Irinotecan in metastatic colorectal cancer: dose intensification and combination with new agents, including biological response modifiers

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Phase I/II studies suggest that the combination of irinotecan with capcitabine is feasible and has promising activity. Diarrhea and neutropenia are dose limiting. Overall response rates (RRs) in the 40% to 60% range are seen from preliminary data. Work in progress is assessing the combination of irinotecan with UFT/leucovorin (LV). The use of irinotecan together with raltitrexed is also being investigated, as is its combination with oxaliplatin. Two phase II studies of irinotecan plus oxaliplatin in second-line patients report median survivals of 11–12 months. It seems possible to safely escalate the dose of single-agent irinotecan to 500 mg/m² in patients showing good tolerance of the drug. Irinotecan can be used in combination with LV/5FU2 at doses up to 260 mg/m², especially if only one bolus of 5-fluorouracil (5-FU) is given. Control of tumor growth is achieved in 90% of patients. Preliminary data suggest that regimens based on 5-FU/LV and irinotecan can safely be combined with the anti-epidermal growth factor receptor (EGFR) antibody cetuximab. In patients with EGFR-positive tumors, this may prove an effective means of increasing response rate or combating treatment resistance. Following evidence that COX-2 inhibition can slow progression in familial adenomatous polyposis, celecoxib is to be studied in metastatic colorectal cancer (CRC). In vitro, the cyclin-dependent kinase inhibitor flavopiridol enhances the induction of apoptosis by chemotherapy. Clinically, it can safely be administered with irinotecan, and studies in CRC are planned.

Introduction

The use of 5-fluorouracil/leucovorin (5-FU/LV) with irinotecan has proved one of the most active combinations in colorectal cancer (CRC), as is evidenced elsewhere in this Supplement [1, 2]. There is interest in determining whether the i.v. 5-FU/LV component of the combination can be replaced by an oral fluoropyrimidine such as capcitabine or uracil/tegafur (UFT)/LV, and whether irinotecan itself can be given orally.

Capecitabine and irinotecan in combination

The mechanism of action of the fluoropyrimidine prodrugs such as capcitabine differs from that of irinotecan. The toxicities of the two types of agent are at least partially non-overlapping, providing a further rationale for their use in combination.

Two randomized studies have shown that capcitabine can achieve the equivalent 12.9 month survival time to the Mayo Clinic bolus 5-FU/LV regimen, while proving significantly more active in terms of response rate (RRs 26% versus 13%, P < 0.001) (Table 1)[3]. In terms of toxicity, capcitabine was also superior to bolus 5-FU/LV, being associated with significantly less neutropenia, diarrhea, stomatitis, emesis and alopecia. The rate of hand-foot syndrome, however, was greater with capcitabine than with bolus 5-FU/LV [4].

Following these trials, and supported by in vitro evidence of synergy between capcitabine and irinotecan in xenograft models, an extended phase I study was conducted at the West German Cancer Center. Capcitabine given twice a day on days 1–14 and 22–36 was combined with weekly irinotecan administered according to the weekly ×6 Arbeitsgemeinschaft Internische Onkologie (AIO) schedule every 49 days [5].

At the first dose level, capcitabine was administered at 1000 mg/m² together with irinotecan 70 mg/m², increasing at the second level to capcitabine 1250 mg/m² plus irinotecan 70 mg/m², and at level three to capcitabine 1250 mg/m² plus irinotecan 80 mg/m². The third level proved to be the maximum tolerated dose (MTD), with diarrhea and neutropenia the dose-limiting toxicities (DLTs).

The study was extended at the second dose level to include 15 patients. In the first cycle, National Cancer Institute Common Toxicity Criteria (NCI CTC) grade 3 or 4 diarrhea was observed in five (33%) and neutropenia in two (13%) patients. This incidence of 33% [95% confidence interval (CI) 12% to 62%] DLTs proved unacceptable. Further patients were recruited at dose level 2 (capcitabine 1000 mg/m², irinotecan 70 mg/m²) until a total of 16 patients had been treated. At this dose combination, toxicity was considered acceptable. The main adverse event after multiple cycles was diarrhea, which occurred at grade ≥3 in four out of 16
patients (25%). This incidence is similar to that seen with the combination of irinotecan with infusional 5-FU/LV.

The efficacy of the capecitabine 1000 mg/m² plus irinotecan 70 mg/m² regimen appears promising, with a RR of 38% (95% CI 21% to 58%) in the 29 patients evaluable.

The Italian group of Cassata et al. [6] has also investigated the combination of irinotecan with capecitabine. In a randomized phase II study, first-line patients received capecitabine 1250 mg/m² twice daily on days 2–14 (later reduced to 1000 mg/m²) plus irinotecan on one of two schedules: either 300 mg/m² (later reduced to 240 mg/m²) every 22 days or 150 mg/m² (later reduced to 120 mg/m²) on days 1 and 8.

Of the 102 patients enrolled, preliminary results are available for 47 [6]. The major toxicity was grade 3/4 diarrhea, which occurred with an incidence of ~21% on the 3 week schedule and 17% in the day 1 and 8 schedule. Grade 3/4 hand-foot syndrome occurred in ~17% of patients in the every 3 week schedule but did not affect any of the patients administered irinotecan on days 1 and 8. RRs were again encouraging: for both schedules the RR (in 34 evaluable patients) was 62%.

In a third first-line trial, Kerr [7] administered capecitabine 1000 mg/m² twice a day on days 1–14, with irinotecan 300 mg/m² (reduced to 250 mg/m²) on day 1, every 3 weeks. In this ongoing phase II study, the RR in an initial 26 patients is reported to be 55%.

**UFT/LV and irinotecan**

In two large randomized trials UFT/LV showed an overall survival of 12.2 and 12.4 months, similar to that achieved with bolus 5-FU/LV (Table 2) [8]. Furthermore, no significant difference in remission rate was seen between UFT/LV and bolus 5-FU/LV.

The risk of hand-foot syndrome with UFT/LV is low and contrasts with the 60% rate reported in patients treated with capecitabine. These data should encourage further work on the combination of UFT/LV with irinotecan. Indeed, a Spanish group has recently published in abstract a first-line phase II study of UFT/LV three times daily (UFT 200 mg/m², LV 45 mg/m²) on days 1–21, together with irinotecan 125 mg/m² on days 1, 8 and 15, every 29 days [9]. The RR in 30 patients was 33% and the time to progression was 7 months.

The oral administration of irinotecan has been investigated in two phase I trials [10, 11]. In both, irinotecan was given once daily, at either 30 mg/m² for 14 days every 3 weeks, or 80 mg/m² for 5 days every 3 weeks. In the 30 mg/m² trial, the DLTs were diarrhea and vomiting and on the 80 mg/m² for 5 days schedule, neutropenia and gastrointestinal toxicity.

The combination of an oral irinotecan with an oral fluoropyrimidine-based prodrug should be considered a possibility for the future.

**Irinotecan plus oxaliplatin or raltitrexed**

A second major avenue for the development of combination therapy is to consider whether irinotecan can be combined with other newer agents.

In two ongoing phase II trials, first-line patients are receiving raltitrexed 3 mg/m² plus irinotecan 350 mg/m² every 22 days [12, 13]. Diarrhea, nausea and vomiting, asthenia and neutropenia are the DLTs. Promising RRs of 30% to 40% are cited in preliminary reports (Table 3).

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**Table 1.** Fluoropyrimidine-based ‘prodrugs’: capecitabine versus bolus 5-FU/LV (Mayo Clinic) [3]

<table>
<thead>
<tr>
<th></th>
<th>Capcitabine (n = 603)</th>
<th>5-FU/LV (n = 604)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate (%)</td>
<td>22.4</td>
<td>13.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival (months)</td>
<td>12.9</td>
<td>12.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

5-FU, 5-fluorouracil; LV, leucovorin; NS, not significant.

**Table 2.** Fluoropyrimidine-based ‘prodrugs’: UFT/LV versus bolus 5-FU/LV (Mayo Clinic) [8]

<table>
<thead>
<tr>
<th></th>
<th>UFT/LV (n = 409)</th>
<th>5-FU/LV (n = 407)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response rate (%)</td>
<td>12</td>
<td>15</td>
<td>0.232</td>
</tr>
<tr>
<td>TTP (months) (95% CI)</td>
<td>3.5 (3.0–4.4)</td>
<td>3.8 (3.6–5.0)</td>
<td>0.011</td>
</tr>
<tr>
<td>Survival (months) (95% CI)</td>
<td>12.4 (11.1–13.6)</td>
<td>13.4 (11.6–15.4)</td>
<td>0.391</td>
</tr>
</tbody>
</table>

UFT, uracil/tegafur; LV, leucovorin; 5-FU, 5-fluorouracil; TTP, time to progression.

**Table 3.** Raltitrexed combined with irinotecan: phase II studies in first-line colorectal cancer [12, 13]

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Response rate (%) (95% CI)</th>
<th>Main toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raltitrexed 3 mg/m², irinotecan 350 mg/m², q22d [12]</td>
<td>72</td>
<td>40% (26–54)</td>
<td>Diarrhea, nausea and vomiting</td>
</tr>
<tr>
<td>Raltitrexed 3 mg/m², irinotecan 350 mg/m², q22d [13]</td>
<td>63</td>
<td>28% (11–45)</td>
<td>Diarrhea, asthenia, neutropenia, nausea and vomiting</td>
</tr>
</tbody>
</table>

aBoth trials are ongoing.

bFifty patients and 29 patients re-assessable for efficacy.

CI, confidence interval; q22d, every 22 days.
There have been two second-line phase II studies combining irinotecan 200 mg/m² every 22 days with oxaliplatin 85 mg/m² [14, 15]. These report RRs of 17% and 23%, and overall survival figures of 11–12 months (Table 4). In the first-line setting, Scheithauer et al. [16] have achieved a 16 month overall survival and a 44% RR in 46 patients given oxaliplatin 85 mg/m² plus irinotecan 175 mg/m² every 15 days, followed by second-line raltitrexed (Table 4).

### Dose intensification of irinotecan monotherapy and in combination with 5-FU/LV

Given the wide range of cytotoxic combinations reviewed, much attention will be focused on identifying groups of patients most likely to benefit from specific interventions. This is equally true of efforts directed at the dose intensification of irinotecan.

A dose–efficacy relationship has been demonstrated with irinotecan, and it is likely that a higher than conventional dose could be administered to selected patients proven to tolerate the drug well.

The first French phase I study of irinotecan in 1995 established that the DLTs were diarrhea and hematological toxicity. The recommended dose of irinotecan without loperamide was established as 350 mg/m² [17]. By administering high-dose loperamide, it was possible to increase the dose to 750 mg/m² before reaching the DLT of granulocytopenia. A dose of 600 mg/m² therefore appeared feasible.

Merrouche et al. [18] conducted a phase II study of every 3 weeks irinotecan monotherapy, in which first- and second-line performance status (WHO PS) 0–1 patients received either 500 or 600 mg/m² of the drug. The higher dose was associated with a 78% incidence of grade 3/4 neutropenia and a 50% incidence of diarrhea. However, the neutropenia rate was only 41% and that of diarrhea 24% in the 17 patients receiving irinotecan 500 mg/m² every 3 weeks.

More recently, Van Cutsem et al. [19] undertook a randomized phase II trial of three approaches to irinotecan therapy in a mixed group of first- and second-line patients. In the control arm, a fixed dose of irinotecan 350 mg/m² was given once every 3 weeks. In the escalation arm, the starting dose of 250 mg/m² was increased to 350 mg/m², and then 500 mg/m² if no grade 2 or greater toxicities occurred. In the third arm, patients were assigned a priori to a dose of 250, 350 or 500 mg/m² depending on baseline hematological risk factors, organ involvement, creatinine level and PS (WHO).

The escalation protocol proved the most effective means of achieving high doses of irinotecan and was judged to have the most favorable benefit/risk ratio. In this group, 31% of patients could be escalated to irinotecan 500 mg/m² without an unacceptably high incidence of neutropenia or diarrhea, without granulocyte colony-stimulating factor (G-CSF) (Table 5). A median overall survival of 12.1 months was achieved.

In a second study using dose escalation, Ychou et al. [20] achieved a RR of 36% in 31 of 49 patients to whom 500 mg/m² could be delivered. The overall median survival in the 49 patients accrued to the study was 19.5 months. There were no major toxicity problems.

### High-dose irinotecan in combination

A phase I trial established that the recommended dose of irinotecan in combination with the de Gramont LV5FU2 regimen was 180 mg/m² [21]. At this level, there were no major toxicities, or requirements for dose reduction or delay. However, in the phase I study it was possible to increase the dose to 300 mg/m², but three of four patients experienced delays and/or reductions without major toxicities and this dose was defined as the MTD.

A multicenter phase II trial was therefore undertaken in which irinotecan 260 mg/m² was given to first-line metastatic CRC patients together with either the standard LV5FU2 regimen (first 25 patients) or a simplified schedule in which the 5-FU bolus was given on day 1 only (30 patients) (Figure 1) [22, 23]. The aim of the modification in schedule was to reduce hematological toxicity. G-CSF was recommended if there was grade ≥2 neutropenia at day 15, or if there had been febrile neutropenia in the previous cycle.

Preliminary data are available for 44 patients. The median age was 56 years, 45% were PS 0 and 55% PS 1. The median number of organs involved was two. Thirty per cent had received prior chemotherapy, 7% radiotherapy and 7% metastatectomy.

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### Table 4. Oxaliplatin combined with irinotecan: randomized phase II studies (first and second line) [14–16]

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Response rate (%) (95% CI)</th>
<th>Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second-line CRC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin 85 mg/m², irinotecan 200 mg/m², q22d [14]</td>
<td>30</td>
<td>23 (10–42)</td>
<td>12.3</td>
</tr>
<tr>
<td>Oxaliplatin 85 mg/m², irinotecan 200 mg/m², q22d [15]</td>
<td>33</td>
<td>17 (6–36)</td>
<td>11</td>
</tr>
<tr>
<td><strong>First-line CRC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin 85 mg/m², irinotecan 175 mg/m², q15d [16]</td>
<td>46</td>
<td>43.5 (29.0–58.9)</td>
<td>16</td>
</tr>
</tbody>
</table>

q15d, every 15 days; q22d, every 22 days.
The simplified schedule showed that neutropenia seemed to be somewhat reduced compared with standard LV5FU2: the proportion of cycles complicated by grade 4 neutropenia fell from 18% to 12% and the number of patients who had at least one episode of febrile neutropenia fell from 4% to 0%. Grade 3 diarrhea occurred in 16% of standard LV5FU2 patients and in 10% of those receiving the simplified regimen.

Among 42 evaluable patients, the RR was 54%, with a further 36% experiencing stable disease. The suggestion that a regimen combining high-dose irinotecan with 5-FU/LV can achieve disease control in 90% of patients is promising. Only 5% of patients had progressive disease at the first evaluation.

Higher doses may be particularly appropriate in maximizing the benefits of irinotecan in patients with good PS and organ function who require down-staging of liver metastases with a view to resection. A two-step increase of the dose of irinotecan could be the best way to intensify combined chemotherapy, as was the case in previous monotherapy studies.

### Irinotecan and biological response modifiers

Even if chemotherapy can be tailored to tumor characteristics such as thymidilate synthase level, it is clear that many patients will continue to be unresponsive to conventional drugs. Along with new cytotoxic combinations involving irinotecan, and with dose intensification, there is therefore great interest in combining the drug with agents targeted specifically against molecular mechanisms critical in neoplastic disease. Among these agents are the epidermal growth factor receptor (EGFR) antagonists.

The EGFR autocrine pathway contributes to a number of processes central to the development of cancer. These include cell proliferation, apoptosis, angiogenesis and metastatic spread [24]. Activation of the transforming growth factor \( \alpha \)–EGFR pathway can be attributed to several mechanisms. Overexpression of EGFR, increased concentration of ligands, decreased phosphatase activity, decreased receptor turnover and mutations such as EGFRvIII (which has an activated tyrosine kinase domain that stimulates cell proliferation independently of ligand activation) may all play a part [25].

Inhibition of EGFR signaling can be achieved either by using an antibody such as IMC-C225 (cetuximab) or by small molecules (e.g. Iressa or OSI-774) that bind (reversibly or irreversibly) to the ATP domain of tyrosine kinase, so inhibiting phosphorylation [26, 27].

### Cetuximab and irinotecan

There is clear preclinical rationale for the use of IMC-225 (cetuximab) in combination with chemotherapy agents such as irinotecan. In the mouse xenograft HT-29 model of human CRC, for example, growth of tumor while on irinotecan could be reversed by combining irinotecan with cetuximab, but not by cetuximab alone [28].

**Table 5. Approaches to high-dose irinotecan therapy [19]**

<table>
<thead>
<tr>
<th>No. patients receiving 50 mg/m²</th>
<th>Fixed dose control (n = 36)</th>
<th>Escalation (n = 62)</th>
<th>Risk-factor related (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3–4 toxicity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>47</td>
<td>30</td>
<td>44</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>6</td>
<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival (months)</td>
<td>12.5</td>
<td>12.1</td>
<td>10.9</td>
</tr>
</tbody>
</table>

**Figure 1. Treatment design for a high-dose irinotecan study [21, 22].**

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In CRC cell lines resistant to SN-38 and the fluoropyrimidines, there is significant expression of EGFR, which is highly phosphorylated and activated [29]. When signaling is inhibited by blocking tyrosine kinase function, resistance to SN-38 cytotoxicity is completely reversed. Early clinical data suggest this phenomenon could be important for the further development of irinotecan combinations.

Following preclinical work suggesting likely efficacy, Saltz et al. [30] investigated a population of 5-FU- and irinotecan-refractory CRC patients, administering cetuximab (at a loading dose of 400 mg/m² and 250 mg/m² weekly thereafter) plus irinotecan at the dose and schedule the patients had previously received and progressed on. Of the patients screened, 72% proved EGFR-positive on immunohistochemistry and were offered treatment. A total of 121 patients with documented 5-FU and irinotecan failure received therapy. Their median age was 56 years, with a Karnofsky PS 90. Of the 120 evaluable patients, 19% achieved a partial remission, with a median duration of 182 days.

Currently, three German centers (Dresden, Hannover and Ulm) are conducting a related phase I study [31]. Chemotherapy-naive patients receiving weekly infusional 5-FU/LV (the AIO regimen using either 1500 or 2000 mg/m² 5-FU) combined with weekly irinotecan 80 mg/m² receive in addition a loading dose of cetuximab 400 mg/m² on day 1 followed by weekly maintenance 250 mg/m² of the antibody. Approximately 70% of patients included were positive for EGFR.

Among the 21 patients enrolled (15 of whom have received the high dose of 5-FU 2000 mg/m²), the DLTs in this context were primarily neutropenia, diarrhea and folliculitis. An acniform rash appears to be a typical side effect of cetuximab. However, it is generally reversible, even with continued treatment. Among nine evaluable patients, there has been one complete response, five partial responses and three cases of stable disease.

In a more recent study, the irreversible tyrosine kinase inhibitor EBK 569 is being given to first-line CRC patients treated with the FOLFIRI regimen combining 5-FU/LV with irinotecan 180 mg/m².

**COX-2 inhibitors and chemoprevention**

Epidemiological studies have documented a 40% to 50% reduction in the incidence of CRC among people taking non-steroidal anti-inflammatory drugs. This is believed to relate to the inhibition of COX enzyme activity. COX-2 overexpression is associated with the progression from adenoma to adenocarcinoma [32].

Steinbach et al. [33] have demonstrated that use of 400 mg/m² twice daily of the selective COX-2 inhibitor celecoxib is associated with a significant reduction compared with placebo in progression of familial adenomatous polyposis. It is likely that this effect is mediated by a range of mechanisms affecting apoptosis, angiogenesis and cell cycle regulation [32].

Preclinical work in various models provides a rationale for the use of celecoxib in combination with existing therapies. In 7,12-dimethylbenzanthracene (DMBA)-induced mammary carcinoma in rats, the antibody adds to the effectiveness of hormone therapy; in mouse sarcoma, COX-2 inhibitors act as radiation sensitizers; and in the human CRC HT-29 xenograft model it has been demonstrated that celecoxib potentiates the effect of irinotecan and the effect of 5-FU on tumor growth.

With this background, the EORTC is planning a study in metastatic CRC in which patients will be randomized initially to either infusional 5-FU plus irinotecan according to the schedule of Douillard [32a] or to Kerr et al.’s [7] schedule of capecitabine plus irinotecan. This will be followed by a second randomization to either control or celecoxib 400 mg/m² twice daily.

**Developing flavopiridol in combination**

Resistance to standard chemotherapy represents the failure of therapy to induce apoptosis. This draws attention to the molecules that are critical to this process.

Molecular checkpoints guard genetic fidelity by arresting cells at specific points in the cell cycle. Cell cycle checkpoints at the G₁/S and G₂/M interface are tightly regulated by a broad range of proteins, including cyclin dependent kinases (CDKs). For every CDK there is a CDK inhibitor [34, 35].

Work has been undertaken with the small molecule flavopiridol, which acts as a pan-CDK inhibitor (by binding to the ATP binding site) [36]. Flavopiridol was identified by NCI screening as a means of inducing cell cycle arrest. The agent derives initially from *Dysoxylum binectariferum*, a plant native to India.

Flavopiridol appears to have considerable potential as means of reversing chemotherapy resistance through induction of apoptosis.

Proof of principle was obtained by demonstrating that flavopiridol enhanced cell kill by mitomycin C in a human gastric cancer cell line [37]. This was followed by demonstration that a similar effect was achieved when paclitaxel and flavopiridol are given sequentially [38]. The sequential use of docetaxel and flavopiridol has also shown substantial effects in MKN 74 gastric cancer xenografts (M. Mowant, C. Rizzo, F. Sirotnak, Y. She and G.K. Schwartz, submitted).

In the HCT-116 p21-intact colon tumor xenograft model in the nude mouse, which is normally refractory to irinotecan, use of the drug followed by flavopiridol achieves inhibition of tumor growth [39]. When irinotecan is followed 7 h later by flavopiridol, inhibition of tumor growth approaches 90% and a complete response is achieved in approximately one-third of animals (Table 6). This effect appears to be mediated by activation of caspase-3, which cannot be achieved by chemotherapy alone.

In an attempt to translate these findings into the clinic, a phase I study was undertaken in which patients with advanced solid tumors received weekly irinotecan 100 mg/m² followed 7 h later by flavopiridol 10, 30, 50, 60 or 70 mg/m² over 1 h every 4 weeks, with 2 weeks rest between cycles [40].

The 33 patients entered to date (23 of whom had already been exposed to irinotecan) have a median age of 58, with 24 patients male, and a median Karnofsky PS of 90. Nineteen patients had colon cancer.

It was possible to escalate the weekly flavopiridol dose to 60 mg/m² with irinotecan at 100 mg/m² before hematological toxicity became apparent. It may also be possible to administer flavopiridol 60 mg/m² with irinotecan 125 mg/m² in a less heavily treated
Table 6. Tumor regressions in HCT-116 colon cancer xenografts treated with irinotecan and flavopiridol [39]

<table>
<thead>
<tr>
<th>Treatment*</th>
<th>Decrease in tumor volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>10</td>
</tr>
<tr>
<td>Irinotecan; flavopiridol after 4 h</td>
<td>10</td>
</tr>
<tr>
<td>Irinotecan; flavopiridol after 7 h</td>
<td>10</td>
</tr>
<tr>
<td>Irinotecan; flavopiridol after 16 h</td>
<td>7</td>
</tr>
</tbody>
</table>

*Irinotecan 100 mg/kg; flavopiridol 11 mg/kg; irinotecan (100 mg/kg) + flavopiridol 3 mg/kg, i.p., administered twice a week for a total of five injections.

References

19. Van Cutsem E, Dirix L, Van Laethem J-L et al. A randomized phase II trial of three different regimens of irinotecan (CPT11): a fixed dose of 350mg/m² (A), or an individual dose optimisation (B) or a risk factor optimisation (C) in patients (pts) with metastatic colorectal cancer (MCRC) previously treated with 5FU. Proc Am Soc Clin Oncol 2000; 19: 244a (Abstr 946).


