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COLORECTAL CARCINOMA is the second most common malignancy in the Western hemisphere, affecting approxi-

mately one in every 20 individuals. At least two thirds of patients presenting with colorectal cancer will undergo apparently curative resection, but despite this intention, 35–60% will subsequently die with liver metastases. As a consequence of the portal venous drainage system, colorectal cancers metastasise early to the liver. The liver may be the only site of spread in as many as 30–40% of patients with advanced disease [1, 2], but in less than 10% of such patients will surgical resection be possible. Thus, palliative chemotherapy is currently the standard treatment offered to most patients with hepatic metastatic colorectal cancer.

Unfortunately, this disease is relatively unresponsive to chemotherapy [3], despite an increasing understanding of drug mechanisms of action at the molecular level. To date, systemic 5-fluorouracil (5-FU) modulated with folinic acid (FA) is considered the optimum treatment for metastatic colorectal cancer, yielding response rates of 25–30% and median survival of around 12 months [4]. These disappointing results reflect, in part, the narrow therapeutic ratio of 5-FU and the presence of associated severe systemic side-effects limiting dose escalation. Regional chemotherapy affords an alternative method of cytotoxic drug administration which circumvents the constraints of systemic administration, while introducing the concept of targeted drug delivery to metastatic disease localised to specific components of the body [5].

Hepatic arterial infusion (HAI) of chemotherapy as a means of directly targeting hepatic metatatic colorectal cancer has actually been the subject of investigation dating back over 35 years [6], with the intention of improving both patient response and survival. However, despite such a protracted period of study, the place for this treatment modality in the management of this disease has still not been clearly defined. The reasons for this persisting uncertainty, the pros and cons of HAI chemotherapy, have been addressed in the preceding articles and it remains only to summarise these arguments.

FIRST THE CONS

It would be fair to say, given that phase III trial data for regional chemotherapy is limited to the randomisation of 654 patients only, that skeptics are justified in their plea for this treatment modality to remain within the confines of controlled clinical trials for the time being. Of note, no individual trial of regional versus systemic therapy has, to date, shown a statistically significant survival advantage for HAI therapy, neither did the recently published meta-analysis of these seven trials [7]. The two trials purporting to show survival benefit actually compared HAI chemotherapy with an *ad libidum* control group, in which many patients received no chemotherapy at all. They, therefore, simply provide further evidence to support the claim that some chemotherapy is better than no chemotherapy in the management of advanced colorectal cancer [4], and should not be used to vindicate regional chemotherapy as a standard treatment in this setting.

One of the main features which has sustained interest in regional drug administration is the potential to achieve higher tumour response rates over systemic therapy, and the meta-analysis confirmed these to be highly statistically significantly in favour of HAI infusion (overall, $P < 10^{-10}$); 41% for patients allocated HAI therapy (complete response (CR), 3%; partial response (PR), 38%), compared with 14% (CR, 2%; PR, 12%) for patients allocated i.v. therapy. However, median duration of response was less impressive: 38 weeks for HAI and 32 weeks for i.v. patients. One wonders whether the response advantage would still hold if these studies were repeated, incorporating more conventional systemic regimens in the standard arm. Optimised thymidylate synthase inhibitor regimens, primarily based around infusional 5-FU +/− FA [8, 9] currently achieve response rates of around 30%; at least double that determined by the meta-analysis. So the margin of benefit with regional chemotherapy in terms of response may actually be an overestimate.

Even if response was accepted to favour regional therapy, could HAI drug administration ever be delivered to large numbers of patients systematically? The technique is fraught with practical hazards. For example, some patients with presumed disease confined to the liver will be found to have extrahepatic metastases at laparotomy, or aberrant arterial anatomy may preclude catheter insertion. Once inserted, technical problems associated with infusion devices include catheter thrombosis, blockage and possible displacement. FUdR administered intra-arterially is associated with a significant risk of hepatobiliary toxicity and peptic ulcer disease. Formal evaluation of patient convenience, quality of life and treatment cost associated with regional chemotherapy has not been the subject of most previous studies, yet clearly needs to be addressed before this treatment modality can ever be considered standard therapy. More and better designed randomised trials utilising modern systemic therapy in the control arm, appropriately powered to detect a survival difference, are clearly needed.

NOW THE PROS

Probably the most important reason for supporting research into regional chemotherapy is its sound pharmacological rationale, making it an attractive therapeutic strategy, at least in theory. Early studies with regional FUdR, by virtue of its almost entire hepatic extraction, indicated high response rates could be achieved and this has been borne out in the randomised trials. Response rates superior to those achieved with systemic chemotherapy are likely to be clinically relevant, since several studies, albeit in small numbers of advanced colorectal cancer patients, have shown that response to therapy equates with improved quality of life [10–12].

Although clinical trials have failed to demonstrate any statistical survival advantage with regional drug administration, median survival duration has consistently shown a trend in favour of HAI therapy: from the meta-analysis, 16 months for HAI versus 12.2 months for i.v. therapy; $P = 0.14$). Survival was determined using data which included a large cross-over study [13]. One could argue that this factor may dilute the true survival benefit of a particular treatment modality being tested, while these studies were analysed on an intention-to-treat basis and significant numbers of patients allocated to HAI therapy never started treatment because of technical problems or the discovery of extrahepatic disease at the time of catheter insertion. Thus,

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the meta-analysis findings may be an underestimate of the true value of regional chemotherapy in this setting.

In the same way that skeptics have criticised suboptimal chemotherapy being used in the systemic arm of regional chemotherapy trials published to date, advocates of regional therapy have shown that single agent FUdR is, itself, probably a suboptimal HAI regimen. For example, Metzger and colleagues [14] have combined regional 5-FU (2000 mg daily for 5 days) with mitomycin C (10 mg/m^2 on day 1) on a 6 weekly schedule. Median survival of patients was 18 months, with a 57% partial response rate. Alternatively, Kemeny and coworkers have shown that FUdR combined with dexamethasone [15] and/or FA [16] have produced response rates as high as 71%, median survivals of 22–27 months and a 2-year survival of 66%. These novel regimens now require testing in controlled trials.

FUdR OR 5-FU?

The most disappointing aspect of these clinical trials of regional chemotherapy is the finding that potentially promising response rates do not translate to clear survival benefit. It is possible that the very characteristic of FUdR being exploited by regional administration—an extremely high hepatic extraction—is also its Achilles' heel. As has previously been recognised, the meta-analysis clearly demonstrates that, for patients who received HAI FUdR, most relapsed with extrahepatic disease. Extrahepatic metastases develop in 40–70% of patients receiving HAI FUdR and can occur even when the patient is still responding in the liver.

This failure to prevent recurrence of disease outside of the liver, an event which ultimately leads to patient death, suggests the need to achieve adequate cytotoxic drug exposure both within the liver and in the systemic circulation. One approach taken has been to administer alternate cycles of HAI and i.v. chemotherapy to patients [17]. Another approach has been to revisit the use of 5-FU in regional regimens.

A number of studies have shown that elimination kinetics of 5-FU are non-linear, with both systemic clearance and hepatic extraction of the drug decreasing at very high dose rates [18]. These observations are consistent with the loss in selective regional advantage achieved with HAI of 5-FU administered at the maximum tolerated dose. What initially appeared to be a negative feature of regional 5-FU administration has subsequently been recognised to be a positive advantage for achieving both intrahepatic and extrahepatic disease control. Also, while the solubility and potency of 5-FU is lower than that of FUdR, necessitating higher volume infusions, an external pump and surgical placement of an arterial catheter, regional 5-FU is consider-

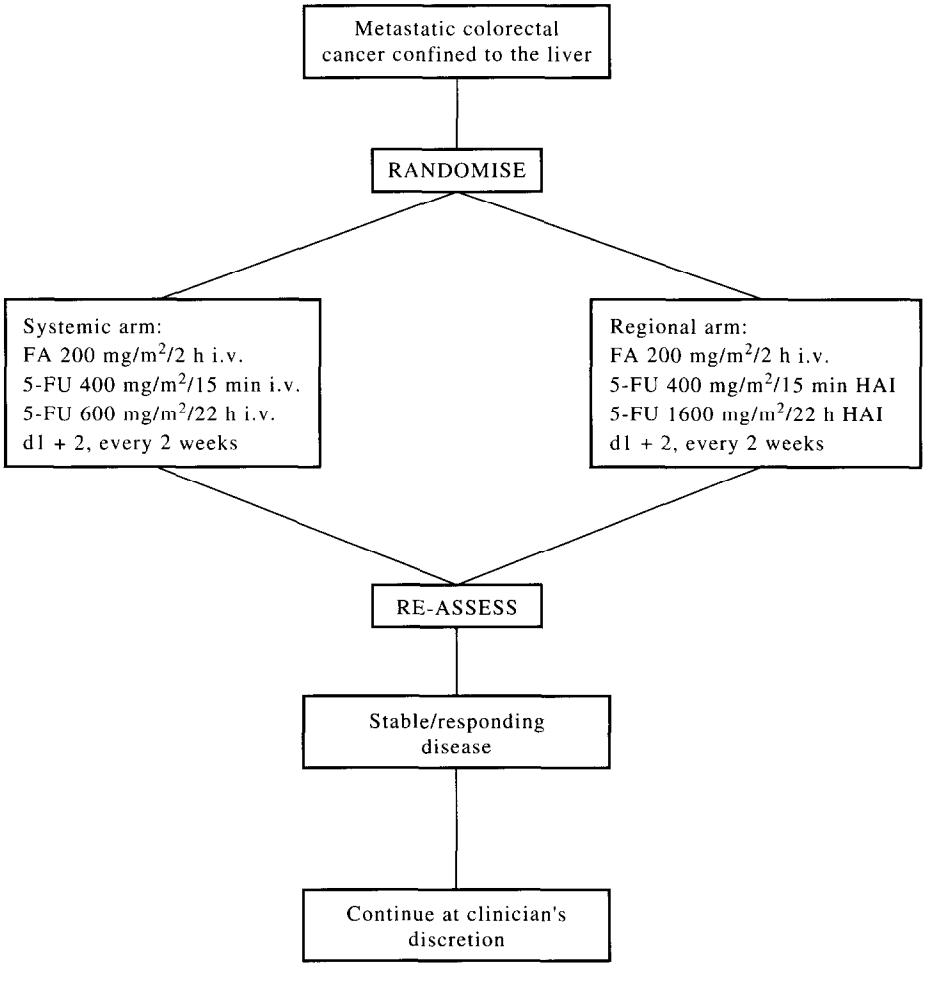

Figure 1. U.K. MRC CR05 phase III trial design of regional versus systemic 5-FU/FA chemotherapy in unresectable hepatic metastatic colorectal cancer.

ably less toxic than FUdR and hepatobiliary toxicity is not a feature.

In a series of pharmacokinetically guided studies, it has been shown that 24 h HAI infusion of 5-FU confers significant pharmacological advantage relative to i.v. infusions or intra-arterial bolus administration [19, 20]. Further evidence suggests that modulation of regional 5-FU administration with FA confers significant therapeutic advantage [21].

Combining both approaches, a phase I study was undertaken of HAI 5-FU and systemic FA in a schedule mimicking the de Gramont regimen of 48 h i.v. 5-FU/FA [22, 23], with the aim of generating high intrahepatic 5-FU concentrations whilst maintaining adequate therapeutic systemic levels [24]. A fixed dose of i.v. FA (200 mg/m^2, over 2 h), followed by a loading dose of HAI 5-FU (400 mg/m^2, over 15 min), followed by a 22-h infusion of 5-FU at doses ranging from 0.8–1.84 g/m^2, repeated on day 2, was administered to patients every 2 weeks. The recommended dose for the 22-h infusion was 1.6 g/m^2. At this dose, pharmacokinetic plasma sampling determined there to be sufficient spillover to achieve steady-state systemic 5-FU levels similar to those achieved with the de Gramont regimen. Based upon these data, a phase II study was performed [25]. 59 patients with histologically proven metastases confined to the liver received HAI 5-FU/i.v. FA in the regimen described above. The response rate of evaluable patients was 48%, with predicted median survival of 19 months. The site of first progression was more balanced between hepatic (42%) and extrahepatic (58%) disease, while systemic toxicity was low and treatment complication rate was low, in the order of 12%. These data, therefore, compare favourably with those achieved with HAI FUdR. The therapeutic potential for this 5-FU-based HAI regimen is currently being tested in a U.K. MRC-sponsored phase III clinical trial, randomising patients with disease confined to the liver against systemic de Gramont 5-FU/FA; 312 patients randomised will allow detection of a 50% increase in median survival—or an increase from 10% to 22% survival at 18 months—with 90% power (Figure 1). The conclusions from this trial will be a major determinant of subsequent continued research interest in HAI chemotherapy in the U.K.

SUMMARY

Regional chemotherapy, from a theoretical and pharmacological stand point, would seem to offer significant advantage over systemic therapy for the treatment of hepatic metastatic colorectal cancer patients. Clinical experience has shown us that the technique itself is fraught with practical problems, but over the years, specialist centres have learned to overcome many of these, making the technique safer and minimising the possibility of complications and toxicity. As a consequence, there is no doubt that high response rates can be achieved with HAI fluoropyrimidines. However, randomised data have only been obtained from small numbers of patients in suboptimally designed trials and, to date, true patient benefit in terms of either survival or quality of life has not been adequately demonstrated. In parallel with the U.S. Intergroup study, the U.K.-based MRC phase III clinical trial of regional versus systemic 5-FU/FA warrants urgent support and we would welcome collaboration with interested European and American centres. The outcome of this trial will fully define the role of HAI chemotherapy in the management of unresectable hepatic metastatic colorectal cancer, in the context of modern, modulated 5-FU.

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