Phase I/II dose-escalation study of pemetrexed plus irinotecan in patients with advanced colorectal cancer.

BACKGROUND: Pemetrexed and irinotecan have demonstrated antitumor activity as single agents in lung, pancreatic, breast, and colorectal cancer (CRC). The distinct mechanisms of action and patterns of resistance displayed by pemetrexed and irinotecan make them attractive agents for combination therapy.

PATIENTS AND METHODS: This phase I/II, nonrandomized, open-labeled, single-arm study was composed of 3 segments. The initial phase II portion of the study enrolled 23 patients with advanced CRC who had received 1 previous dose of 5-fluorouracil (5-FU)-based chemotherapy for advanced disease. Because of poorer than anticipated efficacy, a phase I dose-escalation study using vitamin supplementation (n = 12) was added to the original protocol. The phase II dose-escalation portion of the study enrolled 36 patients (64% with previous oxaliplatin-based therapy) who received pemetrexed 500 mg/m2 followed by irinotecan 300 mg/m2 on day 1, every 21 days. RESULTS: For the 35 evaluable patients in the phase II dose-escalation study, the objective response rate was 11.4% (95% confidence interval, 3.2%-26.7%); there was 1 patient with a complete response, 3 with partial responses, and 17 with stable disease. Three of four responders had received previous oxaliplatin-based combination therapy. Grade 3/4 hematologic toxicities
included leukopenia (5.6%), anemia (2.8%), and thrombocytopenia (2.8%). Grade 3/4 nonhematologic toxicities included diarrhea (11.1%), increased aminotransferase levels (8.3%), nausea (8.3%), febrile neutropenia (5.6%), vomiting (5.6%), and reduced creatinine clearance (2.8%).

CONCLUSION: Pemetrexed plus irinotecan appears to be at least as active as FOLFIRI (leucovorin/5-FU/irinotecan) for second-line therapy of CRC following 5-FU-based combination chemotherapy. Further studies are warranted.