Simultaneous Administration of CPT-11 and Fluorouracil: Alteration of the Pharmacokinetics of CPT-11 and SN-38 in Patients With Advanced Colorectal Cancer

Drug interactions in pharmacokinetics as well as in pharmacodynamics must be considered not only to conduct combination chemotherapy but also to decide the optimal combination timing of the drugs. Fluorouracil (5-FU) is the most widely used single agent for the treatment of colorectal cancer. CPT-11 (7-ethyl-10-[4-(1-piperidino)-1-piperidino] carboxyloxy-camptothecin) is a water-soluble camptothecin derivative (7). One of our investigators has reported a high response rate to the use of CPT-11 for colorectal cancer (2). We report here the pharmacokinetic drug interaction of CPT-11 or SN-38 (7-ethyl-10-hydroxycamptothecin), a major active metabolite of CPT-11, and 5-FU in the course of a phase I study of treatment with the combination of CPT-11 and 5-FU for metastatic colorectal cancer.

The pharmacokinetics of CPT-11, SN-38, and 5-FU were analyzed in 12 patients (five male and seven female; median age, 52 years; range, 42-69 years; and Eastern Cooperative Oncology Group performance status 0 and 1) with histologically confirmed metastatic colorectal cancer. Three patients were treated with 100 mg/m² of CPT-11 (Daiichi Pharmaceutical Co. Ltd., Tokyo, Japan), three with 125 mg/m², and six with 150 mg/m². CPT-11 was administered by intravenous-drip infusion for a period of 90 minutes. After the end of CPT-11 infusion, all the patients had follow-up of continuous infusion of 5-FU at a dose of 400 mg/m² per day for 7 days. The protocol of this phase I study was modified and is now ongoing. The tentative results have been reported elsewhere (3). Written informed consent was obtained according to the institutional guideline, and the study was approved by the Institutional Review Board.

The previously reported dataset of 36 patients who were administered CPT-11 alone at a dose of 100 mg/m² intravenously infused for a 90-minute period (which was the same administration schedule of CPT-11 as the combined regimen) was used as a historic control (4). The eligibility criteria of both studies were identical except for the tumor type.

Blood samples for pharmacokinetics were obtained before CPT-11 infusion and at 30, 60, and 90 minutes after the start of infusion. Blood samples were then obtained at 15, 30, 60, 120, 240, 480, and 720 minutes and at 24, 48, 72, 96, 120, 144, and 168 hours after the end of the infusion. The plasma levels of CPT-11, SN-38, and 5-FU were measured as previously reported (5,6).

The pharmacokinetic parameters of both CPT-11 and SN-38 were calculated by the moment method (7), and the area under the concentration x time curve (AUC) was calculated by the trapezoidal method using the MULTI computer program (8). The steady-state concentration (Cₚₛₛ) of 5-FU was calculated from the mean obtained on the 24-, 48-, 72-, 96-, 120-, 144-, and 164-hour samples. The two-tailed Mann–Whitney U test was used to compare the AUC of CPT-11 or SN-38 between the combined group and the control group (Table 1).

The plasma concentration or AUC of CPT-11 was higher in the combined group than in the control group (Fig. 1, A, and Table 1). By contrast, the plasma concentration or AUC of SN-38 was much higher in the control group than in the combined group (Fig. 1, B, and Table 1), although nine of 12 patients in the combined group received a higher dose of CPT-11 than the control patients. The Cₚₛₛ of 5-FU was not influenced by CPT-11 at the three dose levels with a mean Cₚₛₛ of 0.165 μg/mL, which was almost comparable with that reported by other investigators (6).

Combination chemotherapy is often conducted on the basis of preclinical pharmacodynamic combination effect. However, studies have addressed the importance of pharmacokinetic drug interactions in paclitaxel and cisplatin (9) and in etoposide and cyclosporine (10). The present findings indicated that the AUC of CPT-11 significantly (P = .0029) increased, whereas the AUC of...
Table 1. Comparative pharmacokinetic parameters of CPT-11 and SN-38*

<table>
<thead>
<tr>
<th>Infusion</th>
<th>T&lt;sub&gt;max&lt;/sub&gt;, h</th>
<th>C&lt;sub&gt;max&lt;/sub&gt;, ng/mL</th>
<th>MRT, h</th>
<th>AUC ng h/mL</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT-11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone‡</td>
<td>Mean</td>
<td>1.45</td>
<td>6.90</td>
<td>6410</td>
<td>.0029</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.18</td>
<td>1.59</td>
<td>1660</td>
<td></td>
</tr>
<tr>
<td>Combined§</td>
<td>Mean</td>
<td>1.46</td>
<td>6.10</td>
<td>8620</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.18</td>
<td>0.85</td>
<td>2470</td>
<td></td>
</tr>
<tr>
<td>SN-38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone‡</td>
<td>Mean</td>
<td>2.08</td>
<td>9.15</td>
<td>236.14</td>
<td>.0196</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.67</td>
<td>1.29</td>
<td>91.99</td>
<td></td>
</tr>
<tr>
<td>Combined§</td>
<td>Mean</td>
<td>1.87</td>
<td>8.51</td>
<td>169.90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.57</td>
<td>1.71</td>
<td>89.65</td>
<td></td>
</tr>
</tbody>
</table>

*<sup>T<sub>max</sub> = time to detect peak plasma concentration after starting CPT-11; C<sub>max</sub> = peak plasma concentration; MRT = mean residence time.
†Difference between AUC for CPT-11 administered alone and the combined administration of CPT-11 and 5-FU as calculated by the two-tailed Mann-Whitney U test.
§N = 36. CPT-11 was administered at a dose of 100 mg/m² by intravenous infusion for a period of 90 minutes.
$N = 12$. CPT-11 was administered at a dose of 100-150 mg/m² by intravenous infusion for a period of 90 minutes followed by continuous intravenous of 5-FU at a dose of 400 mg/m² per day for 7 days.

SN-38 significantly (P = .0196) decreased in the patients administered CPT-11 followed by 5-FU infusion (see Fig.1). Although we did not conduct a cross-over design, the backgrounds of the patients in the two cohorts were similar, and nine patients in the combined group received 125 or 150 mg/m² CPT-11. In addition, we observed unexpectedly mild toxicity in this combination regimen (2). CPT-11 is reported to be metabolized into SN-38 by carboxylesterase (11). 5-FU or its metabolite may inhibit the activity of carboxylesterase. CPT-11 is active against colorectal cancer, and the most effective combination timing with 5-FU should be established in the near future on the basis of the pharmacokinetics and pharmacodynamics.

Y. SASAKI  
Division of Oncology and Hematology  
A. OHTSU  
Y. SHIMADA  
Division of Gastrointestinal Oncology  
K. ONO  
Development Research Laboratories  
National Cancer Center Hospital  
Kashiwa, Japan  
N. SAITO  
Pharmacology Division  
Daiichi Pharmaceutical Co. Ltd.  
Kashiwa

References


Fig. 1. Plasma concentration x time curves of CPT-11 (A) and SN-38 (B) determined by high-pressure liquid chromatography in 36 patients treated with CPT-11 alone at a dose of 100 mg/m² for a period of 90 minutes and in 12 patients treated with 100-150 mg/m² of CPT-11 for a period of 90 minutes followed by 400 mg/m² per day of 5-FU continuously infused for 7 days. Points represent means ± SD. A) CPT-11 + 5-FU = open circle; CPT alone = closed circle. B) CPT-11 + 5-FU = open square; CPT-11 alone = closed square.
Feasibility of High-Dose Platinum Delivery With Combined Carboplatin and Oxaliplatin

A retrospective analysis of clinical trials, as done by Levin et al. (1) in ovarian carcinoma, suggests that the administered dose intensity of cisplatin is a determinant in the tumor control of platinum-sensitive tumors. Dose-limiting toxic effects (renal, auditory, and neurologic) present a barrier to further cisplatin dose-intensity therapeutic incremental exploration (2).

Carboplatin, which when compared with cisplatin has a nonoverlapping toxicity profile, is the only alternative platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motivated studies of the platinum compound available. This distinction has motiva...