival (PFS) of 35 + 7 % compared to 17 + 4 % in patients who did not [1]. Every attempt should be made at a complete surgical resection when safe to maximize survival. Also, for most children greater than 3 years old, focal radiotherapy has become standard. One of the main unanswered questions regarding the standard of care, however, surrounds the uncertain role of chemotherapy.

Children's Cancer Group study-943 randomized children to either weekly vincristine during radiation (XRT) (54 Gy) followed by maintenance prednisone, lomustine, and vincristine (pCV) or XRT alone [3]. Five-year event-free survival was 46 % in the chemo-radiotherapy group versus 18 % utilizing XRT alone [3]. The follow-up study, CCG945, randomized patients to receive either pCV or 8-in-1, and there was no statistical difference between them [1]. CCG943, however, had already established the addition of chemotherapy as the accepted treatment paradigm [3]. No one chemotherapeutic agent has been universally accepted as standard therapy.

The Children's Oncology Group (COG) ACNS0126 trial evaluated temozolomide as a radiosensitizer followed by maintenance temozolomide [2]. This was pursued after this strategy proved beneficial in adults as compared to XRT alone [4]. ACNS0126 was a single-arm phase II study utilizing CCG-945 as the historic control and showed no statistically significant improved outcomes as compared to CCG-945 [2]. ACNS0126 demonstrated similar survivals but with less toxicity compared to previous nitrosourea-based regimens [2]. This may be one reason some clinicians utilize temozolomide/XRT as a standard. Also, temozolomide is an oral agent adding to its ease of administration. Finally, similar to CCG-945, ACNS0126 showed DNA methyltransferase (MGMT) over-expression was adversely associated with outcome, suggesting that there may be a specific role for

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temozolomide in those patients with MGMT methylation and diminished MGMT expression [2].

The current COG ACNS0822 trial is a phase II/III that randomizes patients to one of three regimens during XRT (vorinostat, temozolomide or bevacizumab). All three arms are followed by maintenance chemotherapy with temozolomide and bevacizumab. The temozolomide/XRT arm is classified as the “control.” If either of the other two arms shows superiority, a phase III direct comparison will be pursued. It is unclear whether temozolomide/XRT is universally accepted as standard. Therefore, we conducted an internet-based survey to assess what physicians perceive as the standard of care in pediatric HGGs.

An eight question survey was e-mailed to 120 physicians identified through an International Symposium on Pediatric Neuro-Oncology database. It was completed by 62.5 % with 86.7 % practicing in the USA. Eighty-three percent were Pediatric Oncologists/Neuro-Oncologists. The remaining were Pediatric Neurosurgeons, Radiation-Oncologists or Neurologists. Most had greater than 10 years experience (65 %), worked at large academic or cancer centers (84 %) and their institution saw more than five newly diagnosed HGGs yearly (70 %).

Participants were asked, “after a maximal safe surgical resection, what do you consider to be the standard of care in treating children (greater than 3-years-old) with newly diagnosed intracranial high grade glioma?” They were given numerous options (A, B, C etc.), including one that allowed free text. The most common response was any available phase I/II clinical trial (26.7 %); second was treatment per ACNS0126 (25.3 %) and third was “it depends upon the patient,” (21.4 %). Participants were then asked the exact same question in the absence of an available clinical trial. The most common answer given was “it depended upon the patient,” (40 %); second was per ACNS0126 (30.7 %) and third was XRT with temozolomide and bevacizumab followed by maintenance temozolomide/bevacizumab (16 %).

Our response rate was good (62.5 %), and demographics indicated experienced physicians at large academic/cancer centers with regular exposure to pediatric HGGs. There was no clear consensus/majority in identifying a perceived standard of care. Even the most common responses were given by 40 % or less of participants. Our survey was not intended to define a standard of care or to make any statistical conclusions. One limitation was the manner in which the questions were phrased and asked (multiple choice versus open-ended) which may have influenced participant’s answers. However, the survey supports the sentiment that there is no clear consensus about the standard of care in pediatric HGGs among the Neuro-Oncology community represented by our survey. It also begs the question, “What is the best control arm for pediatric HGG clinical trials?” This uncertainty makes designing relevant phase II and III trials difficult as it is not clear what control to utilize for comparison.

Clinical trials are generally readily available for newly diagnosed pediatric HGGs. Treatment decisions may be more difficult when a patient for any reason (geographic, family choice, ineligibility etc.) cannot be enrolled on a trial. Historic data shows that maximal

surgical resection followed by radiation therapy is an appropriate backbone, however, what chemotherapeutic agent/s to utilize outside of a clinical trial is unclear [1, 2]. We believe it is the clinician's responsibility to educate the family and provide the best recommendation based upon the current literature and personal experiences which may include knowledge about MGMT status, patient's ability to tolerate oral medications, toxicity, and quality of life issues. Although we may not all agree upon one chemotherapeutic standard of care, this simply highlights that there is no one "right" answer. The Pediatric Neuro-Oncology community continues to strive towards improved survivals through a better understanding of tumor biology and prospective multi-institutional trials.

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