Oral Fluoropyrimidine-Based Combination Therapy in Gastrointestinal Cancer

By Udo Vanhoefer, MD [2] and Hans Jochen Wilke, MD [3]

Significant emphasis has been placed recently on designing more effective fluorouracil (5-FU)-based combination protocols for gastrointestinal cancer. Promising results were seen with 5-FU/leucovorin in combination with

**Introduction**

For the past 3 decades, fluorouracil (5-FU)-based chemotherapy has been the mainstay of therapy for advanced gastrointestinal cancer. When given alone to colorectal cancer patients as a weekly intravenous bolus or for 5 consecutive days every 4 to 5 weeks, 5-FU produced response rates ranging from 11% to 17% and was associated with a median survival of approximately 1 year.[1-3] Although the increased efficacy of 5-FU (in terms of higher response rates) via biomodulation with leucovorin has been well established, a meta-analysis of clinical studies failed to demonstrate a clear survival benefit.[4,5]

Moreover, evidence has accumulated that prolonged infusion of 5-FU may improve its antitumor effect when compared with 5-FU bolus regimens.[6,7] However, no significant differences in overall survival time were found when bolus 5-FU, administered according to the North Central Cancer Treatment Group (NCCTG)-regimen, was given with one of several 5-FU regimens including infusional 5-FU.[8] These data correspond with the recent results of a randomized trial conducted by the European Organization for Research and Treatment of Cancer (EORTC-GICCTG) that compared low-dose leucovorin-modulated bolus 5-FU with a weekly schedule of high-dose infusional 5-FU/leucovorin in patients with metastatic colorectal cancer.[9] Thus, significant emphasis has been placed on designing more effective 5-FU-based combination protocols. Promising results were achieved recently with combinations of 5-FU/leucovorin and either irinotecan (CPT-11, Camptosar) or oxaliplatin (Eloxatin). These combinations proved superior to conventional 5-FU/leucovorin schedules, especially in colorectal cancer.[10-16]

**5-FU-Based Combination Protocols**

Irinotecan and Fluorouracil

For the combination of irinotecan and 5-FU, three schedules were carried forward in two large randomized phase III trials: (a) irinotecan at 125 mg/m², leucovorin at 20 mg/m², and 5-FU at 500 mg/m on a weekly × 4 schedule (Saltz regimen).[17] (b) irinotecan at 80 mg/m² in combination with leucovorin at 500 mg/m (2-hour infusion), and 5-FU at 2.6 g/m (24-hour infusion) on a weekly × 6 schedule (AIO schedule).[18] or (c) the biweekly schedule of irinotecan at 180 to 200 mg/m in combination with leucovorin-modulated infusional 5-FU administered according to the de Gramont schedule (leucovorin at 200 mg/m (2-hour infusion), followed by 400 mg/m of 5-FU bolus, and then 600 mg/m of 5-FU by continuous infusion over 22 hours on days 1 and 2 every 14 days).[19]

**Saltz Regimen**

In the first trial, the weekly × 4 regimen of irinotecan and bolus 5-FU/leucovorin (Saltz regimen) was compared with conventional low-dose leucovorin/5-FU (Mayo-Clinic protocol).[12] In an intent-to-treat analysis, treatment with the combination of irinotecan and 5-FU/leucovorin resulted in a significantly higher remission rate (P < .001), significantly longer progression-free survival time (P = .004), and significantly longer median survival (P = .04) when compared to leucovorin/5-FU alone. National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3 and 4 diarrhea was observed
in 23% of patients in the combination arm and 13% of patients treated with leucovorin/5-FU alone. On the other hand, there was a significantly higher incidence of grade 4 neutropenia (42%) in patients receiving 5-FU/leucovorin alone compared to those receiving irinotecan/5-FU (24%). Furthermore, it could be demonstrated that treatment with the combination of irinotecan/leucovorin/5-FU had no detrimental effect on overall quality of life and global health status compared to 5-FU/leucovorin alone.

**AIO Schedule or de Gramont Regimen**

The second randomized trial used two forms of 5-FU infusion, either the weekly × 6 schedule of high-dose leucovorin followed by a 24-hour infusion of 2.3 g/m² of 5-FU (AIO schedule) or the biweekly de Gramont regimen.[13] Participating centers had to choose one of the two schedules. In the experimental arm, irinotecan was added to the same 5-FU infusion protocol (80 mg/m² per week for the AIO schedule or 180 mg/m² every 2 weeks for the de Gramont schedule).

A response rate of 41% was achieved with the combination compared to 23% with leucovorin/5-FU alone (P < .001). Moreover, the median time to disease progression (P < .001) and median survival (P < .028) showed a significant advantage for the combination arm with irinotecan vs the control arm. The incidence of grade 3 and 4 neutropenia was higher in the irinotecan/5-FU arm, but did not translate into a significantly higher incidence of either neutropenic fever or infection. There was also slightly more grade 3 and 4 diarrhea (24% of patients) in the combination arm compared to leucovorin/5-FU alone (11% of patients).

**Oxaliplatin Combinations**

Oxaliplatin, a trans-1-diaminocyclohexan-oxalato [DACH]-platinum analog, has also shown efficacy in colorectal cancer.[10] Oxaliplatin in combination with leucovorin/5-FU given either chronomodulated or in accordance with the de Gramont schedule has been compared to the same leucovorin/5-FU regimen alone in two randomized multicenter phase III trials.[15,16] The combination of oxaliplatin with leucovorin/5-FU significantly improved overall response rate and median time to disease progression in both trials; however, median survival was not significantly prolonged in these studies.

**UFT Combinations**

UFT is an orally administered fixed combination of tegafur and uracil in a 1:4 molar ratio. Tegafur (1-[2-tetrahydrofuryl]-5-fluorouracil) is absorbed intact via the gastrointestinal tract and is then converted to 5-FU by hepatic microsomal cytochrome P450 enzymes, as well as through soluble enzyme hydroylisis. Uracil is a competitive inhibitor of dihydropyrimidine dehydrogenase (DPD). Preclinical studies demonstrated that the addition of uracil to tegafur in these concentrations significantly increased the tumor-to-serum and tumor-to-normal tissue ratios of 5-FU.[3,20,21] Co-administration of leucovorin to UFT further enhanced the activity of UFT as shown in preclinical and clinical studies.[21,22]

The results of clinical trials demonstrate that UFT, with or without leucovorin, can be safely administered over weeks and even months. The compound is associated with a favorable toxicity profile compared to bolus 5-FU/leucovorin, with diarrhea being the main toxicity.[23,24]

UFT, with or without leucovorin, induces overall response rates in gastrointestinal tumors comparable to those achieved with bolus 5-FU/leucovorin.[20,23-29] These experiences prompted further investigation of UFT as part of combination chemotherapies in esophageal, gastric, pancreatico-biliary tract, and colorectal cancers.

**Capecitabine**

Capecitabine (Xeloda) (N4-pentyloxycarbonyl-5’-deoxy-5-fluorocytidine) is a novel fluoropyrimidine carbamate that is converted to fluorouracil by three enzymes located in the liver and tumor tissue.[30,31] The final step is the conversion of 5’-deoxy-5-fluorouridine (5’S-dFUr) to 5-FU by thymidine phosphorylase preferentially in tumor tissue.
The high thymidine phosphorylase expression in tumor cells selectively enhances 5-FU concentrations, and may result in higher antitumor activity and decreased drug levels in nontumor tissue, with a consequent reduction in systemic toxicity.[32] Preclinical studies on human tumor xenografts suggest that the antitumor efficacy of capecitabine is superior to that of UFT or 5-FU. In these in vivo models, capecitabine was less toxic to the intestinal tract, indicating a higher therapeutic potential.[31] Capecitabine is associated with significant antitumor efficacy in various malignancies, including colorectal cancer and breast cancer.[33-36]

In two large randomized trials in metastatic colorectal cancer, capecitabine was significantly superior to bolus 5-FU/leucovorin (Mayo Clinic protocol) in terms of response rate (25.7% vs 16.7% confirmed responses; \( P < .0002 \) [integrated results of 1,207 patients]).[37] However, in both trials no significant differences in time to disease progression and overall survival were observed between capecitabine and bolus 5-FU/leucovorin (time to progression: 4.6 months vs 4.7 months, respectively, and overall survival time 12.9 months for both).

Although hand-foot-syndrome occurred more often in patients receiving capecitabine than in those receiving bolus 5-FU/leucovorin, it resulted in only two hospitalizations. Furthermore, the treatment-related hospitalization rate was significantly reduced in patients treated with capecitabine. The results of the integrated analysis of both trials demonstrate that capecitabine offers a convenient alternative to bolus 5-FU/leucovorin with a superior safety profile and equivalent antitumor efficacy.

Considering the antitumor activity and safety profile of the oral fluoropyrimidine prodrugs (UFT, capecitabine), different combinations with other cytotoxic agents active in gastrointestinal cancer, such as mitomycin C (Mutamycin), irinotecan, and the platinum analogs are currently under clinical investigation in gastrointestinal cancer.

**UFT/Leucovorin Combination Therapy**

The combination of irinotecan and UFT, with or without leucovorin, is under investigation in different schedules as first- and second-line therapy for advanced colorectal cancer.[38,39] Escuder and coworkers conducted a phase I/II trial of a weekly \( \times 3 \) schedule of irinotecan at a dose of 80 mg/m\(^2\) to 120 mg/m\(^2\) and UFT at a fixed dose of 250 mg/m\(^2\), days 1 to 21, repeated every 4 weeks.[38] Of 18 patients entered into the trial, one had received prior chemotherapy for advanced disease. The recommended doses for further phase II studies were irinotecan at 110 mg/m\(^2\) and UFT at 250 mg/m\(^2\). Dose-limiting toxicity consisted of diarrhea. No objective responses were observed but 12 of 18 patients (66%) had stable disease and the median time to disease progression was 3.5 months.

Hill and coworkers recently reported the results of a phase I/II trial of irinotecan (dose range: 200 mg/m\(^2\) to 300 mg/m on day 1) in combination with UFT (dose range: 250 mg/m to 350 mg/m, days 1 to 14) and a fixed dose of leucovorin (90 mg per day).[39] The study enrolled 33 patients who received treatment with the recommended dose of irinotecan at 250 mg/m and UFT at 250 mg/m. The dose limiting toxicities were neutropenic fever and diarrhea. So far, 16 patients are response-evaluable including those being entered into the phase II part of the study. One patient achieved a complete response and 3 of 16 patients (18.8%) achieved a partial response.

Gravalos and coworkers reported the results of a phase I study of UFT/leucovorin in combination with irinotecan administered on a once-every-3-week schedule.[40] The study enrolled 17 pretreated patients with advanced colorectal cancer. The maximum tolerated dose was UFT at 300 mg/m, leucovorin at 45 mg po (fixed dose) on days 1 to 14, and irinotecan at 300 mg/m on day 1, repeated every 3 weeks. Diarrhea was the dose-limiting toxicity and 4 of 13 patients achieved an objective response.

**Oxaliplatin and UFT/ Leucovorin**

The combination of oxaliplatin with UFT/leucovorin has been evaluated in a phase II study as first-line therapy for metastatic colorectal cancer.[41] Oxaliplatin was administered at a dose of 85 mg/m on
days 1 and 14, UFT at a dose of 390 mg/m$^2$ per day for 14 days plus l-leucovorin 250 mg/m$^2$ on day 1 followed by l-leucovorin at a dose of 7.5 mg po every 12 hours on days 2 to 14. Cycles were repeated every 3 weeks.

High intestinal toxicities in this study (grade 3 and 4 diarrhea and nausea occurred in 56% and 18%, respectively) resulted in a reduction in the dose of UFT to 300 mg/m$^2$ after the first 16 patients received treatment. A partial response was achieved by 12 of 34 patients (35%). The final results of other phase I studies of UFT/leucovorin in combination with either irinotecan or oxaliplatin are not yet published.[42,43]

**UFT Plus Raltitrexed**

The synergistic cytotoxic interactions between raltitrexed (Tomudex) and 5-FU in preclinical models led to a phase I/II dose-escalation study of UFT (dose range: 200 mg/m$^2$ to 350 mg/m$^2$, days 1 to 28) and raltitrexed (dose range: 2.0 mg/m$^2$ to 3.5 mg/m$^2$ IV, days 1 and 21) followed by a 2-week rest.[44] The dose-limiting toxicity was diarrhea. To date, 22 patients have been enrolled and the maximum tolerated dose has not been reached at dose-level 5 (raltitrexed 3.0 mg/m$^2$; UFT 300 mg/m$^2$) suggesting that both drugs can be combined at the doses recommended for monotherapy.

Based on the results of a phase I trial of UFT and mitomycin (recommended dose for phase II trials: UFT 400 mg/m$^2$, mitomycin 6 mg/m$^2$), 21 response-evaluable patients were treated with this combination. The overall response rate was 24% (5 of 21 patients) and 38.5% (5 of 13 patients) for previously untreated patients.[45]

**UFT/Leucovorin Combinations in Esophageal and Stomach Cancer**

UFT/leucovorin-based combinations have also been investigated in carcinomas of the esophagus, the esophagogastric junction, and the stomach. Most of these trials were conducted as small phase I or II trials in Japan. In a randomized trial, Yonemura and coworkers treated 55 patients with advanced disease with a combination of cisplatin (Platinol) at a dose of 75 mg/m$^2$, mitomycin 10 mg/m$^2$ on day 1, and etoposide (VePesid) (150 mg/m$^2$ IV) and UFT 400 mg/day on days 3, 4, and 5 (PMUE).[46] The regimen was administered to 29 patients in a neoadjuvant setting and 26 patients, postoperatively. Observed response rates were 62% and 35%, respectively.

In another trial, a response rate of 23.5% (4 of 17 response evaluable patients) was reported for the combination of UFT, cisplatin, and mitomycin. Grade 3 and 4 toxicities were reported in 20% of patients.[47]

**Cisplatin and UFT/Leucovorin**

The combination of cisplatin (50 mg/m$^2$, continuous infusion [CI] days 1 and 2), 5-FU (500 to 750 mg/m$^2$ CI, days 2 to 7) and UFT (400 mg/d, days 8 to 28) induced a response rate in 2 of 8 patients (25%) with esophageal cancer and in 4 of 13 patients (31%) with gastric cancer.[48] Major side effects of this regimen were anorexia, nausea/vomiting, and leukocytopenia. When UFT was added to a regimen of etoposide, doxorubicin (Adriamycin), and cisplatin (Platinol) (UFT-EAP) in 34 patients with advanced tumors, the response rate was 47% and included four complete responses and a median remission duration of 12 months.[49] This regimen was felt to be well tolerated; myelosuppression was the main side effect.

A 28-day course of UFT (400 mg/m$^2$) and cisplatin (30 mg/m$^2$, days 1 to 3) resulted in a response rate of 43% (6 of 14 patients) and a median survival time of 11.4 months.[50] With a different schedule of cisplatin (80 mg/m$^2$ on day 8) and UFT (400 mg/m$^2$, days 1 to 21), a response rate of 52% and a median survival of 8.3 months were reported by Sato et al.[51] This regimen was associated with acceptable toxicities.

The Spanish Oncopaz Cooperative Group evaluated UFT (390 mg/m$^2$, days 1 to 14) plus leucovorin (500 mg/m$^2$ IV on day 1, then 15 mg every 12 hours orally on days 2 to 14) in combination with etoposide (100 mg/m$^2$ IV, day 1 and 200 mg/m orally on days 2 and 3).[52] Responses among 46
patients included 5 (11%) complete and 12 (26%) partial responses, and a median survival of 9 months. Grade 3 and 4 diarrhea (according to WHO) was observed in 17% of all patients; 1 patient died of neutropenia and sepsis.

**Epirubicin, Cisplatin, and UFT/Leucovorin Combinations**

Based on the positive results reported with epirubicin, cisplatin, and 5-FU (ECF) administered as continuous infusion over 21 weeks, three groups replaced 5-FU in the ECF regimen with UFT/leucovorin.[53-55] Kim and coworkers administered epirubicin (50 mg/m\(^2\)) and cisplatin (60 mg/m\(^2\)) on day 1 and UFT (360 mg/m\(^2\)) plus a fixed dose of leucovorin (40 mg po) for 21 days.[53] Cycles were repeated every 4 weeks. Of 46 patients with advanced gastric cancer entered into the trial, 3 achieved a complete response and 22 achieved a partial response resulting in an overall response rate of 54.3% and a median survival of 10 months. Treatment-related grade 3 and 4 toxicities were leukopenia (36%), mucositis (6%), and diarrhea (6%). The authors considered this regimen significantly active and tolerable.

In a phase I/II study, 30 previously untreated patients with advanced upper gastrointestinal cancer were treated with the same doses of epirubicin and cisplatin administered every 3 weeks and a continuous administration of UFT (150 mg/m\(^2\) to 325 mg/m\(^2\)) plus a fixed dose of oral leucovorin (45 mg on days 1, 8, and 15).[54] The dose of UFT recommended for further study was 200 mg/m\(^2\) per day. Among 15 patients with gastroesophageal cancer, 9 objective responses including 2 complete responses were reported. Severe side effects were infrequent with this combination. Both studies indicate that UFT/leucovorin in combination with cisplatin and epirubicin may be comparable in efficacy to the original ECF regimen. These results need to be confirmed further in randomized studies.

The preliminary toxicity analysis of another ongoing trial indicates that a regimen of epirubicin/cisplatin/UFT (ECU) is less toxic and more convenient compared to the ECF regimen.[55]

Gallardo et al reported the results of a combination of epirubicin, cisplatin, and oral tegafur (ECT) in patients with advanced gastric cancer.[56] In this study, 20 patients received epirubicin at 60 mg/m\(^2\) and cisplatin at 70 mg/m IV on day 1, oral tegafur at 700 mg/m for 14 days in combination with a fixed dose of oral l-leucovorin (25 mg). The overall response rate was 50% (7 of 14 response evaluable patients) and six patients had stable disease. Major toxicities included grade 3 and 4 neutropenia and grade 3 thrombocytopenia.

In addition, combination chemotherapy of UFT, with or without leucovorin, was also evaluated in cancer of the pancreatico-biliary tract. Feliu et al investigated the combination of gemcitabine (Gemzar) at a dose of 1,000 mg/m on a once-weekly × 3 schedule in combination with UFT (390 mg/m, days 1 to 14) plus leucovorin (l-form 250 mg/m IV on day 1 followed by 7.5 mg every 12 hours on days 2 to 14).[57] Cycles were repeated every 4 weeks and 42 patients with measurable pancreatic cancer were entered into the study.

Among 38 response evaluable patients, six (16%) achieved a partial response and 15 (39%) had stable disease. An improvement in performance status and symptoms was reported in 29% and 45% of patients, respectively, with 18 patients (47%) achieving a response. The regimen was well tolerated and appeared to be a meaningful palliative treatment for this tumor entity.

**Capecitabine Combination Therapy**

The modest toxicity of capecitabine, particularly its low incidence of neutropenia, makes it a suitable candidate for fluoropyrimidine combination therapies involving other cytotoxic agents (eg, irinotecan and oxaliplatin) that are active in gastrointestinal cancer. Moreover, most of the fluoropyrimidine combinations either with oxaliplatin or irinotecan are based on infusional 5-FU regimens (AIO- or de Gramont schedule) associated with the inconvenience of central catheters and portable pumps.[13,15,16] Thus, capecitabine combinations with irinotecan or oxaliplatin are currently under clinical investigation for colorectal cancer.[58-60]
Capecitabine and Irinotecan

An extended phase I study evaluated the combination of capecitabine with a weekly schedule of irinotecan.[58] Capecitabine was administered on days 1 to 14 and 22 to 35 every 7 weeks at doses of 1,000 mg/m² or 1,250 mg/m² twice daily. Irinotecan was administered on a weekly × 6 schedule at doses of 70 mg/m² and 80 mg/m. All patients had metastatic colorectal cancer, measurable disease, and had received no prior chemotherapy for metastatic disease. Preliminary data from 37 patients demonstrated significant antitumoral activity, with neutropenia and diarrhea being dose-limiting. Notably, only a few patients experienced hand-foot syndrome. The dose of 1,000 mg/m² of capecitabine twice daily for days 1 to 14 and 22 to 35 in combination with weekly irinotecan at a dose of 70 mg/m² has been considered the recommended dose for further phase II studies.

A second pilot study investigated two different doses and schedules of capecitabine and irinotecan in advanced colorectal cancer: (a) irinotecan at 300 mg/m² on day 1 every 3 weeks; or (b) irinotecan at a dose of 150 mg/m² on days 1 and 8 every 3 weeks. Capecitabine was administered with both schedules of irinotecan at 1,250 mg/m² twice daily for 14 days followed by a 1-week rest period. This study entered 19 patients, 5 of whom had received prior chemotherapy for metastatic disease.[59] For both schedules, the most common related toxicities were diarrhea, neutropenia, and hand-foot-syndrome. Partial responses were reported for 13 of 17 response-evaluable patients (76%, 95% confidence interval: 50%-93%).

Oxaliplatin and Capecitabine

Oxaliplatin has significant efficacy in colorectal cancer.[10] Moreover, preclinical data suggest that the synergistic antitumor activity of the fluoropyrimidines and oxaliplatin may partially overcome resistance to the fluoropyrimidines. Thus, the combination of capecitabine with oxaliplatin has been investigated.[60] In a phase I study of advanced solid tumors, the dose of capecitabine was escalated from 500 mg/m² (starting dose) to 1,250 mg/m² twice daily on days 1 to 14 followed by a 1-week rest period. Oxaliplatin was administered at a fixed dose of 130 mg/m² on day 1 of each 21-day cycle. Twenty-three patients who had progressed with prior chemotherapy have been enrolled. Dose-limiting toxicities were diarrhea, thrombocytopenia, and neutropenia. The doses recommended for further phase II studies were suggested as follows: capecitabine at 1,000 mg/m² twice daily for 14 days combined with oxaliplatin at 130 mg/m² on day 1 every 21 days. Five of nine patients (56%) with advanced colorectal cancer achieved a response.

The results of this phase I trial demonstrate that the combination of capecitabine and oxaliplatin was well tolerated and had promising antitumor activity in colorectal cancer. The combination of capecitabine and oxaliplatin is currently under clinical evaluation as first-line therapy for patients with metastatic colorectal cancer.

Conclusions

Oral fluoropyrimidine prodrugs could become an important component of our therapeutic armamentarium in the treatment of gastrointestinal cancer. Two large randomized phase III trials in metastatic colorectal cancer demonstrated that capecitabine offers a convenient alternative to bolus 5-FU/leucovorin with a superior safety profile and equivalent antitumor activity.[35,36] Similar results have been achieved with UFT/leucovorin in two randomized trials.[23,24] S-1, a fixed combination of 5-chloro-2,4-dihydropyrimidine (CDHP), fторafur, and oxonic acid is also under investigation in gastrointestinal cancer and may constitute another promising approach in the treatment of gastrointestinal cancer.[61]

Based on these results, fluoropyrimidine prodrug-based combination therapy (eg, combinations with either irinotecan, oxaliplatin, anti-EGF- or VEGF-receptor mAb, or tyrosine kinase inhibitors) for gastrointestinal cancer deserves further clinical investigation in the metastatic or adjuvant setting.

Questions and Answers

Dr Haller: Just a question in terms of choosing the weekly irinotecan regimen vs a less frequent
regimen as you approach myelosuppression. It’s hard to use growth factors with weekly regimens. Could you contemplate doing the same schedule of capecitabine with thrice weekly irinotecan, thereby allowing for use of growth factors?

**Dr. Vanhoefer:** With the weekly schedule of irinotecan in combination with capecitabine, we have not observed significant myelosuppression, so we did not have to use growth factors.

**Dr. Haller:** Part of your dose limiting toxicity (DLT) was neutropenia though. Is this correct.

**Dr. Vanhoefer:** Yes, neutropenia was reported in 2 of 17 patients.

**Dr. Saltz:** I have two thoughts about that. One is that we have been able in those rare patients where neutropenia alone is the DLT, to use G-CSF with weekly irinotecan and I think it seems to get them through it. My concern is that we already have to stretch a little bit to go for the rationale of the oral fluorinated pyrimidine with the parenteral other agent, be it oxaliplatin or irinotecan, and I don’t know that we know yet if that’s the right thing to do.

**Dr. Vanhoefer:** There’s a difference between Europe and the United States. In Europe, combination regimens are based on infusional schedules of fluorouracil such as the biweekly deGramont or weekly AIO schedule. These regimens are associated with portable pumps. In addition, drug intake and toxicity may be better managed by a weekly schedule. Therefore, it might be a very interesting approach to substitute capecitabine for the infusional 5-FU.

**Dr. Saltz:** The interesting question that I’ve been concerned about and thinking about in combining all of these agents with irinotecan, is to what effect the rise in bilirubin that we see on occasion will influence irinotecan metabolism. Any idea?

**Dr. Vanhoefer:** For those patients, who have been treated with capecitabine, we have had no problems.

**Dr. Saltz:** In this trial, have you seen people with rise in the bilirubin?

**Dr. Vanhoefer:** No. We also have no problems with the phase I and II trials.

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