A feasibility, pharmacokinetic and frequency-escalation trial of intraperitoneal chemotherapy in high risk gastrointestinal tract cancer


Abstract

Aims: To assess the feasibility, pharmacokinetics and maximum tolerable frequency (MTF) of intraperitoneal (IP) 5-fluorouracil and leucovorin (FU/LV) added, as a regional boost, to intravenous chemotherapy after resection of gastrointestinal cancer.

Methods: Fifty-three patients were recruited following gastrointestinal cancer resection (43 colon; 10 stomach/small bowel) with serosal involvement. Peritoneal ports were implanted and IP fluid distribution evaluated ultrasonically. Twelve patients were studied for pharmacokinetics; 44 (41 evaluable) for MTF. Treatment was weekly intravenous bolus FU/LV for 6 months; to this was added IP FU/LV (400/20 mg/m² in 1500 ml 4% icodextrin) with increasing frequency from 4 weekly to 1 weekly in four successive cohorts.

Results: Peritoneal fluid distribution was excellent. Intraperitoneal FU exposure (AUC) after IP treatment was >1000-fold plasma AUC after IP treatment (regional pharmacokinetic advantage), and >100-fold plasma AUC after intravenous treatment (regional therapeutic advantage). IP therapy was well tolerated if given every 4, 3 or 2 weeks, but not weekly: 11/13, 7/8, 10/13 and 0/7 patients respectively completed treatment without IP modification in these cohorts. Problems with peritoneal access occurred in 20% of patients.

Conclusion: Adding fortnightly IP FU/LV to a standard intravenous regimen is safe, tolerable and provides high peritoneal FU exposure. More reliable peritoneal access is needed to improve the feasibility of this otherwise promising therapeutic approach.

Keywords: Colonic neoplasms; Stomach neoplasms; Fluorouracil; Leucovorin; Intraperitoneal drug therapy

Introduction

Serosal involvement in gastrointestinal cancer

For most gastrointestinal cancers, serosal involvement is common. It is an independent predictor of poor outcome in operable colon7 or stomach8 cancer. Tumour cells are frequently detectable in peritoneal washings at the time of apparently curative surgery for colon,3 stomach3,4 or pancreatic5 cancer, in all cases correlating with risk of relapse. Once established, peritoneal metastases carry a poor prognosis and cause major symptoms during terminal illness, but are relatively insensitive to standard palliative chemotherapy.6,7 For all these reasons, interrupting peritoneal spread and preventing peritoneal relapse are important therapeutic goals, and to this end several groups have explored the administration of anticancer drugs directly into the peritoneal cavity. Approaches have included intraoperative instillation of hyperthermic drug solution, brief postoperative drug administration, or repeated dosing over several months.
Intraperitoneal (IP) therapy

The use of IP therapy to eradicate free carcinoma cells or peritoneal surface micrometastases is most attractive for diseases which are confined to the peritoneum. In pseudomyxoma peritonei, radical surgery with hyperthermic IP chemotherapy gives promising results, although randomised data are lacking. In ovarian cancer, three large randomised trials have provided evidence of benefits of IP therapy.

However, for the common gastrointestinal cancers, the status of IP therapy is uncertain. Adjuvant IP therapy studies in gastric cancer have been promising but inconclusive. In operable colon cancer, an early trial in just 66 patients, comparing a year of fluorouracil (FU) by IP or intravenous (IV) administration, showed no difference in overall survival but a marked reduction in peritoneal recurrences after IP therapy. More recently, a trial of brief (6 days) IP FU alone was negative, however two randomised trials investigating 6 months of adjuvant IV plus IP FU/leucovorin (FU/LV) showed significant survival benefits compared with no adjuvant treatment or IV FU/levamisole. These investigations have not led to further major trials or changes of practice: their results, although promising, were inconclusive; IP drug administration is daunting for oncologists and patients; and, perhaps most importantly, recent progress in systemic adjuvant drug therapy lessened the imperative to seek progress through regional drug techniques. However, as pilot data they provide support for the concept of supplementing adjuvant therapy, even optimised, modern adjuvant therapy, with an intraperitoneal “boost”.

IP therapy presents some practical and pharmacological challenges. One group reported a pilot study using continuous ambulatory peritoneal dialysis with FU in the dialysis fluid. Steady-state peritoneal FU levels 1000-fold plasma levels were achieved, but a high drop-out rate was encountered due to toxicities and complications of the administration system. Studies with repeated-dose IP mitoxantrone identified the problem of chemotherapy-induced peritoneal adhesions resulting in loculation of IP administered drugs (F. Zoetmulder, Netherlands Cancer Institute). Others identified the potential for IP drugs to affect the pharmacokinetics or toxicity of concurrent IV therapy.

We wished to develop an optimal IP regimen of FU/LV with the potential to use alongside systemic therapy for future studies in the adjuvant setting. Based on these previous data, we anticipated achieving high peritoneal drug concentrations, and reasoned that frequency or duration of exposure would be a more important variable than dose in determining both efficacy and toxicity. Therefore, rather than performing a conventional dose-escalation study, we elected to determine the maximum tolerable frequency of a fixed dose of IP therapy. For the peritoneal fluid vehicle we chose 4% icodextrin, an isotonic glucose polymer, as it has been shown to maintain a well-tolerated artificial ascites with constant volume for over 24 h and to reduce the formation of peritoneal adhesions induced by surgery or chemotherapy. These factors would help achieve the goals of prolonged and repeated drug exposure over the entire peritoneal surface.

Patients, materials and methods

This open design study was conducted in three consecutive phases: peritoneal access, pharmacokinetics and frequency-escalation. Patients were first fitted with a peritoneal catheter and assessed for IP fluid distribution. Those with successful catheter placement were eligible to participate in either or both of the subsequent phases.

At the time of the study, single-agent FU/LV therapy was accepted evidence-based adjuvant therapy for high-risk colorectal cancer. There was no single accepted adjuvant therapy for gastric cancer, but FU/LV was considered a reasonable option for high-risk patients. Therefore FU/LV, using a weekly intravenous bolus schedule, was the systemic therapy platform to which IP therapy would be added.

Patients

Patients were recruited at three hospitals. Research Ethics Committee approval and written informed consent were obtained.

Eligibility criteria were designed to select a homogeneous group to assess the tolerability (not efficacy) of postoperative IP therapy. Eligible patients had recently undergone resection of colonic, small bowel or gastric carcinoma, with serosal involvement (T4 colon, T3 stomach). Patients were required to have had complete macroscopic clearance of disease at surgery, or to have no more than 5 mm residual peritoneal seeding. In patients recruited more than 6 weeks after resection, weekly IV FU/LV was permitted during the screening period to avoid delaying adjuvant treatment.

IP catheter placement and fluid distribution assessments

Multi-side-holed silastic peritoneal catheters with subcutaneous injection ports (InfuKT™, Wescott, UK) were used. Under general anaesthesia, the catheter was inserted into the peritoneum and tunnelled subcutaneously to the injection port, secured over the lower ribs. The port and catheter were flushed with heparin solution (1000 units/ml).

The injection port was accessed 7–10 days later using a reverse-bevelled (Huber) needle (HC 2225™, Wescott, UK). 1500 ml sterile 4% icodextrin solution (Dexemel®, ML Laboratories PLC, UK) was instilled at room temperature under gravity or, in the event of slow flow, using a syringe and 3-way tap. Distribution of fluid within the peritoneal cavity was assessed 1–3 h later with ultrasound.
Pharmaceutical stability

The in vitro pharmaceutical stability of FU plus LV in 4% icodextrin solution was assessed over 6 days at 37 °C, 20 °C and 4 °C at concentrations representing dosing for body surface area in the range 1.0–2.5 m², all experiments in sextuplet, using HPLC (see below) for FU and LV. This confirmed >98% stability of both drugs for 4 days at 37 °C.

Pharmacokinetics

Separate informed consent was obtained, in 12 patients, for participation in a pharmacokinetic substudy. Sampling for pharmacokinetic (PK) analysis was performed on three occasions over a 4-week period. On weeks 1 and 2, patients received, in random order, IP FU/LV in 1500 ml normal saline and in 1500 ml 4% icodextrin solution. Doses were 400 mg/m² FU, 20 mg/m² LV. The IP instillations were timed over 40 min. Peritoneal fluid and blood samples were obtained at baseline; 40 min (end of instillation); and 1, 2, 4, 6, 8 and 20 h.

On week 4, patients received IV bolus FU/LV (400/20 mg/m²) over 5 min followed, 1 h later, by IP FU/LV (at the same doses) in 1500 ml 4% icodextrin. Blood samples were obtained at 0, 5, 10, 15 and 30 min from the start of the IV bolus injection. Blood/peritoneal sampling was thereafter as for weeks 1–2.

PK samples were collected into lithium heparin tubes on ice and separated within 15 min (at 1200 × g, 4 °C for 7 min); supernatants were stored at −40 °C pending analysis. FU was assayed by reverse-phase HPLC as described previously. Samples were run against standard curves (0.1–60 μg/ml) prepared in each matrix. IP samples collected at early time-points were diluted in drug-free IP fluid to ensure the measured concentration was within the standard range. Intra-assay variability was <10% at three concentrations (low, medium and high) in both plasma and IP fluid.

The pharmacokinetics of FU in plasma and IP fluid were determined using non-compartmental analysis (Kinetta version 4, Innaphase Corporation, Philadelphia, PA, USA). Area under the concentration–time curve (AUC) was calculated using the trapezoidal method to tm, and the logarithmic trapezoidal method to the last measured time point (t). Area under the moment curve (AUMC) was calculated from the product of concentration and time at each time point. AUC and AUMC were not extrapolated to infinity after IP dosing as, with continuing absorption of FU from the peritoneal cavity, it was not possible reliably to determine the elimination rate constant of FU in plasma. AUC after IV dosing was extrapolated to infinity using the elimination rate constant (k). The elimination half-life (t) was calculated as 0.693/k. The mean residence time (MRT) was calculated as AUMC/AUC. Bioavailability and IP/IV AUC ratios after IP FU were derived using IV AUC/C and 400/20 mg/m²; on IV bolus FU/LV was given at the same dose, 400/20 mg/m², on IV bolus FU/LV (at the same doses) in 1500 ml 4% icodextrin, infused over 20–40 min, starting 1 h after the IV bolus, and left to dwell without drainage.

Progression to the next cohort was considered when 6 patients had entered the current cohort and 4 of them had received at least 2 months of treatment. However, recruitment was not paused between cohorts, so more than 6 patients could be recruited to each cohort. The maximum tolerated frequency (MTF) was defined as the highest frequency of IP therapy tolerated by ≥75% of ≥6 patients.

Patients received IV bolus FU/LV weekly up to a maximum of 24 weeks. To this schedule was added IP therapy using a cohort design: once every 4 weeks (cohort 1); 3 weeks (cohort 2); 2 weeks (cohort 3) or once weekly (cohort 4). Thus the maximum total number of IP instillations over 24 weeks was 6 (cohort 1), 8 (cohort 2), 12 (cohort 3) and 24 (cohort 4). For patients who had participated in the PK study, the final PK treatment served as the first treatment of this frequency-escalation phase. All IP administrations comprised FU/LV 400/20 mg/m² in 1500 ml 4% icodextrin, infused over 20–40 min, starting 1 h after the IV bolus, and left to dwell without drainage.
persisted despite this, with dose frequency de-escalation or cessation of IP therapy.

**Results**

**IP catheter placement and fluid distribution**

Fifty-seven patients were registered, but four were withdrawn before IP catheter insertion (disease progression; toxicity during pre-study chemotherapy; anaesthetic contra-indication; patient choice).

Characteristics of the 53 patients entering the study are given in Table 1. Forty-four had successful IP catheter placement and went on to receive a total of 299 IP treatments. Two had catheters placed but were withdrawn for early disease progression before starting. However, seven patients had failures of IP access: three pain on accessing; two leakage; one port-site infection; one bowel perforation. The last, although serious, recovered fully and the patient completed standard IV adjuvant therapy off-trial. Of the 44 patients with initially successful IP access, three subsequently failed (one leakage; two clot/blockage). Thus, overall, 10/51 (20%) patients experienced a technical failure of IP access.

Distribution of IP fluid around the peritoneal cavity was better than expected. Baseline ultrasound assessment was performed in 42 patients and demonstrated adequate distribution in all but one case. An end-of-treatment ultrasound assessment was performed in 27 patients, after receiving between 5 and 13 (median 8) IP treatments, and all but one still had adequate IP fluid distribution.

**Pharmacokinetics**

Twelve patients entered the PK study. One was withdrawn because of failure of IP access. Among the remaining eleven, complete series of blood and peritoneal fluid samples were obtained on each study day from the numbers indicated in Table 2.

The PK data are summarised in Table 2 and Fig. 1. The systemic bioavailability of FU after IP administration was approximately 10%, was similar for both the fluid vehicles and did not change with repeated dosing. IP instillation of FU in either vehicle produced a high peritoneal fluid AUC, and peritoneal FU concentrations were high and sustained out to the 20 h sample. Differences between peritoneal PK parameters with the two vehicles did not reach $p < 0.01$ by ANOVA.

The regional pharmacokinetic advantage was 1119-fold for IP therapy using icodextrin and 817-fold using saline. The regional therapeutic advantage was 110-fold and 70-fold respectively, indicating that IP administration achieves substantially higher exposure of the peritoneal surface to FU than is possible with IV dosing.

**Maximum tolerable frequency**

Forty-four patients participated in the frequency-escalation study. Three developed leakage or blockage of the IP port during treatment and discontinued IP therapy, leaving 41 evaluable for MTF:

(1) Cohort 1 (IP therapy every 4 weeks): 13 patients. Two patients experienced abdominal pain attributed at least in part to IP therapy. However 6/13 patients required IV dose reduction because of side-effects temporally related to the higher-dose FU given during intervening weeks. The protocol was therefore modified, reducing the IV FU dose from 500 to 400 mg/m² for the remainder of the study.

(2) Cohort 2 (IP therapy every 3 weeks): 8 patients. Seven completed treatment without dose-reduction or delay. One declined further IP therapy after two IP treatments because of grade 2 abdominal pain. No other grade ≥2 toxicity occurred.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline patient characteristics</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Catheter placement study</td>
</tr>
<tr>
<td>Number entered</td>
<td>53</td>
</tr>
<tr>
<td>Sex male:female</td>
<td>36:17</td>
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<tr>
<td>Age: median (range)</td>
<td>60.9 (33.4–74.8)</td>
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<td>Primary cancer site (%)</td>
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<tr>
<td>Colon</td>
<td>43 (81)</td>
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<tr>
<td>Stomach</td>
<td>8 (15)</td>
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<tr>
<td>Small bowel</td>
<td>2 (4)</td>
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<tr>
<td>Cancer surgery (%)</td>
<td></td>
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<tr>
<td>Complete resection</td>
<td>49 (92)</td>
</tr>
<tr>
<td>Residual peritoneal seeding (&lt;5 mm)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Cancer stage (%)</td>
<td></td>
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<tr>
<td>Serosal involvement</td>
<td>53 (100)</td>
</tr>
<tr>
<td>Nodal involvement</td>
<td>39 (74)</td>
</tr>
<tr>
<td>Interval from surgery to study: median (range) days</td>
<td>57 (15–148)</td>
</tr>
</tbody>
</table>
(3) Cohort 3 (IP therapy every 2 weeks): initially 10 patients. Nine patients completed treatment without dose-reduction or delay. One patient stopped after 5 weeks with a combination of systemic FU toxicities and abdominal pain. After closure of cohort 4, a further three patients were treated in cohort 3, of whom 2 stopped early because of toxicity (abdominal pain; diarrhoea).

(4) Cohort 4 (IP therapy every week): 7 patients, none of whom completed treatment as planned. Four withdrew from IP treatment within the first 4 weeks because of toxicity, predominantly abdominal pain. Thereafter, the remaining three patients were electively de-escalated to IP therapy every 2 weeks (as per cohort 3), and all tolerated this regimen with no additional adjustments and went on to complete treatment. Thus IP treatment was tolerated by 87% of eight patients in cohort 2, 90% of 10 patients in cohort 3 (77% of 13

### Table 2
Pharmacokinetic data

<table>
<thead>
<tr>
<th>Treatment administered</th>
<th>IP FU/LV (saline vehicle)</th>
<th>IP FU/LV (icodextrin vehicle)</th>
<th>IV FU alone (PK from 0–1 h)</th>
<th>IV + IP FU (icodextrin vehicle)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 6</td>
<td>n = 9</td>
<td>n = 11</td>
<td>n = 11</td>
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<tr>
<td><strong>FU pharmacokinetics in plasma</strong></td>
<td></td>
<td></td>
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<tr>
<td>AUC_{0–} (μg/ml h)</td>
<td>0.97 ± 0.45</td>
<td>1.12 ± 0.61</td>
<td>—</td>
<td>11.53 ± 2.40</td>
</tr>
<tr>
<td>AUC_{0–} (μg/ml h)^a</td>
<td>—</td>
<td>—</td>
<td>10.58±2.42</td>
<td>—</td>
</tr>
<tr>
<td>AUMC_{0–} (μg/ml)</td>
<td>1.86 ± 1.00</td>
<td>2.47 ± 1.70</td>
<td>3.01 ± 0.79</td>
<td>5.95 ± 1.64</td>
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<tr>
<td>C_{MAX} (μg/ml)</td>
<td>0.49 ± 0.26</td>
<td>0.54 ± 0.31</td>
<td>37.1 ± 13.2</td>
<td>37.1 ± 13.2</td>
</tr>
<tr>
<td>T_{MAX} (h)</td>
<td>1.31 ± 0.51</td>
<td>1.51 ± 0.57</td>
<td>0.11 ± 0.04</td>
<td>0.11 ± 0.04</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>2.78 ± 1.00</td>
<td>2.71 ± 1.27</td>
<td>0.32 ± 0.06</td>
<td>0.80 ± 0.43</td>
</tr>
<tr>
<td>Clearance (L h^{-1}/m^2)</td>
<td>—</td>
<td>—</td>
<td>39.9±10.2</td>
<td>—</td>
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<tr>
<td>Bioavailability (%; AUC_{0–})</td>
<td>9.5 ± 3.9</td>
<td>11.1 ± 6.6</td>
<td>(100)</td>
<td>112.3 ± 5.6^b</td>
</tr>
<tr>
<td><strong>FU pharmacokinetics in peritoneal fluid</strong></td>
<td></td>
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<tr>
<td>AUC_{0–} (μg/ml h)</td>
<td>789 ± 477</td>
<td>1148 ± 567</td>
<td></td>
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<tr>
<td>C_{MAX} (μg/ml)</td>
<td>288 ± 93</td>
<td>388 ± 75</td>
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<tr>
<td>T_{MAX} (h)</td>
<td>0.94 ± 0.38</td>
<td>0.84 ± 0.52</td>
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<tr>
<td>MRT (h)</td>
<td>4.4 ± 3.8</td>
<td>3.2 ± 1.5</td>
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<tr>
<td><strong>FU pharmacokinetic ratios</strong></td>
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<tr>
<td>“Regional PK advantage”: <strong>AUC_{0–}</strong> peritoneal plasma (after IP dosing)</td>
<td>817 ± 287</td>
<td>1119 ± 871</td>
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<tr>
<td>“Regional therapeutic advantage”: peritoneal AUC (after IP dosing)</td>
<td>70 ± 46</td>
<td>110 ± 54</td>
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</table>

^a AUC after IV dosing was extrapolated to infinity from the 0–1 h data using the elimination half-life (t_{1/2}), which was calculated as 0.693/elimination rate constant (k_e).

^b Bioavailability after IV + IP dosing is >100% as it compares plasma AUC with plasma AUC after IV dosing alone.

Figure 1. Pharmacokinetics of FU in the plasma and in peritoneal fluid samples. The data points represent the mean ± SD. values for 6–11 patients as indicated in Table 2.
including the patients added at the end of the study), and 0% of seven patients in cohort 4. IP therapy every 2 weeks (cohort 3) is therefore the MTF of IP administration.

Discussion

Adjuvant drug therapy for the common gastrointestinal malignancies is developing rapidly. In colonic cancer, it is now known that adding oxaliplatin to standard fluoropyrimidines improves disease-free survival; in gastric cancer, perioperative combination therapy improves survival; likewise, adjuvant FU/LV after resection of pancreatic cancer. In each case, novel molecular-targeted agents are now under evaluation, and are likely to further improve results. However, although novel drugs are bringing welcome advances, they do not eliminate the need for other strategies. Patients with serosal involvement remain at high risk of recurrence; indeed, if the poor efficacy of systemic palliative chemotherapy for established peritoneal metastases is mirrored in the adjuvant setting, additional therapy aimed at peritoneal control will become ever-more important. It therefore remains relevant to consider whether regional therapy may add to the benefits of modern systemic treatment.

Pharmacokinetic benefits

We have confirmed previous reports that IP administration of FU/LV is tolerable, with a very large regional pharmacokinetic advantage. With the icodextrin vehicle, the mean peritoneal AUC was over 100-fold the plasma AUC produced by the same dose given intravenously (the “regional therapeutic advantage”). Thus a course of 8–12 IP administrations will provide peritoneal surfaces with a regional boost equivalent to around 25–40 times the total systemic FU exposure of a standard course of 24 intravenous doses of FU/LV. A major reservation of IP therapy is the question of distribution within the peritoneal cavity. The icodextrin vehicle used in this study maintains a stable artificial ascites for over 24 h. This, combined with our findings of prolonged IP pharmacokinetics (Fig. 1) and excellent fluid distribution even after multiple IP installations, provides some confidence that the apparent large regional therapeutic advantage of IP therapy is clinically achievable.

Problems with peritoneal access

The technical failure rate of the IP catheter/injection port system was high (20%). Problems included infection, leakage from the port/catheter connection, difficulty accessing deeply placed ports in obese patients and blockage or displacement of the catheter. In retrospect, the disadvantages of the subcutaneous injection-port system outweighed its benefits. Multi-side-holed catheters were chosen to facilitate withdrawal of peritoneal samples for the PK study, however when removed, it was apparent that the side-holes had provided a focus for clot formation. For future IP therapy studies, a simple end-hole transdermal cuffed catheter, such as the single-lumen Hickman line, may avoid some of these problems. However, peritoneal access remains a significant hurdle in the development of IP therapy and further studies are required to identify the optimum technique.

Future directions

The frequency escalation study demonstrated that, at the doses used, fortnightly IP FU/LV therapy is tolerable for 77% of patients. Therefore, 2–3 weekly IP dosing is recommended for future studies. In this study, a median of 51 days elapsed from surgery to the start of IP therapy; earlier treatment may be desirable to maximise efficacy, but some caution will be needed as we have not confirmed its tolerability. With systemic FU bioavailability of only around 10%, this IP schedule could potentially be added to other full-dose systemic regimens provided, as in this study, care is taken to avoid potential pharmacokinetic interaction between IP and IV components. With recent advances in adjuvant therapy, the systemic drug platform to which IP therapy might be added has moved on and, in future studies, will not be weekly IV bolus FU/LV. However, the information from the current study provides a useful basis on which to design future IP + IV regimens, and a strong rationale for doing so. For example, a trial design of “optimum standard systemic therapy ± intraperitoneal FU/LV” for high-risk colon cancer might currently use “FOLFOX” as its systemic therapy, although this may soon be superseded by newer regimens. Consideration may also be given to intraperitoneal administration of newer agents, where there is sound rationale for exploiting a regional pharmacokinetic advantage, e.g., if further dose/response relationship is expected above the range obtained with standard systemic dosing or where systemic toxicity is a particular concern. Oxaliplatin would be a good candidate for investigation: high regional concentrations could potentially overcome platinum-resistance, whilst avoiding the major systemic toxicities of neurotoxicity and myelotoxicity.

Conflict of interest

None

Acknowledgements

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