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COMMENTARY

Going past the data for temozolomide

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Abstract The benefit of six cycles of adjuvant temozolomide was documented in a randomized phase III (EORTC-NCIC CE.3) trial, and this therapy, following combined temozolomide and radiation, is the standard of care for patients with newly diagnosed glioblastoma. We comment on the differences in the length of adjuvant therapy in both clinical practice and national studies (e.g. RTOG 0825), usually doubling the length in the EORTC/NCIC study, and relate to historic adjuvant trials for solid tumors.

Keywords Glioblastoma · Temozolomide · Adjuvant therapy · Brain tumor

The benefit of six cycles of adjuvant temozolomide was documented in a randomized phase III (EORTC-NCIC CE.3) trial, and this therapy, following combined temozolomide and radiation, has become the standard of care for patients with newly diagnosed glioblastoma (GBM) [1]. Forty percent of patients in this phase III trial did not complete the planned six cycles of adjuvant temozolomide. The most common reason noted for patients receiving less than six cycles was disease progression. Following the acceptance of this therapy as the standard of care, it is apparently not uncommon to continue temozolomide for longer than six cycles—sometimes for an arbitrary number of cycles and sometimes until disease progression. The feasibility and tolerability of such long-term therapy have been documented in case series and single institution reports in both the recurrent and adjuvant settings [2–8] However, the benefit of long-term therapy cannot be documented in these uncontrolled experiences—patients have to live long enough or live long enough without progression in order to receive more cycles. The rationale for administering more cycles, especially in the adjuvant setting, is not clear. It does not appear to be extent of disease resection—gross complete resection versus subtotal resection. In a phase II study evaluating survival at 16 months following informed consent, bevacizumab was added to combined temozolomide and radiation, and bevacizumab and irinotecan were added to adjuvant temozolomide [4]. The initial study treatment plan specified six cycles of adjuvant therapy. The treatment plan was later changed to allow up to twelve cycles of adjuvant treatment, in response to patients' hesitancy or unwillingness to discontinue after six cycles. A landmark analysis of those who received six versus those who received more than six cycles demonstrated no difference in progression-free or overall survival between these two groups [4]. Two subsequent, ongoing phase III trials, the primary objectives of which are overall survival, with the addition of bevacizumab to standard adjuvant temozolomide, and with dose intensive versus standard dose adjuvant temozolomide, respectively, specify six cycles in all treatment arms, with the option to continue to a maximum of twelve cycles, provided there is evidence of continued

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benefit [9, 10]. This option for up to twelve cycles of maintenance temozolomide has also been widely applied to investigation of the Stupp regimen in lower-grade gliomas: Grade II: E3F05 [11] and Grade III: NCCTG-N0577 and RTOG-0834 [12, 13]. This arbitrary doubling of standard duration of treatment would be unacceptable for many adjuvant trials for solid tumors and likely challenges statistical interpretation.

The response to patients' desires to continue for more than six cycles is understandable. But we would argue that the benefit of more than six cycles has not been proven in a randomized controlled trial. Further, there is a small but documented risk of serious hematologic adverse events with temozolomide, including aplastic anemia [14, 15], myelodysplastic syndrome [14, 16] and treatment-related acute myeloid leukemia [14, 17]. The risk/benefit ratio could change with deviations from the well-studied regimen, and it may not be in the best interest of patients to continue beyond six cycles, in the absence of documented benefit.

It is also possible that less than six cycles of adjuvant therapy could prove to be as effective as the standard six cycles. In stage IIIB non-small-cell lung cancer, the results of a phase II study led to the frequent use of three cycles of consolidation docetaxel after completion of two cycles of cisplatin and etoposide with concurrent chest radiation therapy [18]. However, when the role of docetaxel consolidation was formally evaluated in a randomized phase III trial, no benefit was seen, and patients in the consolidation arm experienced greater toxicity [19].

In recent months, there has been considerable discussion and debate following reports of second primary malignancies in patients receiving long-term lenalidomide for multiple myeloma, leading to the premature termination of lenalidomide maintenance in the French IFM 2005–2002 trial [20]. It is true that time to progression and survival time in myeloma are generally longer than those in GBM, thus patients with GBM may not live long enough to develop treatment-related complications. But without a documented benefit, is it appropriate to expose patients to any increased risk?

In today's world of exciting research to discover molecular markers that predict response or toxicity, and manipulation of treatments to prevent or overcome resistance, a randomized comparison of standard versus prolonged or less than standard adjuvant temozolomide may seem somewhat boring. But studies designed to answer similar questions in breast cancer [21], testicular cancer [22] and colon cancer [23] have led to improved outcomes or improved tolerability, or both.

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