

A search for the “Goldilocks zone” with regard to the optimal duration of adjuvant temozolomide in patients with glioblastoma

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See the article by Blumenthal et al on pages 1119–1126.

In astronomy, the “Goldilocks zone” refers to an area of space in which a planet is just the right distance from its home star so that its surface is neither too hot nor too cold to support life. Similarly, there has long been a quest to determine the optimal duration of adjuvant chemotherapy in patients with cancer. Too little adjuvant therapy may result in early relapses and death, while too much could lead to excessive toxicities and costs as well as a reduction in quality of life and perhaps even early death. Randomized clinical trials designed specifically to address this question have been conducted in a wide variety of systemic cancers. These trials have included cancers with very favorable outcomes (germinomas and hematologic malignancies), cancers in which adjuvant therapy improves cure rates (breast, colon, and lung cancer), and cancers (breast, lung, ovarian, and colon) that are metastatic at presentation and where one could make a case for indefinite therapy.^{1–6} Data from these trials have consistently demonstrated that extending cytotoxic therapy beyond 4–6 months does not improve survival and have driven treatment guidelines to recommend the more abbreviated regimens, as is evident in the National Comprehensive Cancer Network Guidelines.⁷ The most likely reason for this is that after months of therapy, the surviving cancer cells are likely resistant to the administered chemotherapy.

The manuscript by Blumenthal and colleagues seeks to determine whether continuing adjuvant temozolomide for more than 6 months leads to better survival outcomes in patients with newly diagnosed glioblastoma.⁸ It presents an unplanned retrospective analysis of 624 patients from 4 large randomized clinical trials who had completed standard concurrent radiation and temozolomide followed by 6 cycles of adjuvant temozolomide without radiographic or clinical evidence of progressive disease or dose-limiting temozolomide toxicity. These studies allowed patients to discontinue adjuvant temozolomide after 6 months or to prolong the duration of therapy at the discretion of the individual patient and health care provider. Of note, patients in the United States were far more likely to receive prolonged adjuvant therapy than

their counterparts in Canada or Europe. This analysis provides a convincing argument that more than 6 cycles of adjuvant temozolomide does not improve survival in patients with newly diagnosed glioblastoma with either methylated or unmethylated O⁶-DNA methylguanine-methyltransferase (MGMT).

As noted by the authors of this manuscript, there are significant inherent methodologic limitations to this retrospective analysis. However, the dataset is large, the information was prospectively collected, and the results are similar to those found in definitive studies evaluating the duration of adjuvant chemotherapy in other cancers. As a result, a large, lengthy, and expensive prospective randomized trial formally addressing this question in patients with glioblastoma is unlikely to occur or to provide a different conclusion. Therefore, this retrospective study may remain the definitive manuscript on this subject.

Although the optimal duration of adjuvant temozolomide has been controversial, the results reported in this manuscript should not come as a major surprise to the neuro-oncology community given other available data in this disease. The European Organisation for Research and Treatment of Cancer (EORTC) trial 26981, which documented that concurrent radiation and temozolomide followed by 6 months of adjuvant temozolomide was superior to radiation alone, was designed without prior evidence that the 6 months of adjuvant temozolomide was beneficial.⁹ Furthermore, the median number of adjuvant temozolomide cycles administered to patients on the experimental arm of EORTC 26981 was 3 (range 0–7) rather than the 6 that were planned, and 22% of the 223 patients on this treatment arm actually received no adjuvant temozolomide. The Radiation Therapy Oncology Group (RTOG) trial 0525, which was specifically designed to determine whether intensive dose-dense adjuvant temozolomide would improve outcomes in this patient population, resulted in increased toxicity without any improvement in survival.¹⁰ Blumenthal’s data strongly suggest that 12 months of adjuvant temozolomide provides no added

benefit over the standard 6 months regardless of MGMT methylation status. The fact that a median of 3 cycles of adjuvant temozolomide were administered to patients on EORTC 26981 raises the question as to whether 3 months (or even less) of adjuvant chemotherapy might be similar to 6 months, as it is possible that the primary benefit of this treatment regimen results from the concurrent administration of daily temozolomide with radiation.

The data described above suggest that while we are slowly working to define the “Goldilocks zone” for the optimal duration of adjuvant temozolomide in patients with newly diagnosed glioblastoma, we still have important work to do. Prolonged adjuvant chemotherapy that does not improve survival is ill advised. Not only does this add costs, treatment burden, and toxicities without benefit to our patients, it limits our ability to explore other potentially more effective adjuvant therapies and may even reduce the effectiveness of novel immunologic approaches. Instead, our mission should be to define the critical components of this temozolomide regimen and to build upon these to ultimately improve patient outcomes.

Conflict of interest statement. There are no potential conflicts of interest for Drs Grossman or Kleinberg.

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