Cancer Therapy: Clinical

Phase I Trial of Single-Dose Temozolomide and Continuous Administration of O\textsuperscript{6}-Benzyguanine in Children with Brain Tumors: a Pediatric Brain Tumor Consortium Report

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Purpose: To estimate the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of escalating doses of temozolomide combined with O\textsuperscript{6}-benzyguanine in patients \( \geq 21 \) years with recurrent brain tumors.

Experimental Design: Treatment strata consisted of patients who had previously received no or local radiotherapy (Str1) and patients who had undergone craniospinal radiotherapy or myeloablative chemotherapy (Str2). One-hour i.v. administration of O\textsuperscript{6}-benzyguanine at 120 mg/m\textsuperscript{2} was followed by 48-h continuous infusion at 30 mg/m\textsuperscript{2}/day. Single-dose temozolomide at five dosage levels (267, 355, 472, 628, and 835 mg/m\textsuperscript{2}) was given at least 6 h after completion of O\textsuperscript{6}-benzyguanine bolus. Treatment was repeated after recovery from toxicities at least 4 weeks apart for a maximum of 12 courses. Dose escalation followed the modified continual reassessment method. Pharmacokinetic analyses of temozolomide and 5-triazeno imidazole carboxamide (MTIC) were done in 28 patients.

Results: A total of 44 and 26 eligible patients were enrolled on Str1 and Str2, respectively. Median age at study entry in each stratum was 8.6 and 11.3 years, respectively. Predominant diagnoses were high-grade/brainstem glioma in Str1 and medulloblastoma in Str2. Whereas the estimated MTDs of temozolomide for Str1 and Str2 were 562 and 407 mg/m\textsuperscript{2}, respectively, the doses recommended for phase II investigations are 472 and 355 mg/m\textsuperscript{2}, respectively. DLTs were predominantly neutropenia and thrombocytopenia. Three patients with gliomas experienced centrally confirmed partial responses to therapy. Four patients completed all planned therapy. Temozolomide and MTIC exposures were statistically associated with temozolomide dosage.

http://clincancerres.aacrjournals.org/cgi/content/abstract/13/22/6712
http://www.brainlife.org/
Conclusions: The current schedule of temozolomide and $O^6$-benzylguanine is safe and showed modest activity against recurrent brain tumors in children.