Efficacy of Combination Chemotherapy Using a Novel Oral Chemotherapeutic Agent, TAS-102, with Irinotecan Hydrochloride on Human Colorectal and Gastric Cancer Xenografts

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Abstract. TAS-102 is a novel oral nucleoside antitumor agent consisting of trifluridine and tipiracil hydrochloride at a molar ratio of 1:0.5. TAS-102 was approved in Japan in March 2014 for the treatment of patients with unresectable, advanced or recurrent colorectal cancer that is refractory to standard therapies. In the present study, enhancement of the therapeutic efficacy using a combination therapy of TAS-102 and irinotecan hydrochloride (CPT-11) was evaluated in a colorectal and gastric cancer xenograft-bearing nude mouse model. TAS-102 was orally administered twice a day from day 1 to 14, and CPT-11 was administered intravenously on days 1 and 8. The growth-inhibitory activity was evaluated based on the tumor volume and the growth-delay period, which was estimated based on the period required to reach a tumor volume that was five-times greater than the initial volume (RTV5). The tumor growth-inhibitory activity and the RTV5 of the group receiving TAS-102 with CPT-11 were significantly superior to those of both agents as monotherapy for mice with KM12C, KM12C/5-FU, DLD-1/5-FU, and SC-2 xenografts (p<0.01). No significant decrease in body weight was observed. The present pre-clinical findings indicated that the combination of TAS-102 and CPT-11 is a promising treatment option for colorectal or gastric cancer, not only for chemo-naïve tumors, but also for recurrent tumors after 5-fluorouracil (5-FU)-based chemotherapy.

Worldwide, colorectal cancer is the third most common cancer in men (10%) and the second most common in women (9.2%), and it was the fourth leading cause of cancer-related death in 2012 (1). For the treatment of unresectable metastatic colorectal cancer, systemic chemotherapy agents such as fluoropyrimidines, irinotecan hydrochloride (CPT-11) and oxaliplatin, and targeted-agents such as bevacizumab (a monoclonal antibody to vascular endothelial growth factor), cetuximab, and panitumumab (monoclonal antibodies to epidermal growth factor receptor) are currently used, and the survival of patients with unresectable metastatic colorectal cancer has improved (2-5). Even if these standard therapies are initially effective, many patients relapse due to onset of drug resistance and are subsequently placed on salvage chemotherapy. In 2013, the multi-kinase inhibitor regorafenib demonstrated that it prolonged overall survival when compared to placebo for the treatment of unresectable refractory colorectal cancer in 2013 (6).

TAS-102 is a novel antitumor nucleoside. It is a combination of an anti-neoplastic thymidine-based nucleoside analogue, trifluridine (FTD) and a thymidine phosphorylase inhibitor, tipiracil hydrochloride (TPI) at a molar ratio 1:0.5. FTD is the active antitumor component of TAS-102; its monophosphate form inhibits thymidylate synthase, and its triphosphate form is incorporated into DNA in tumor cells. The incorporation into DNA is known to have antitumor effects, since the inhibition of thymidylate synthase caused by oral FTD rapidly disappears after the drug’s elimination (7-9).

When FTD is administered orally, it is rapidly degraded to its inactive form by thymidine phosphorylase in the intestines and liver (first-pass effect) (8). Consequently, TPI was synthesized to maintain adequate plasma concentrations of orally-administered FTD and to potentiate the antitumor activity of FTD (10). The optimal molecular ratio of FTD to TPI was shown to be 1:0.5 (11). In pre-clinical studies, FTD...
and TAS-102 were found to exhibit some unique antitumor effects, such as their efficacy against 5-FU-resistant colorectal tumor cells not only in vitro but also in vivo (12-14), and a continued effect persisted after the end of drug administration (9, 15).

In a randomized phase II trial of patients with metastatic colorectal cancer refractory to or who were intolerant of standard chemotherapies, the overall survival period of those receiving TAS-102 with best supportive care (9.0 months), was significantly longer than a group treated with placebo with best supportive care (6.6 months, \( p=0.0011 \)) (16). Recently, TAS-102 led to a significant improvement in overall and progression-free survival, and had a favorable safety profile in comparison to placebo in patients with metastatic colorectal cancer refractory to standard chemotherapies in an international multi-center randomized double-blind phase III study (RECOURSE); patients in both arms received the best supportive care (17). TAS-102 was approved for clinical use in Japan in March 2014.

CPT-11 is a key drug, as a monotherapy or in several combination chemotherapies, has been widely used to treat colorectal (2, 18-20) and gastric cancer (21). In the present study, we evaluated the antitumor effects of TAS-102 in combination with CPT-11 on gastrointestinal tumor xenografts, including 5-FU-resistant sublines, in a nude mouse model.

**Materials and Methods**

**Chemicals.** FTD and TPI, which are components of TAS-102, were synthesized at Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan). CPT-11 was purchased from Yakult Honsha Co., Ltd. (Tokyo, Japan). Hydroxypropyl methylcellulose (HPMC) was purchased from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). CPT-11 was purchased from Yakult Honsha Co., Ltd. (Tokyo, Japan). Hydroxypropyl methylcellulose (HPMC) was purchased from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan).

**Tumor cells.** The human colon cancer cell line DLD-1 was purchased from DS Pharma Biomedical Co., Ltd. (Osaka, Japan), while Dukes’ B2 human colon carcinoma cell line KM12C (22) was provided by Dr. Kiyoshi Morikawa of the National Cancer Center Japan. The 5-FU-resistant cell line DLD-1/5-FU was established using a long-term culture in the presence of 5-FU in vitro (14). KM12C/5-FU was established by long-term passage with 5-FU administration in vivo (23). The human gastric cancer cell line SC-2 (24) was obtained from the Central Institute for Experimental Animals (Kawasaki, Japan). All the tumor cells were maintained by implantation into the right axilla of nude mice at 3-week intervals.

**Antitumor activity in vivo.** Male nude mice were purchased from CLEA Japan Inc. (Tokyo, Japan) and housed under specific pathogen-free conditions, with food and water provided ad libitum. After the animals had been placed in quarantine for one week, they were implanted subcutaneously with a solid human tumor, the volume of which was approximately 8 mm\(^3\). To evaluate the antitumor activity, mice were randomized according to tumor volume once the mean tumor volume reached about 150 to 200 mm\(^3\) (on day 0). Each group consisted of six mice.

TAS-102 was prepared by mixing FTD and TPI at a molar ratio of 1:0.5 in 0.5% HPMC. The dose of TAS-102 was expressed according to the amount of FTD. TAS-102 was administered orally from day 1 to 14, twice a day, with approximately a 6-hour interval at the reported effective dose (150 mg/kg/day) (7,11). For the control group, 0.5% HPMC alone was administered at 10 ml/kg according to a similar schedule. CPT-11 (40 mg/kg) was administered intravenously on days 1 and 8, once a day.

The tumor diameters were measured twice a week, and the tumor volume was estimated as \( 0.5 \times \text{length} \times \text{width}^2 \). The relative tumor volume (RTV) was calculated using the following formula: \( \text{RTV} = \frac{\text{tumor volume on measured day}}{\text{tumor volume on day 0}} \). On day 28 or 29, the tumor growth inhibition (TGI) ratio was calculated using the following formula: \( \text{TGI} = \left[ 1 - \frac{\text{RTV of the treated group}}{\text{RTV of the control group}} \right] \times 100 \% \).

The antitumor activity was evaluated according to the RTV5 value, which indicates the period of time required for the RTV to reach 5. To estimate the RTV5, the RTV change for each mouse was plotted and the date on which the RTV reached 5 was estimated using linear-regression based on two dates on which the RTV reached around 5 (25).

To evaluate the toxicity, the body weight change (BWC) was calculated using the following formula: \( \text{BWC} \% = \frac{\text{(body weight on the last day)} - \text{(body weight on day 0)}}{\text{(body weight on day 0)}} \times 100 \% \). In cases where mean body weight loss was more than 20\%, or in those that toxic death was observed as a result of the treatment, the treatment was designated as toxic.

All the animal studies were performed according to the guidelines and under the approval of the Institutional Animal Care and Use Committee of Taiho Pharmaceutical Co., Ltd. (Approval number was OT7TB02 and 14TB02).

**Statistical analysis.** The significance of the differences in the mean RTV between the treated and the control groups on day 28 or 29 was analyzed using the Aspin-Welch two-sided \( t \)-test. The combinational effect of TAS-102 and CPT-11 on the antitumor activity was analyzed according to a closed testing procedure using the Aspin-Welch two-tailed \( t \)-test (26). The statistical analysis of RTV5 was evaluated using the log-rank test according to the method reported in (27). In cases where the RTV of the treated animal was not reached 5.0, the data were censored and the RTV5 was designated as 28 or 29. In any case, a \( p \)-value of less than 0.05 in statistical analyses was considered significant, as calculated using EXSUS (ver. 8.1; Arm Systex Co., Ltd., Osaka, Japan).

**Results**

Increased antitumor activity of CPT-11 administered in combination with TAS-102 in KM12C and its 5-FU-resistant cell line KM12C/5-FU in vivo. The antitumor activities of TAS-102 and CPT-11 administered alone and in combination were evaluated. The RTV change and the BWC in the KM12C-bearing nude mice are shown in Figure 1a and b, respectively. As shown in Table I, the antitumor activity of the combination-treated group on day 29 was significantly superior to that of both monotherapy groups \( (p<0.01) \). The mean RTV5 of both the CPT-11-and TAS-102-treated groups was significantly \( (p<0.001) \) longer than that of the control group. For the combination-treated group, the RTV value on
day 29 was 1.07, and the RTV5 was significantly ($p<0.001$) longer than that of both monotherapy-treated groups (Figure 1a) (Table I). The body weight of the KM12C-bearing nude mice in the control group decreased by more than 20%, accompanied by tumor growth, similar to cancer-induced cachexia. Interestingly, the body weight loss induced by KM12C was alleviated in the combination group because of the high growth-inhibitory activity. Neither CPT-11 nor TAS-102 monotherapy was able to prevent body weight loss. These results indicate that this combination is active for the treatment of colorectal cancer without increasing toxicity (Figure 1b) (Table I). We also evaluated the antitumor activity against the 5-FU-resistant cell line KM12C/5-FU. The RTV change and the BWC in the KM12C/5-FU-bearing nude mice are shown in Figure 2a and b, respectively. TAS-102 monotherapy had a significant antitumor activity against KM12C/5-FU in vivo. Furthermore, the antitumor activity in the combination-treated group on day 29 was significantly ($p<0.01$) superior to that under both monotherapies. The mean RTV5 of the TAS-102 group was significantly ($p<0.001$) longer than that of both the control group. In addition, the RTV5 of the combination-treated group was significantly longer than that of both the CPT-11 and TAS-102 monotherapy groups (Table II). The

Table I. Antitumor activity of treatment with TAS-102 and irinotecan hydrochloride (CPT-11) and body weight changes in mice implanted with KM12C human colorectal tumor.

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg/day)</th>
<th>Schedule</th>
<th>RTV (mean±SD)</th>
<th>n</th>
<th>TGI (%)</th>
<th>RTV5 (days)</th>
<th>BWC (mean±SD, g)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>–</td>
<td>–</td>
<td>42.27±6.09</td>
<td>7</td>
<td>0</td>
<td>5.20±0.38</td>
<td>−5.7±2.0</td>
<td>−22.1</td>
</tr>
<tr>
<td>TAS−102</td>
<td>150</td>
<td>Day 1−14 (b.i.d.)</td>
<td>23.29±3.75</td>
<td>7</td>
<td>44.9</td>
<td>8.98±0.34</td>
<td>−6.4±1.3</td>
<td>3NS</td>
</tr>
<tr>
<td>CPT−11</td>
<td>40</td>
<td>Day 1, 8</td>
<td>12.51±3.78</td>
<td>7</td>
<td>70.4</td>
<td>23.34±1.02</td>
<td>−3.7±0.6</td>
<td>15.2</td>
</tr>
<tr>
<td>Combination</td>
<td>150+40</td>
<td>Day 1−14 + 1, 8</td>
<td>1.07±0.92a,b</td>
<td>7</td>
<td>97.5</td>
<td>&gt;29.00d</td>
<td>0.3±1.9a</td>
<td>1.2</td>
</tr>
</tbody>
</table>

RTV: Relative tumor volume on day 29; TGI: tumor growth-inhibition ratio on day 29; RTV5: the period RTV takes to reach a value of 5; BWC: body weight change from day 0 to day 29. *p<0.01 vs. Control using the two-sided Aspin-Welch t-test; **p<0.01 by closed testing procedure using two-sided Aspin-Welch t-test; †p<0.001 vs. Control using log-rank test; ‡p<0.001 vs. either monotherapy using log-rank test; NS: not significant ($p>0.05$) vs. Control using two-sided Aspin-Welch t-test.

Figure 1. Relative tumor volume (RTV) of KM12C human colorectal tumor (a) and body weight change of KM12C-bearing nude mice (b). Mice were randomized according to tumor volume on day 0. Mice were treated with the 0.5% hydroxypropyl methylcellulose or TAS-102 (150 mg/kg), administered orally twice daily from days 1 to 14. Irinotecan hydrochloride (CPT-11) (40 mg/kg) was administered intravenously alone or in combination with TAS-102 on days 1 and 8. The tumor volume and body weight were measured twice a week. The values indicate the mean ±SD (n=7). The horizontal dotted line indicates an RTV of 5.
BWC of the TAS-102 group was smaller \( (p<0.05) \) compared to that of the control group, but that of the combination group was less than 10%; therefore, the toxicity of this combination therapy appeared to be tolerable (Table II).

**Increased antitumor activity of CPT-11 administered in combination with TAS-102 in the DLD-1 cell line and its 5-FU-resistant cell line DLD-1/5-FU in vivo.** The antitumor activities of TAS-102 and CPT-11 administered alone and in combination were evaluated. The RTV change and the BWC in the DLD-1-bearing nude mice are shown in Figure 3a and b, respectively. In these mice, CPT-11 and TAS-102 monotherapies significantly inhibited tumor growth. The growth-inhibitory activity for the combination therapy was higher than that of both monotherapies, but the differences were not significant. The RTV5 in the combination-treated group was longer than that in both monotherapy groups, but these differences were also not significant (Table III). As the BWC was less than 5%, the toxicity was deemed tolerable (Table III).

The RIV change and the BWC in the DLD-1/5-FU-bearing nude mice are shown in Figure 4a and b, respectively.

In the DLD-1/5-FU-bearing nude mice, however, the antitumor activity of the combination was significantly...
superior to that of both monotherapies \( (p<0.01) \). The mean RTV5 of the group treated with the combination was significantly longer than those of the TAS-102 monotherapy, the CPT-11 monotherapy, and the control groups (Table IV). The body weight of the DLD-1/5-FU-bearing mice decreased gradually, depending on the tumor growth; however, no significant difference of the group treated with the combination from that of the control group was observed; the BWC value was \(-10.9\%\). Therefore, this combination was deemed tolerable (Table IV).

Increased antitumor activity of CPT-11 administered in combination with TAS-102 in the human gastric cancer SC-2 cell line in vivo. The RTV change in the SC-2-bearing nude mice is shown in Figure 5. The antitumor activity of the combination on day 29 was significantly superior to that of both monotherapies. The mean RTV5 of both the CPT-11 monotherapy and the TAS-102 monotherapy groups was significantly longer than that of the control. On day 29, the RTV value for the combination group was 2.6, and the RTV5 value was significantly longer \( (p<0.001) \) than that of both monotherapy-treated groups. As the BWC of the

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**Table III. Antitumor activity of treatment with TAS-102 and irinotecan hydrochloride (CPT-11) and body weight changes in mice implanted with DLD-1 human colorectal tumor.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg/day)</th>
<th>Schedule</th>
<th>RTV (mean±SD)</th>
<th>n</th>
<th>TGI (%)</th>
<th>RTV5 (days)</th>
<th>BWC (mean±SD, g)</th>
<th>BWC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>–</td>
<td>–</td>
<td>17.52±1.75</td>
<td>7</td>
<td>0</td>
<td>11.02±0.81</td>
<td>0.6±2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>TAS-102</td>
<td>150</td>
<td>Day 1-14 ( (b.i.d.) )</td>
<td>15.52±0.98\textsuperscript{a}</td>
<td>7</td>
<td>11.4</td>
<td>15.31±0.84\textsuperscript{d}</td>
<td>1.2±1.6\textsuperscript{NS}</td>
<td>4.7</td>
</tr>
<tr>
<td>CPT-11</td>
<td>40</td>
<td>Day 1, 8</td>
<td>8.83±2.71\textsuperscript{b}</td>
<td>7</td>
<td>49.6</td>
<td>22.51±3.12\textsuperscript{d}</td>
<td>1.5±1.7\textsuperscript{NS}</td>
<td>6.0</td>
</tr>
<tr>
<td>Combination</td>
<td>150+40</td>
<td>Day 1-14 + 1, 8</td>
<td>7.00±1.02\textsuperscript{c}</td>
<td>7</td>
<td>60.0</td>
<td>24.27±1.68\textsuperscript{c}</td>
<td>1.1±0.8\textsuperscript{NS}</td>
<td>4.5</td>
</tr>
</tbody>
</table>

RTV: Relative tumor volume on day 29; TGI: tumor growth-inhibition ratio on day 29; RTV5: the period RTV takes to reach a value of 5; BWC: body weight change from day 0 to day 29; \( ^{a}p<0.05 \) vs. Control using two-sided Aspin-Welch \( t \)-test; \( ^{b}p<0.01 \) by closed testing procedure using two-sided Aspin-Welch \( t \)-test; \( ^{c} \)not significant \( (p>0.05) \) vs. CPT-11 alone; \( ^{d}p<0.001 \) vs. Control using log-rank test; \( \text{NS} \): not significant \( (p>0.05) \) vs. Control using two-sided Aspin-Welch \( t \)-test.

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Figure 3. Relative tumor volume (RTV) of DLD-1 human colorectal tumor (a) and body weight change of DLD-1-bearing nude mice (b). Mice were randomized according to tumor volumes on day 0. Mice were treated with the 0.5% hydroxypropyl methylcellulose or TAS-102 (150 mg/kg) administered orally twice daily from days 1 to 14. Irinotecan hydrochloride (CPT-11) (40 mg/kg) was administered intravenously alone or in combination with TAS-102 on days 1 and 8. The tumor volume and body weight were measured twice a week. The values indicate the mean ±SD \( (n=7) \). The horizontal dotted line indicates an RTV of 5.

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combination group was less than 5%, this combination was deemed tolerable (Table V).

Discussion

In the present study, combination therapy consisting of TAS-102 and CPT-11 was shown to be significantly effective against colorectal cancer (KM12C, KM12C/5-FU, DLD-1/5-FU) and gastric cancer (SC-2) xenografts implanted into nude mice, when evaluated according to tumor-growth inhibition and the tumor growth delay period, compared to both monotherapies.

TAS-102 alone was confirmed to be active against two 5-FU-resistant colorectal tumor cell lines (KM12C/5-FU and DLD-1/5-FU), and its antitumor activity was not inferior to that against the parent cell line in terms not only of tumor-growth inhibition, but also the growth delay period (Figures 2 and 3). As these two 5-FU-resistant cell lines were established using long-term exposure to 5-FU, these cell lines might mimic refractory tumors after 5-FU-based chemotherapy. 5-FU reportedly exerts its antitumor activity by inhibiting thymidylate synthase through phosphorylated 5-FU and by inducing RNA dysfunction when F-UTP is incorporated into RNA (28, 29). The mechanisms by which DLD-1/5-FU and
KM12C/5-FU exhibit 5-FU resistance reportedly involve a decrease in RNA incorporation into RNA (14) and thymidylate synthase overexpression (23), respectively. On the other hand, the main antitumor mechanism of TAS-102 is thought to be the incorporation of the triphosphate form of FTD into DNA when it is administered according to clinical schedules (7-9). Thus the mechanism of TAS-102 differs from that of 5-FU, possibly explaining the lack of cross-resistance of TAS-102 with 5-FU.

The body weight loss of nude mice bearing KM12C in the combination-treated group was lower than that in the control group in both monotherapy-treated groups. The body weight loss induced by a colon-26 mouse tumor, which induces...

Table V. Antitumor activity of treatment with TAS-102 and irinotecan hydrochloride (CPT-11) and body weight changes in mice implanted with SC-2 human gastric tumor.

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg/kg/day)</th>
<th>Schedule</th>
<th>RTV (mean±SD)</th>
<th>n</th>
<th>TGI (%)</th>
<th>RTV5 (days)</th>
<th>BWC (mean±SD, g)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>–</td>
<td>–</td>
<td>48.27±5.17</td>
<td>6</td>
<td>0</td>
<td>8.48±0.23</td>
<td>1.0±1.8</td>
<td>3.7</td>
</tr>
<tr>
<td>TAS-102</td>
<td>150</td>
<td>Day 1-14</td>
<td>12.10±1.62a</td>
<td>6</td>
<td>74.9</td>
<td>15.24±1.05c</td>
<td>0.2±1.8NS</td>
<td>0.5</td>
</tr>
<tr>
<td>CPT-11</td>
<td>40</td>
<td>Day 1, 8</td>
<td>19.65±3.86a</td>
<td>6</td>
<td>59.3</td>
<td>16.11±1.11c</td>
<td>2.0±1.3NS</td>
<td>8.2</td>
</tr>
<tr>
<td>Combination</td>
<td>150 + 40</td>
<td>Day 1-14 + 1, 8</td>
<td>2.58±0.41ab</td>
<td>6</td>
<td>94.7</td>
<td>&gt;29.00d</td>
<td>1.3±1.4NS</td>
<td>5.0</td>
</tr>
</tbody>
</table>

RTV: Relative tumor volume on day 29; TGI: tumor growth-inhibition ratio on day 29; RTV5: the period RTV takes to reach a value of 5; BWC: body weight change from day 0 to day 29. a p<0.01 vs. Control using two-sided Aspin-Welch t-test; b p<0.01 by closed testing procedure using two-sided Aspin-Welch t-test; c p<0.001 vs. Control using log-rank test; d p<0.001 vs. either monotherapy using log-rank test; NS: not significant (p>0.05) vs. Control using two-sided Aspin-Welch t-test.

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Figure 5. Relative tumor volume (RTV) of SC-2 human colorectal tumor (a) and body weight change of SC-2-bearing nude mice (b). Mice were randomized according to tumor volumes on day 0. Mice were treated with the 0.5% hydroxypropyl methylcellulose or TAS-102 (150 mg/kg) administered orally twice daily from days 1 to 14. Irinotecan hydrochloride (CPT-11) (40 mg/kg) was administered intravenously alone or in combination with TAS-102 on days 1 and 8. The tumor volume and body weight were measured twice a week. The values indicate the mean ±SD (n=7). The horizontal dotted line indicates an RTV of 5.
severe tumor cachexia, was reportedly recovered after surgical removal of the tumor (32). As the body weight of nude mice bearing KM12C decreased according to tumor growth, KM12C appeared to induce tumor cachexia. As the combination therapy using TAS-102 and CPT-11 almost completely suppressed tumor growth, body weight loss might have been prevented in the combination-treated group.

The most frequently observed toxicities were gastrointestinal and hematological in phase II and III clinical studies of TAS-102 (16, 17). The incidence of diarrhea and nausea in phase II study was significantly higher vs. that in a placebo-treated group (p-values of 0.037 and <0.0001, respectively), but the incidences of grade 3/4 diarrhea and nausea were 6% and 4%, respectively. Grade 3/4 toxicities associated with CPT-11 were granulocytopenia and delayed diarrhea (33). The mechanism of both TAS-102 and CPT-11 is targeting of DNA, and myelosuppression and diarrhea are shared toxicities. Therefore, these toxicities are likely to be a concern under this combination therapy. In this study, severe toxicity was not observed in the group treated with this combination, as judged based on BWC and the absence of drug-related deaths. However, blood cell counts and intestinal symptoms were not examined. Careful monitoring of the overall side-effects, including hematological and gastrointestinal toxicities, are required to evaluate the efficacy of this combination therapy in clinical studies.

In conclusion, we demonstrated that combination therapy using TAS-102 and CPT-11 is active against colorectal and gastric cancer, even for 5-FU-resistant colorectal tumors. A clinical study of this combination therapy is now ongoing (JapicCTI-132099), and the results are expected to be soon reported.

References


