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Promoter CpG island hypermethylation of the DNA repair enzyme MGMT predicts clinical response to dacarbazine in a phase II study for metastatic colorectal cancer.

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Abstract

PURPOSE: O(6)-methylguanine-DNA-methyltransferase (MGMT) is a DNA repair protein removing mutagenic and cytotoxic adducts from O(6)-guanine in DNA. Approximately 40% of **colorectal** cancers (CRC) display MGMT deficiency due to the promoter hypermethylation leading to silencing of the gene. Alkylating agents, such as **dacarbazine**, exert their antitumor activity by DNA methylation at the O(6)-guanine site, inducing base pair mismatch; therefore, activity of **dacarbazine** could be enhanced in CRCs lacking MGMT. We conducted a phase II study with **dacarbazine** in CRCs who had failed standard therapies (oxaliplatin, irinotecan, fluoropyrimidines, and cetuximab or panitumumab if KRAS wild-type).

EXPERIMENTAL DESIGN: All patients had tumor tissue assessed for MGMT as promoter hypermethylation in double-blind for treatment outcome. Patients received **dacarbazine** 250 mg/m(2) intravenously every day for four consecutive days, every 21 days, until progressive disease or intolerable toxicity. We used a Simon two-stage design to determine whether the overall response rate would be 10% or more. **Secondary** endpoints included association of response, progression-free survival, and disease control rate with MGMT status.

RESULTS: Sixty-eight patients were enrolled from May 2011 to March 2012. Patients received a median of three cycles of **dacarbazine** (range 1-12). Grades 3 and 4 toxicities included: fatigue (41%), nausea/vomiting (29%), constipation (25%), platelet count decrease (19%), and anemia (18%). Overall, two patients (3%) achieved partial response and eight patients (12%) had stable disease. Disease control rate (partial response + stable disease) was significantly associated with MGMT promoter hypermethylation in the corresponding tumors.

CONCLUSION: Objective clinical responses to **dacarbazine** in patients with **metastatic** CRC are confined to those tumors harboring epigenetic inactivation of the DNA repair enzyme MGMT.

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