Dose-dense temozolomide regimens: antitumor activity, toxicity, and immunomodulatory effects.

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Abstract
Temozolomide is an oral alkylating agent with established antitumor activity in patients with primary brain tumors and melanoma. The originally approved temozolomide dosing regimen is 150 to 200 mg/m² per day (Days 1 to 5 every 28-day cycle [5 of 28 days]). However, extended dosing regimens (eg, 7 of 14 days, 21 of 28 days, 6 of 8 weeks, or continuously daily) allow for administration of a higher cumulative dose per cycle and have been shown to deplete O(6)-methylguanine-DNA methyltransferase, which may enhance cytotoxic activity. This article reviews efficacy and safety data from studies that investigated dose-dense temozolomide regimens in patients with recurrent glioma and advanced metastatic melanoma. The clinical benefits of these dose-dense regimens compared with the standard 5 of 28-day regimen have yet to be established. Although the toxicity profile of dose-dense temozolomide is generally similar to that of the standard 5 of 28-day regimen, it is associated with an increased incidence and severity of lymphocytopenia. The clinical management of temozolomide-associated lymphodepletion and the potential risks and benefits of extended dosing with temozolomide are discussed. Preclinical and clinical evidence suggests that temozolomide-associated lymphodepletion may enhance the host immune response to tumor-associated antigens and/or immunotherapy and may overcome tumor-mediated immunosuppression. Further studies exploring the clinical implications of lymphodepletion are warranted.


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