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# Tumor O(6)-methylguanine-DNA methyltransferase inactivation by oral lomeguatrib.

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**PURPOSE:** A major mechanism of resistance to chlorethylnitrosoureas and methylating agents involves the DNA repair protein O(6)-methylguanine-DNA methyltransferase (MGMT). We sought to determine the dose of oral 6-(4-bromo-2-thienyl) methoxy purin-2-amine (lomeguatrib), a pseudosubstrate inactivator of MGMT, required to render active protein undetectable 12 hours after dosing in prostate, primary central nervous system (CNS), and colorectal cancer patients. **EXPERIMENTAL DESIGN:** Lomeguatrib was administered orally as a single dose (20-160 mg) approximately 12 hours before tumor resection. Dose escalation was projected to continue until grade 2 toxicity or until complete inactivation of tumor MGMT was encountered. Total MGMT protein levels were quantified by ELISA, and active protein levels were quantified by biochemical assay. MGMT promoter methylation was determined in glioblastoma DNA by methylation-specific PCR. **RESULTS:** Thirty-seven patients were dosed with lomeguatrib, and 32 informative tumor samples were obtained. Mean total MGMT level varied between tumor types: 554 +/- 404 fmol/mg protein (+/-SD) for prostate cancer, 87.4 +/- 40.3 fmol/mg protein for CNS tumors, and 244 +/- 181 fmol/mg protein for colorectal cancer. MGMT promoter hypermethylation did not correlate with total protein expression. Consistent total MGMT inactivation required 120 mg of lomeguatrib in prostate and colorectal cancers. Complete consistent inactivation in CNS tumors was observed only at the highest dose of lomeguatrib (160 mg). **CONCLUSIONS:** Total MGMT inactivation can be achieved in prostate, primary CNS, and colorectal cancers with a single administration of 120 or 160 mg lomeguatrib. The dose needed did not correlate with mean total MGMT protein concentrations. One hundred twenty to 160 mg/d of lomeguatrib should be administered to achieve total MGMT inactivation in future studies.

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