Extended exposure to alkylator chemotherapy: delayed appearance of myelodysplasia

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Abstract  Objective A case series of gliomas treated with alkylator-based chemotherapy who subsequently developed myelodysplastic syndrome (tMDS) or acute myelocytic leukemia (AML). Background Alkylator-based chemotherapy is recognized to be leukemogenic; however, it is infrequently described as a delayed consequence of anti-glioma treatment. Methods: Seven patients (4 men; 3 women) ages 34–69 years (median 44), with gliomas (3 Grade 2; 4 Grade 3) were treated with surgery, all but one with involved-field radiotherapy and all with alkylator-based chemotherapy (temozolomide; 6 patients, nitrosoureas; 5 patients, both agents; 5 patients). Results Exposure to alkylator-based chemotherapy ranged from 8 to 30 months (median 24). The diagnosis of tMDS was determined by bone marrow biopsy in 7 patients. Seven patients showed chromosomal abnormalities consistent with chemotherapy induced MDS. Three patients were diagnosed with AML as well (in two determined by bone marrow and one at autopsy). Interval from last chemotherapy exposure to diagnosis of tMDS/AML ranged from 3 to 31 months (median 24 months). Two patients were treated with bone marrow transplantation and 5 received supportive care only. Five patients have died, 2 as a consequence of recurrent brain tumor, 1 as a complication of transplantation, and 2 due to AML. Conclusions Although rare, induction of tMDS/AML following extended use of alkylator-based chemotherapy may become more relevant with the evolving practice to treat gliomas for protracted periods. Future work to determine at risk patients would be important.

Keywords  Alkylator chemotherapy · Gliomas · Treatment-related myelodysplastic syndrome

Introduction

The treatment of gliomas continues to evolve and an increasing prevalent style of practice is extended use of alkylator-based chemotherapy [1–9]. In the pre-temozolomide (TMZ) era, nitrosoureas (BCNU or carmustine; CCNU or lomustine) constituted the primary alkylator chemotherapy for the treatment of gliomas [10–14]. Due to inherent and cumulative toxicity (predominantly myelosuppression), nitrosoureas were administered for up to one year, however, in clinical trials, median exposure was 6–8 months. With the introduction of TMZ, a second generation methylating agent, chemotherapy treatment has been extended for 1–3 years due to the improved toxicity profile and lack of cumulative toxicity [1, 2, 4–9, 15, 16]. Notwithstanding the lack of evidence that prolonged TMZ schedules result in improved outcomes, protracted TMZ treatment is common place and becoming a de facto standard of care in the treatment of adult gliomas. Unclear with such extended alkylator-based chemotherapy treatments are potential treatment-induced delayed toxicities.