Capecitabine/Irinotecan Combination Regimens in Colorectal Cancer

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Capecitabine (Xeloda) and irinotecan (CPT-11, Camptosar) both have demonstrated single-agent activity in patients with colorectal cancer. Oral fluoropyrimidines have the potential to simplify and supplant fluorouracil (5-FU)-based combination chemotherapy for colorectal cancer. Capecitabine (Xeloda) is absorbed intact through the gastrointestinal tract and is activated by a three-step enzymatic cascade. Capecitabine was designed rationally to generate 5-FU preferentially in tumor tissue through exploitation of the higher activity level of thymidine phosphorylase (TP) in tumors rather than in normal tissue. Pooled results of two identical, randomized phase III studies demonstrated that the use of single-agent oral capecitabine provided advantages over administration of intravenous (IV) 5-FU plus leucovorin (Mayo Clinic regimen). When used as first-line therapy for metastatic colorectal cancer (n = 1,207), capecitabine achieved a significantly superior tumor response rate (26% vs 17%; \( P < .0002 \)), equivalent time to disease progression (\( P = .9535 \); hazard ratio = .997; median: 4.6 vs 4.7 months), and equivalent overall survival (\( P = .48 \); hazard ratio = .96; median: 12.9 vs 12.8 months) when compared with results using 5-FU plus leucovorin (Mayo Clinic regimen). Furthermore, the trials demonstrated an improved safety profile of capecitabine, with significantly (\( P < .001 \)) lower incidences of diarrhea, stomatitis, nausea, and grade 3/4 neutropenia than seen with use of 5-FU plus leucovorin. The only side effect that occurred more frequently with capecitabine was the cutaneous condition known as hand-foot syndrome.

Irinotecan (CPT-11, Camptosar), a semisynthetic camptothecin derivative that inhibits topoisomerase I, also has good single-agent activity in colorectal cancer. Two independent phase III studies have shown that irinotecan plus 5-FU plus leucovorin (bolus or infusional regimen) achieves significantly improved overall survival when compared with use of 5-FU plus leucovorin alone in patients with metastatic colorectal cancer.[3,4] Preclinical studies demonstrated that sequential administration of low-dose irinotecan plus capecitabine was highly curative in in vivo xenograft models of human colorectal cancer.[5] These two drugs have distinct mechanisms of action, only partially overlapping toxicities, and single-agent activities in colorectal cancer. It therefore seems logical to identify a capecitabine/irinotecan combination regimen for the treatment of colorectal cancer. In this regard, several phase I/II clinical trials have been initiated that are exploring various treatment schedules (Table 1).

**Trials Exploring First-Line Irinotecan/Capecitabine in Colorectal Cancer**

Results of three phase I/II clinical trials aimed at identifying the optimal regimen of irinotecan plus capecitabine as first-line therapy for colorectal cancer were presented at the European Conference on Clinical Oncology (ECCO 11) held in October 2001.[6-8] In the study conducted in the United Kingdom and the Netherlands, 27 patients with previously untreated, measurable metastatic colorectal cancer received capecitabine (750-1,250 mg/m² twice daily on days 1-14 of a 21-day cycle) in combination with irinotecan (200-350 mg/m² on day 1 of a 21-day cycle) given every 3 weeks.[6] The maximum tolerated dose was 1,250 mg/m² of capecitabine twice daily plus 300 mg/m² of irinotecan. However, the most feasible regimen was identified based on the predominant grade 3/4 side effects that occurred during the first three treatment cycles, which were diarrhea and neutropenia. Thus, the recommended regimen for further clinical development was 1,000 mg/m² of capecitabine twice daily plus 250 mg/m² of irinotecan. The preliminary efficacy data are very promising, with an overall response rate of 52%. Tumor responses have been observed at all dose levels. An extended phase II and pharmacokinetic study is underway. Early data from another phase I pharmacokinetic study also demonstrated some clinical activity with capecitabine plus irinotecan given every 3 weeks in patients with a range of gastrointestinal tumors.
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Final results were presented on the extended phase I study performed by the German group investigating capecitabine with weekly irinotecan in patients with untreated metastatic colorectal cancer.[8] Dose-limiting toxicities were diarrhea and neutropenia. The recommended regimen is 1,000 mg/m² of capecitabine (twice daily, days 1-14 and 22-35) plus 70 mg/m² of irinotecan (weekly × 6), repeated at day 50. The regimen demonstrated impressive activity, with an overall response rate of 41%, including tumor responses in 5 of 13 evaluable patients treated at the recommended dose (Table 2).

Conclusions

It appears that the capecitabine/irinotecan regimen is an active combination in patients with colorectal cancer. This treatment has been fairly well tolerated and has been limited by neutropenia and diarrhea. Consistent response rates of 40% to 60% have been achieved. Randomized trials using this combination are planned in patients with advanced disease and in the adjuvant setting.

References:


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