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Can high-dose fotemustine reverse MGMT resistance in glioblastoma multiforme?

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Abstract

Glioblastoma multiforme (GBM), the highest grade malignant glioma, is associated with a grim prognosis—median overall survival is in the range 12–15 months, despite optimum treatment. Surgery to the maximum possible extent, external beam radiotherapy, and systemic temozolomide chemotherapy are current standard treatments for newly diagnosed GBM, with intracerebral delivery of carmustine wafers (Gliadel). Unfortunately, the effectiveness of chemotherapy can be hampered by the DNA repair enzyme O6-methylguanine methyltransferase (MGMT), which confers resistance both to temozolomide and nitrosoureas, for example fotemustine and carmustine. MGMT activity can be measured by PCR and immunohistochemistry, with the former being the current validated technique. High-dose chemotherapy can deplete MGMT levels in GBM cells and has proved feasible in various trials on temozolomide, in both newly diagnosed and recurrent GBM. We here report the unique case of a GBM patient, with high MGMT expression by immunohistochemistry, who underwent an experimental, high-dose fotemustine schedule after surgery and radiotherapy. Although treatment caused two episodes of grade 3–4 thrombocytopenia, a complete response and survival of more than three years were achieved, with a 30% increase in dose intensity compared with the standard fotemustine schedule.

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