Irinotecan, Epirubicin, and Capecitabine in Metastatic Adenocarcinomas: Preliminary Results of a Phase I Study

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The combination of irinotecan (Camptosar), epirubicin, and capecitabine (Xeloda) has shown an acceptable toxicity profile. In this open-label phase I study, irinotecan was administered IV at a fixed dose of 250 mg/m² on day 1 in combination with capecitabine at a fixed dose of 1,500 mg/m² for days 2 to 7 and epirubicin starting at a dose of 40 mg/m² and escalating by 10 mg/m² in cohorts of three patients for those with metastatic adenocarcinomas. With the addition of granulocyte colony-stimulating factor (G-CSF [Neupogen]) to the regimen, patients received epirubicin at clinically relevant doses after dose-escalation. Results of the topoisomerase activity will be reported with the final results of this phase I study. The dose-limiting toxicity has not yet been reached. This combination regimen in patients with upper gastrointestinal malignancies and breast cancer will be investigated as part of phase II studies, once the dose-limiting toxicity is determined. The appropriate sequencing of the regimen to maximize clinical efficacy will also be determined.

Topoisomerase enzymes I and II play a critical role in preserving DNA topology by producing transient single- and double-strand DNA breaks that relieve supercoiling during replication, recombination, chromosomal decondensation, and RNA transcription.[1] The DNA strand breaks are followed by strand passage and reannealing with relief of DNA torsional strain.[2] There is evidence that topoisomerases complement each other. Thus, when topoisomerase I inhibition occurs with agents such as SN-38 in cell lines, the cells compensate by increasing expression of topoisomerase II and vice versa.[3] This is believed to constitute an important mechanism of resistance to topoisomerase I inhibitors in malignant cells. In cell lines, the cytotoxic effect of topoisomerase I and II is schedule-dependent.[4] For example, topoisomerase I and II have shown antagonism when administered simultaneously,[5] but an additive synergistic effect when administered sequentially.[3] This antagonism might be related to topoisomerase I inhibition of DNA synthesis, which is required for the cytotoxic effect of topoisomerase II-induced cleavable complexes.[3,5] The additive/synergistic effect of sequential topoisomerase I and II inhibitor administration has been examined in vivo in several phase I and II human trials that explored their sequential administration. These trials yielded mixed results.[6,7] In the present study epirubicin was sequenced with irinotecan (Camptosar) and capecitabine (Xeloda), with the primary goal of obtaining the appropriate dose for phase II studies. Methods and Materials This trial is an ongoing open-label phase I study of irinotecan administered intravenously at a fixed dose of 250 mg/m² on day 1 in combination with capecitabine at a fixed dose of 1,500 mg/m² for days 2 to 7 and epirubicin starting at a dose of 40 mg/m² and escalating by 10 mg/m² in cohorts of three patients for those with metastatic adenocarcinomas. The objectives of the study were to determine the maximum tolerated dose and recommended dose for phase II studies of the combination of irinotecan, capecitabine, and epirubicin. In addition, we wanted to characterize the general toxicities of concurrent irinotecan, capecitabine, and epirubicin, determine the pharmacokinetic profile and dose-limiting toxicity (DLT) of these drugs, and finally determine the levels of topoisomerase activity in peripheral mononuclear blood before and at several points during treatment. Patients continued to be treated for a maximum of 6 months, or until documentation of disease progression, death, unmanageable drug-related toxicity, or withdrawal of consent. Responding patients would continue on therapy off study at the investigators’ discretion. Plasma sampling was obtained to perform a pharmacokinetic profile for irinotecan, epirubicin, and the metabolites of both agents. Peripheral mononuclear cells were obtained to determine the levels of topoisomerase I and II mRNA. Study Requirements Patients were enrolled in the study if they were 18 years of age or older, had a clinical diagnosis of metastatic adenocarcinoma that was minimally treated with chemotherapy, had evaluable or measurable disease as defined in the RECIST (Response Evaluation Criteria in Solid Tumors) criteria, and had no symptomatic brain metastasis. Prior chemotherapy was allowed, except for doxorubicin at a dose greater than 300 mg/m². Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and the ability to take oral medications. They could have no
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Signs or symptoms of gastrointestinal obstruction. Adequate organ function was required as defined by an absolute neutrophil count (ANC) of ≥ 1.5 * 10⁹/L, platelets ≥ 100 * 10⁹/L, hemoglobin ≥ 9 g/dL, serum creatinine ≤ 1 mg/dL or calculated creatinine clearance ≥ 50 mL/min, total bilirubin < 1.5 * upper limit of normal, and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) < 3 * upper limit of normal (but < 5* upper limit of normal if liver metastases are present). Eligible patients were registered in the study after they signed an Internal Review Board approved informed consent form. They were then assigned a study number and a treatment dose level. Baseline evaluations included a history and physical exam, laboratory evaluations (including complete blood count, creatinine, AST, ALT, total bilirubin, blood urea nitrogen, glucose, uric acid, inorganic phosphorous, calcium, total protein, albumin, lactate dehydrogenase, alkaline phosphatase, urinalysis, tumor markers, and serum pregnancy test if applicable), electrocardiogram, multiple gated acquisition (MUGA) scan, chest x-ray (PA and lateral), and computed tomography of the chest, abdomen, and pelvis. Patients were assessed weekly during the first two cycles of chemotherapy with an interim history and physical exam, concomitant medication recording, toxicity assessment/ adverse event recording, and laboratory evaluation (complete blood count, serum chemistry, urinalysis). MUGA scan was performed every four cycles or sooner if clinically indicated. Tumor assessment was performed at baseline and after every two cycles of chemotherapy, or sooner if clinical progression was suspected. Results A total of 13 patients have been entered in the study. Tumor types (all adenocarcinomas) included esophageal (1), gastric (1), biliary tree (5), pancreas (2), unknown primary site (3), and liver (1). Seven patients had received prior chemotherapy with evidence of disease progression. Because the first cohort of patients developed grade 4 nonfebrile neutropenia, the study was amended. The doses of irinotecan, epirubicin, and capecitabine were modified to 180 mg/m² on day 1, 30 mg/m² on day 2, and 1.5 g/m² on days 2 to 7, respectively. Two of three patients in the second cohort developed grade 4 marrow toxicity. The first of these had received prior radiation to the esophagus and brain and the second to the biliary area. The protocol was modified a second time to exclude patients with prior radiation therapy or those who had received more than three chemotherapy regimens. In addition, prophylactic granulocyte colony-stimulating factor (G-CSF [Neupogen]) for 3 days was routinely included in the regimen. One patient in the third cohort developed grade 4 neutropenia. This patient had started the G-CSF during his chemotherapy. He was given a second cycle and did not develop further grade 4 neutropenia. To date, we have escalated the dose of epirubicin to 50 mg/m² on day 2 along with fixed-dose irinotecan and capecitabine without reaching DLT. Antitumor Activity Ten of the 13 patients received two or more cycles of chemotherapy so that antitumor activity can be assessed. Two patients, both with metastatic gallbladder adenocarcinoma, had a partial response to treatment that lasted 18 and 33 weeks, respectively. The best response in the remaining patients was disease stability for 8 to 54 weeks. Topoisomerase Profiles Mononuclear cells were separated from plasma, and levels of mRNA topoisomerase I, II-alpha and II-beta were assessed by real-time polymerase chain reaction. Preliminary results reveal a topoisomerase pattern of activity consistent with what has been reported in the literature. Pharmacokinetic Analysis Serum levels of irinotecan were obtained at baseline and at 1, 2, 6, 24, 48, 72, and 168 hours after the start of chemotherapy. Serum levels of epirubicin were obtained at baseline and at 0.5, 1, 2, 4, 6, 24, 48, and 144 hours after onset. As expected, the levels of both chemotherapy agents declined through time. No interaction has been detected between irinotecan and epirubicin in the patients studied thus far. Discussion Preclinical models suggest that upregulation of topoisomerase II is an important mechanism of resistance upon exposure to topoisomerase I inhibitors. [8] In addition, both preclinical and clinical models have demonstrated a favorable antitumor profile with the combination of irinotecan and fluorouracil (5-FU). [9-12] In the present study, we began with the irinotecan/5-FU combination and added epirubicin as the topoisomerase II inhibitor. Preliminary results of this phase I study have demonstrated the tolerability and efficacy of the regimen in patients with metastatic adenocarcinomas with no evidence of pharmacokinetic interaction. Several investigators have studied sequential topoisomerase I and II inhibitors in clinical trials. In a phase I trial, Hammond treated 50 patients with refractory malignancies using dose-escalating levels of topotecan (Hyacamitn) as a continuous infusion for 72 hours (topoisomerase I inhibitor) followed by etoposide (topoisomerase II inhibitor) on days 7 to 9. [6] In addition, levels of topoisomerase I and II were measured in tumors before and after treatment in some patients. The DLT was hematologic, with patients experiencing severe noncumulative neutropenia and thrombocytopenia. Other than nausea/vomiting, which was dose-limiting in two instances, nonhematologic toxicity was mild to moderate. Contrary to findings in preclinical studies, [3,5] the biopsies of tumors in seven patients...
performed at defined time periods did not show a compensatory increase of topoisomerase II immediately and 3 days after topotecan administration. In a phase I dose-escalating study of 22 patients with solid malignancies, Seiden reported the sequential combination of doxorubicin followed 48 hours later by 3 days of a 30-minute infusion of topotecan.[13] At 48 hours, the levels of topoisomerase II mRNA decreased significantly with concomitant elevation of topoisomerase I mRNA levels. The DLT was hematologic (neutropenia and thrombocytopenia), with 7 of 15 evaluable patients showing a partial response to therapy. Nakamura performed a phase II study with sequential administration of irinotecan on days 1, 8, and 15 and etoposide on days 2 to 4 in 51 patients with untreated, extensive-stage small cell lung cancer.[7] The overall response rate was 66%, with a 10% complete response. Toxicities included neutropenia (72%), leukopenia (28%), anemia (4%), thrombocytopenia (4%), pneumonitis (2%), and diarrhea (2%). Saotome reported a phase II trial that used sequential treatment with irinotecan (25 mg/m² on days 1 and 2) and doxorubicin (40 mg/m² on day 3) in patients with refractory or relapsed non-Hodgkin’s lymphoma.[14] Grade 3 and 4 toxicities included leukopenia (76%), anemia (60%), and thrombocytopenia (40%). Complete response was achieved in 36% of patients, with an additional 8% achieving partial response.

**Summary** The combination of irinotecan, epirubicin, and capecitabine has shown an acceptable toxicity profile. With the addition of G-CSF to the regimen, we were able to dose-escalate epirubicin to clinically relevant doses. Once the DLT is reached in this phase I trial, we plan to continue studying this potentially useful combination regimen in patients with upper gastrointestinal malignancies and breast cancer as part of phase II studies. In addition, we will continue to optimize the appropriate sequencing of the regimen to maximize clinical efficacy. Results of the topoisomerase activity will be reported with the final results of this phase I study.

**Disclosures:**
Dr. Becerra is a member of the speaker’s bureau for INCE, which receives an unrestricted educational grant from Roche.

**References:**

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