

Capecitabine Plus Oxaliplatin as First-Line Treatment in Advanced Colorectal Cancer

A Randomized Multicenter Phase II Trial of Two Different Schedules

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Purpose

Capecitabine and oxaliplatin, two new agents with potential synergistic activity, have demonstrated promising antitumor efficacy in advanced colorectal cancer (ACC). Preclinical and clinical evidence indicating that dose intensification of the oral fluorouracil prodrug might result in improved therapeutic results led us to the present randomized multicenter phase II study.

Patients and Methods

Eighty-nine patients with bidimensionally measurable ACC previously untreated for metastatic disease were randomly allocated to receive oxaliplatin 130 mg/m² day 1 plus capecitabine 2,000 mg/m²/d days 1 to 14 every 3 weeks (arm A) or to receive oxaliplatin 85 mg/m² days 1 and 14

combined with capecitabine 3,500 mg/m² days 1 to 7 and 14 to 21 every 4 weeks (arm B). In both treatment arms, chemotherapy was continued for a total of 6 months unless there was prior evidence of progression of disease.

Results

Patients allocated to the high-dose capecitabine combination arm B had a higher radiologically confirmed response rate (54.5% v 42.2%) and a significantly longer median progression-free survival time than those allocated to control arm A (10.5 v 6.0 months; $P = .0013$). Median overall survival times cannot be calculated for either treatment arm at this point. Despite a 34% higher dose intensity of capecitabine in arm B, there was no difference in hematologic toxicity between treatment arms

(neutropenia/ thrombocytopenia: 60%/43% in arm B v 56%/33% in arm A). Similarly, the incidence rate and degree of nonhematologic adverse events were comparable: The most commonly encountered symptoms (all grades, arm A and arm B) included nausea/emesis (A: 58%; B: 62%), diarrhea (A: 44%; B: 31%), peripheral sensory neuropathy (A: 80%; B: 83%), and fatigue (A: 40%; B: 50%).

Conclusion

Results of this study indicate that both combination regimens are feasible, tolerable, and clinically active. The dose-intensified bimonthly capecitabine arm, however, seems to be more effective in increasing both response rate and progression-free survival time. *J Clin Oncol* 21:1307-1312. ©2003 by American Society of Clinical Oncology. **OA**

Oxaliplatin, Capecitabine, and Bevacizumab (Avastin™)

In the Treatment of Metastatic Colorectal Cancer

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Background

Bevacizumab (BV, Avastin™) is a recombinant, humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF). Phase III results have demonstrated a survival advantage for the addition of BV to bolus IFL (irinotecan, 5-fluorouracil, and leucovorin) as first-line therapy for metastatic colorectal cancer (CRC). Recent data, however, suggest that the FOLFOX regimen (biweekly administration of oxaliplatin, leucovorin, and bolus plus continuous infusion of 5-fluorouracil) is

superior to bolus IFL with improved response rate, time to progression, and overall survival. The FOLFOX regimen requires the inconvenience of an ambulatory infusion pump, which limits its use in many patients. We sought to investigate the combination of capecitabine, oxaliplatin, and BV (XELOXA) as a more convenient and active regimen.

Methods

Patients with previously untreated metastatic CRC received oxaliplatin 85 mg/m² day 1, capecitabine 1000 mg/m² bid days 1-5 and 8-12, and BV 10 mg/kg day 1.

Cycles were repeated every 2 weeks. Standard dose reductions for toxicity were permitted.

Results

Twenty-six patients received XELOXA therapy: 14 men, 12 women, median age 55 (range 24-76), and median ECOG performance status 0 (range 0-1). Median follow-up is 5.1 months (range 0.5-11.4 months). Twenty-six are fully evaluable for toxicity and 23 for efficacy. Therapy was generally well tolerated. Diarrhea was the

Continued on Page 32