5. Doroshow JH, Multhauf P, Leong L, *et al.* Prospective randomized comparison of fluorouracil versus fluorouracil and high-dose continuous infusion leucovorin calcium for the treatent of advanced measurable colorectal cancer in patients previously unexposed to chemotherapy. *J Clin Oncol* 1990, **8**, 491–501.
6. Corfu—A Study Group. Phase III randomized study of two fluorouracil combinations with either interferon alfa-2a or leucovorin for advanced colorectal cancer. *J Clin Oncol* 1995, **13**, 921–928.
7. Weiss L, Grundmann E, Torhorst J, *et al.* Haematogenous metastatic patterns in colonic carcinoma: an analysis of 1541 necropsies. *J Pathol* 1986, **150**, 195–203.
8. Ensminger WD, Gyves JW. Clinical pharmacology of hepatic arterial chemotherapy. *Semin Oncol* 1983, **10**, 176–183.
9. Niederhuber JE, Ensminger W, Gyves J, *et al.* Regional chemotherapy of colorectal cancer metastatic to the liver. *Cancer* 1984, **53**, 1336–1343.
10. Kemeny N, Daly J, Reichman B, *et al.* Intrahepatic or systemic infusion of fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma—a randomized trial. *Ann Intern Med* 1987, **107**, 459–465.
11. Hohn DC, Stagg RJ, Friedman MA, *et al.* A randomized trial of continuous intravenous versus hepatic intraarterial floxuridine in patients with colorectal cancer metastatic to the liver: The Northern California Oncology Group trial. *J Clin Oncol* 1989, 7, 1646–1654.
12. Chang AE, Schneider PD, Sugarbaker PH, *et al.* A prospective randomized trial of regional vs systemic continuous 5-FU chemotherapy in the treatment of colorectal metastases. *Ann Surg* 1987, **206**, 685–693.
13. Martin JK, O'Connell MJ, Wieand HS, *et al.* Intra-arterial floxuridine vs systemic fluorouracil for hepatic metastases from colorectal cancer. *Arch Surg* 1990, **125**, 1022–1027.
14. Rougier P, Laplanche A, Huguier M, *et al.* Hepatic arterial infusion of floxuridine in patients with liver metastases from colorectal carcinoma: long-term results of a prospective randomized trial. *J Clin Oncol* 1992, **10**, 1112–1118.
15. Kemeny N, Seiter K, Niedzwiecki D, *et al.* Randomized trial of hepatic arterial floxuridine, mitomycin, and carmustine versus floxuridine alone in previously treated patients with liver metastases from colorectal cancer. *J Clin Oncol* 1993, **11**, 330–335.
16. Kemeny N, Seiter K, Conti J, *et al.* Heptic arterial floxuridine and leucovorin for unresectable liver metastases from colorectal carcinoma: new dose schedules and survival update. *Cancer* 1994, **73**, 1134–1142.
17. Kemeny N, Seiter K, Niedzwiecki D, *et al.* A randomized trial of intrahepatic infusion of fluorodeoxyuridine with dexamethasone versus fluorodeoxyuridine alone in the treatment of metastatic colorectal cancer. *Cancer* 1992, **69**, 327–334.
18. Kemeny N, Conti JA, Cohen A, *et al.* Phase II study of hepatic arterial floxuridine, leucovorin, and dexamethasone for unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 1994, **12**, 2288–2295.
19. Rougier P, Hay JM, Olivier JM, *et al.* A controlled multicentric trial of intrahepatic artery chemotherapy vs. standard palliative treatment for colorectal liver metastases. *Proc Am Soc Clin Oncol* 1990, **9**, 104 (abstract).

PII: S0959-8049(96)00394-2

Contra:

C.-H. Köhne[1] and J. Wils[2]

[1]Department of Oncology and Tumorimmunology, Humboldt-University-Berlin, Virchow-Klinikum, Robert-Rössle-Klinik, 13122 Berlin, Germany; and [2]Laurentius Hospital, 6043 CV Roermond, The Netherlands

THE IDEA of delivering chemotherapy via the hepatic artery in patients with unresectable liver metastases of colorectal cancer was developed in the 1960s [1] when the results of systemic therapy were disappointing. Indeed, the use of 5-fluorouracil (5-FU), the most active drug for this tumour, was associated with a low rate of tumour shrinkage, and any influence on the natural course of the disease was doubtful.

The rationale for intra-arterial therapy was persuasive: to deliver an antineoplastic drug with high-dose intensity via the hepatic artery, known to be the major route of blood supply for malignant tissue [2], while at the same time avoiding systemic toxic effects by a high ratio of hepatic drug extraction [3]. Additionally, the liver was considered to be the major and often first metastatic site in colorectal cancer. A step-wise pattern of metastatic spead starting in the liver and thereafter occurring in other organs has been postulated [4]. Therefore, treating the liver might not only result in tumour regression of the affected organ, but also delay extrahepatic metastasis. Even if this latter goal should not be accurate, it may be hypothesised that an effective treatment of the major tumour burden would eventually prolong patient survival.

Fluorodeoxyuridine (FUdR) appeared to be the ideal compound for intrahepatic use because approximately 95% of the drug was cleared by the liver in contrast to 5-FU with a variable hepatic extraction of 15–50% [3].

The introduction of surgically implantable intra-arterial catheters and infusion pumps [5, 6] offered a major technical advantage by reducing many of the earlier complications, such as dislocation of the catheter tip, inadequate perfusion of the liver, perfusion of upper gastro-intestinal organs, sepsis, bleeding, hepatic artery thrombosis and hospitalisation that accompanied the use of percutaneous catheters [7]. At the same time, prolonged drug delivery on an outpatient basis was possible.

Data from phase II investigations [8] revealed a high rate of objective tumour response of approximately 45% achieved by hepatic arterial infusion (HAI) of FUdR. The median patient survival of approximately 17 months indicated a possible survival advantage for patients treated with HAI compared with historical controls treated with the intravenous drug. Such favourable results have also been

Correspondence to C.-H. Köhne.

Table 1. Randomised trials of HAI versus systemic chemotherapy

Institution [Ref.]	Crossover allowed	Major study endpoints	Number of patients evaluable		Number of evaluable patients with extrahepatic disease	Objective response rate		Median patient survival (months)	
			HAI	i.v.	HAI	HAI	i.v.	HAI	i.v.
MSKCC* [1]	Yes 60%	Response rate	48	51	–	50% $P = 0.001$	20%	17 $P = 0.42$	12
NCOG† [11]	Yes 43%	TTF_{liver}	65	50	8	42% $P = 0.0001$	10%	16.6 $P =$ n.s.	16
NCI‡ [10]	No	Survival	32	32	9	62% $P = 0.003$	17%	17 $P = 0.22$	12
NCCTG§ [12]	No	Survival	36	33	7	48% $P = 0.02$	21%	12.6 $P = 0.53$	10.5

TTF, time to treatment failure; n.s., not significant.

* Randomisation after laparotomy only; † Pretreatment with <10 g 5-FU allowed (4 patients in each arm); ‡ Patients with positive hepatic lymph nodes allowed (5 patients with positive lymph nodes); § i.v. therapy was 5-FU and not FUdR as in the other studies.

observed in systemically pretreated patients, now responding to intra-arterial therapy.

Randomised studies have, therefore, been initiated to define the value of HAI compared with systemic treatment with fluoropyrimidines (Tables 1 and 2). It is important to realise that these trials have been designed to answer different questions. The interpretation of an individual study may, therefore, be limited to certain study endpoints such as toxicity and response rate and not applicable to the comparison of patient survival. Furthermore, the characteristics of the control group will determine the conclusions of such a trial. This is of special importance for those trials that wished to compare HAI with a group of patients that was offered best supportive care.

Four trials [9–12] have used intra-arterial FUdR infusion in comparison with the intravenous application of a fluoropyrimidine. In three trials, the control group received intravenous (i.v.) FUdR while in one study [12], i.v. 5-FU was administered (Table 1). Two trials allowed intra-arterial therapy for patients with disease progression under the initial application of systemic FUdR. This was the case in 60% and 33% of patients in the Memorial Sloan-Kettering Cancer Center (MSKCC) [9] and North Central Oncology Group (NCOG) [11] trials, respectively. The major study endpoints of these trials were, therefore, limited to the comparison of toxicity, response rate or time to treatment failure in the liver, but conclusions regarding survival are not possible. No particular conclusions can be drawn from the retrospective subgroup analysis of patients who were or were not crossed over from systemic to locoregional treatment, because such analyses are well known to be potentially biased. Two trials were specifically designed to find a difference in patient survival [10, 12], and hence did not allow the crossover of patients to HAI therapy. All four studies differ in regard to patient selection and eligibility criteria. The study conducted at the MSKCC randomised patients based on the findings of laparotomy [9]. This experience provides useful information about the difficulties of identifying patients as potential canditates for HAI. 63 out of 162 patients offered for randomisation were excluded at laparotomy because hepatic resection was possible in 25 patients and, more importantly, 33 patients had extrahepatic disease, only apparent during laparotomy. To be eligible for the other three trials, patients underwent a conventional staging procedure with hepatic angiogram including a mesenteric and coeliac angiography and computerised tomographic scan evaluations. A considerable number of patients were found to have extrahepatic metastatic spread at the time of laparotomy for implantation of the catheter and pump. Hepatic lymph node involvement did not exclude patients from receiving HAI in the trial conducted by the National Cancer Institute (NCI) [10]. A retrospective subgroup analysis of this trial suggested that the presence of extrahepatic involvement was a bad prognostic factor. However, this finding will need confirmation in prospective studies. In the NCOG trial, 14 out of 64 patients were excluded based on laparotomy findings and technical reasons precluding cannulation or complete hepatic perfusion [11]. These reports emphasise the difficulties investigators face when designing such a randomised trial. Selecting patients with

Table 2. Randomised trials of HAI versus control group of best supportive care with or without systemic chemotherapy

Author [Ref.]	Crossover	Major study endpoints	Number of patients evaluable		Median patient survival (months)		Quality of life
			HAI	Control	HAI	Control	
Rougier and associates [13]	No	Survival	81	82	15 $P < 0.02$	11	n.d.
Allen-Mersh and associates [15]	No	Survival and quality of life	51	49	13.4 $P = 0.03$	7.5	Improved by HAI

n.d., not done.

tumours confined to the liver is apparently only possible by surgery. As pointed out by Rougier and associates [13], performing an exploratory laparotomy in those patients that will never have a pump implanted is ethically not acceptable. It is for this reason that all patients with a laparotomy prior to randomisation will have a pump implanted and crossover to HAI in case of tumour progression, hence confounding the comparison of patient survival.

Despite these methodological problems, the results of all the trials are consistent in the observed rate of objective tumour responses of approximately 50% (Table 1). This response rate was significantly higher than that achieved by systemic treatment (approximately 20%), was accompanied by a significant prolongation of the response duration [10] and a longer time to intrahepatic failure [11] in some trials. Patients treated with HAI also had a significantly lower rate of intrahepatic progression, but extrahepatic failure was more frequent compared to systemic therapy [9]. However, those trials designed to detect a difference in median survival as well as the two crossover studies failed to demonstrate a significant prolongation of patient survival.

HAI is associated with substantial toxicity, mainly chemical hepatitis occurring in 26–79%, and biliary sclerosis in up to 24% of patients [9–12]. This was the cause of death in 2 patients treated in the NCOG trial [11]. Peptic ulcers and chemical gastritis due to misperfusion occurred in up to 17% of patients [10]. Hepatic artery thrombosis, dislocation of the catheter tip, pump dysfunction, haematoma and infections are less frequent sequelae but troublesome complications in individual patients. Although the occurrence of biliary toxicity may be reduced by the addition of dexamethasone given intra-arterially, this did not prevent the substantial FUdR dose reductions of up to 60% because of biliary toxicity [14]. The systemic application of fluoropyrimidines was mainly associated with mucositis and diarrhoea, but seldom severe or life-threatening. In contrast to HAI, the scheduled dose of the fluoropyrimidine given intravenously can be maintained over a long period of time and several cycles [10].

The data from these four trials allow the conclusion that, at best, a higher response rate may be achieved by HAI compared to intravenous treatment, at the cost of a major surgical procedure, substantial biliary toxicity and without a proven benefit for overall survival.

The value of HAI in comparison to a group of patients offered best supportive care with the possible addition of systemic chemotherapy has been addressed in two recently published trials ([13, 15]; Table 2). In both studies, no crossover of patients was allowed in oder to compare patient survival. In the French trial, 163 patients were allocated to a control group or to receive FUdR via the hepatic artery [13]. Half of the control group was treated with intravenous 5-FU at some point of the study period, while the other half received best supportive care only. The decision whether to offer chemotherapy to patients of the control group was left to the discretion of the responsible physician. In the British trial [15], conventional symptom palliation may have included the use of an antineoplastic agent, but details of how many patients actually received systemic chemotherapy were not given. Both studies demonstrated a statistically significant prolongation of median patient survival in favour of the HAI group: an increase of 4 months (15 versus 11 months) in the French trial and a doubling of the survival time in the British trial (13.4 versus 7.4 months). The latter study also provides information about improved quality of life for patients allocated to HAI treatment. The French study [13] points towards the degree of liver involvement and performance status as prognostic factors that significantly influenced patient survival. However, the experience of the surgical and medical team appeared to be of major prognostic importance, indicating that the use of hepatic arterial infusion should be restricted to experienced institutions.

Do these two trials give sufficient evidence that HAI of FUdR should be the preferred method of treatment for patients with metastatic colorectal cancer limited to the liver? In our opinion, the answer should be 'no'. In both trials, the 'systemic' groups cannot be considered as an adequate control. Rather than establishing the value of intra-arterial therapy, both trials emphasise the benefit of chemotherapy in general, irrespective of the route of administration, as a powerful instrument to improve the quality of life and prolong median survival for patients with metastatic disease. Both studies are important because they have also established the value of antineoplastic therapy in the good risk group of patients having liver metastasis only. Similar results have been demonstrated by others for patients with more advanced disease [16]. Although a rather toxic regimen of cisplatin, 5-FU and folinic acid had been used, the quality of life of patients was maintained by the application of systemic chemotherapy, but deteriorated in those patients offered best supportive care only. Additionally, the median survival of the chemotherapy patients was more than doubled from 5 to 11 months. If systemic chemotherapy was given to patients allocated to the best supportive care groups of the French and British trial, it could be initiated at any time during the study period. However, to delay the application of systemic chemotherapy in patients with metastatic disease decreases median survival compared to an early start of therapy [17]. It is, therefore, very unlikely that the group of patients that received delayed systemic therapy will have influenced the outcome of the whole group of best supportive care substantially.

Recently published phase II evaluations, investigating infusional or folinic acid modulated FUdR or 5-FU given intra-arterially, have observed promising high response rates and patient survival of approximately 24 months or better [18–21]. These trials are preliminary and will need confirmation in a randomised trial.

What is the value of systemic therapy? During the last 10 years, major progress has been achieved in the treatment of patients with metastatic colorectal cancer [22]. Biochemical modulation by folinic acid [23] or methotrexate [24] doubles the rate of objective tumour response (19–21%) compared to 5-FU alone (10–11%). Furthermore, infusional 5-FU, either by the schedule or by the dose-intensity that can be achieved, or both, is superior to bolus injections [25]. However, a prolonged median survival has only been reported in some randomised trials [26] and seems to be marginal considering the data of two recently published meta-analyses [23, 24]. Nevertheless, bolus fluoropyrimidines without a modulator given as systemic therapy are no longer an appropriate therapy to be compared with HAI. The question arises as to the effect of systemic 5-FU

Table 3. Clinical outcome of selected patients with Karnofsky index ⩾ 80 and hepatic metastases receiving intravenous chemotherapy within multicentre randomised trials or multicentre phase II studies

Regimen [Ref.]	Number of patients	Objective response rate (CR/PR) (95% CI)	CR	Median time to treatment failure (months)	Median patient survival (months) (95% CI)
FU_{24h}/FA [29, 30]	60	48% (35–61%)	13%	9.3	21.4 (17.3–25.6)
FU_{24h}/IFN [29, 30]	34	24% (9–38%)	9%	3.5	12.0 (3.7–20.3)
FU_{Bolus}/FA [27, 28]	75	20% (11–39%)	1%	5.6	14.3 (11.2–17.3)

FU_{24h}/FA: weekly 5-FU 2.6 g/m^2 plus folinic acid 500 mg/m^2 ± interferon α-2b 3 MioU s.c. three times per week;
FU_{24h}/IFN: weekly 5-FU 2.6 g/m^2 plus interferon α-2b 3 MioU s.c. three times per week;
FU_{Bolus}/FA: 5-FU 600 mg/m^2 plus folinic acid 300 mg/m^2 d1–3 ± dipyridamole 3 × 75 mg d0–4
5-FU 300–500 mg/m^2 plus folinic acid 200 mg/m^2 d1–5 plus interferon α-2b 5 MioU/m^2 s.c. d1–5.

combined with a modulator administered to patients with liver metastases only. Such patients might represent a favourable subgroup with a good performance status, who are generally fit for a major surgical procedure. We have identified 169 patients with a Karnofsky performance status of 80 or better and metastatic disease affecting the liver only that was determined by standard staging procedures including CT-scan evaluations (Table 3, Figure 1). All patients were chemo-naive and met similar entry criteria for different multicentre protocols. 75 patients treated with modulated 5-FU bolus regimens were derived from a randomised trial (n = 51) [27] and two phase II evaluations (n = 24) [28]. 34 individuals received weekly high-dose 5-FU (2.6 g/m^2) given as 24 h continuous infusion in combination with interferon α-2b (IFN) 3 MioU s.c. three times per week and 60 patients were treated with weekly high-dose 5-FU (2.6 g/m^2) as 24 h continuous infusion plus folinic acid (FA) 500 mg/m^2 given intravenously over 2 h prior to 5-FU with (n = 21) or without (n = 39) the addition of interferon. The latter 94 patients were studied within a randomised protocol of the "Arbeitsgemeinschaft für Internistische Onkologie" (AIO) [29, 30]. The response rate (20–24%) and time to treatment failure (3.5–5.6 months) of the modulated bolus schedules or 5-FU_{24h}/IFN combination appear to be inferior compared to data published on HAI. However, patients receiving a combination including 5-FU_{24h}/FA had a response rate of 48% with 13% complete clinical responses. The median time to treatment failure was 9.3 months. These data indicate an equivalent response rate of folinic acid modulated high dose 5-FU when compared to published HAI data. Patients considered for HAI treatment are probably more rigorously examined to exclude extrahepatic tumour spread. Our patient group might, therefore, represent a more unfavourable population with a higher possibility of extrahepatic disease. Nevertheless, the median survival time of 14.3 months observed in patients receiving modulated bolus schedules is very close to the median survival for HAI patients reported by the French and British trials [13, 15]. Patients treated with a combination including 5-FU_{24h}/FA had a median survival of 21.4 months exceeding the survival time reported in randomised HAI investigations. Although these data have to be interpreted with caution, they demonstrate the favourable outcome of patients given effective systemic therapy.

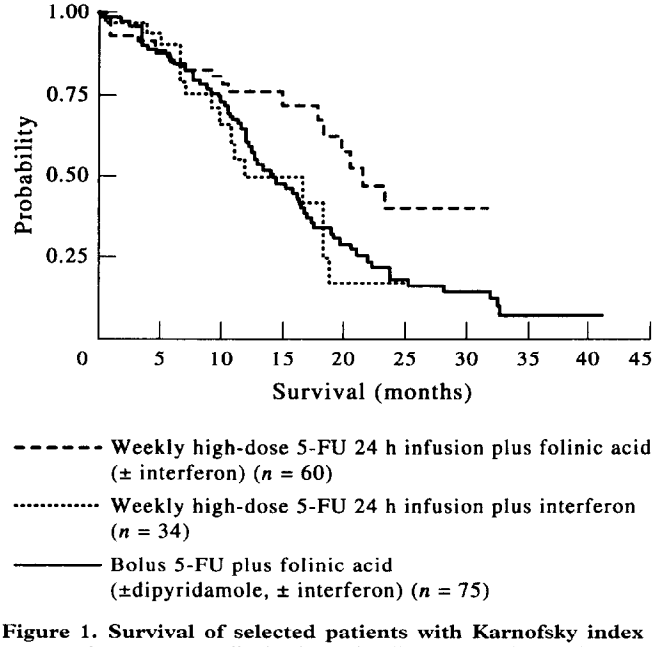

Figure 1. Survival of selected patients with Karnofsky index ⩾ 80 and metastases limited to the liver receiving different regimens of systemic intravenous 5-FU.

In conclusion, intra-arterial chemotherapy via the hepatic artery remains investigational and is associated with a high rate of local toxicity, mainly chemical hepatitis and biliary sclerosis, at least if FUdR is used. Although the response rates achievable with HAI are higher, extrahepatic relapse and progression is frequent, resulting in an equivalent median patient survival as compared to systemic treatment. The routine application of HAI, that requires a surgical procedure, is, therefore, not justified. The use of HAI should be restricted to experienced centres and should only be given to patients within the framework of a controlled clinical trial. In the highly selected group of patients identified for intra-arterial infusion, the recently developed modulated and/or infusional 5-FU schedules are possibly as effective as HAI, and the next generation of randomised protocols should incorporate such regimens as control schedules. It is our opinion that apparently localised disease is still a systemic disease and needs a systemic treatment as effective as possible. Whether a localised approach with consequently less effective systemic drug levels will improve treatment outcome, therefore, appears unlikely. However, it remains possible that a 'combined modality' treatment might be the answer for selected patients and this concept requires further investigation.

1. Sullivan TJ, Sullivan RD, Watkins E Jr, Zurek WZ. Cancer chemotherapy by prolonged ambulatory arterial infusion. *Experientia* 1964, **5**, 543–559.
2. Archer SG, Gray BN. Vascularization of small liver metastases. *Br J Surg* 1989, **76**, 545–548.
3. Collins JM. Pharmacologic rationale for regional drug delivery. *J Clin Oncol* 1984, **2**, 498–504.
4. Weiss L. Metastatic inefficiency and regional therapy for liver metastases from colorectal carcinoma. *Reg Cancer Treat* 1989, **2**, 77–81.
5. Buchwald H, Grage TB, Vassilopoulos PP, Rohde TD, Varco RL, Blackshear PJ. Intra-arterial infusion chemotherapy for hepatic carcinoma using a totally implantable infusion pump. *Cancer* 1980, **45**, 866–869.
6. Ensminger W, Niederhuber J, Dakhil S, Thrall J, Wheeler R. Totally implanted drug delivery system for hepatic arterial chemotherapy. *Cancer Treat Rep* 1981, **65**, 393–400.
7. Watkins E Jr, Khazei AM, Nahra KS. Surgical basis for arterial infusion chemotherapy of disseminated carcinoma of the liver. *Surg Gynecol Obstet* 1970, **130**, 581–605.
8. Kemeny N. Role of chemotherapy in the treatment of colorectal carcinoma. *Semin Surg Oncol* 1987, **3**, 190–214.
9. Kemeny N, Daly J, Reichman B, Geller N, Botet J, Oderman P. Intrahepatic or systemic infusion of fluorodeoxyuridine in patients with liver metastases from colorectal carcinoma. A randomized trial. *Ann Intern Med* 1987, **107**, 459–465.
10. Chang AE, Schneider PD, Sugarbaker PH, Simpson C, Culnane M, Steinberg SM. A prospective randomized trial of regional versus systemic continuous 5-fluorodeoxyuridine chemotherapy in the treatment of colorectal liver metastases. *Ann Surg* 1987, **206**, 685–693.
11. Hohn DC, Stagg RJ, Friedman MA, *et al.* A randomized trial of continuous intravenous versus hepatic intra-arterial floxuridine in patients with colorectal cancer metastatic to the liver: the Northern California Oncology Group trial. *J Clin Oncol* 1989, 7, 1646–1654.
12. Martin JK Jr, O'Connell MJ, Wieand HS, *et al.* Intra-arterial floxuridine vs systemic fluorouracil for hepatic metastases from colorectal cancer. A randomized trial. *Arch Surg* 1990, **125**, 1022–1027.
13. Rougier P, Laplanche A, Huguier M, *et al.* Hepatic arterial infusion of floxuridine in patients with liver metastases from colorectal carcinoma: long-term results of a prospective randomized trial. *J Clin Oncol* 1992, **10**, 1112–1118.
14. Kemeny N, Seiter K, Niedzwiecki D, *et al.* A randomized trial of intrahepatic infusion of fluorodeoxyuridine with dexamethasone versus fluorodeoxyuridine alone in the treatment of metastatic colorectal cancer. *Cancer* 1992, **69**, 327–334.
15. Allen-Mersh TG, Earlam S, Fordy C, Abrams K, Houghton J. Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases. *Lancet* 1994, **344**, 1255–1260.
16. Scheithauer W, Rosen H, Kornek GV, Sebesta C, Depisch D. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *Br Med J* 1993, **306**, 752–755.
17. Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. Nordic Gastrointestinal Tumor Adjuvant Therapy Group. *J Clin Oncol* 1992, **10**, 904–911.
18. Kemeny N, Seiter K, Conti JA, *et al.* Hepatic arterial floxuridine and leucovorin for unresectable liver metastases from colorectal carcinoma. New dose schedules and survival update. *Cancer* 1994, **73**, 1134–1142.
19. Staib-Sebler E, Lorenz M, Gog C, Encke A. Continuous arterial 5-fluorouracil and folinic acid chemotherapy for colorectal liver metastases. *Onkologie* 1995, **18**, 240–244.
20. Kemeny N, Conti JA, Cohen A, *et al.* Phase II study of hepatic arterial floxuridine, leucovorin, and dexamethasone for unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 1994, **12**, 2288–2295.
21. Warren HW, Anderson JH, O'Gorman P, *et al.* A phase II study of regional 5-fluorouracil infusion with intravenous folinic acid for colorectal liver metastases. *Br J Cancer* 1994, **70**, 677–680.
22. Moertel CG. Chemotherapy for colorectal cancer. *N Engl J Med* 1994, **330**, 1136–1142.
23. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. Advanced Colorecal Cancer Meta-Analysis Project. *J Clin Oncol* 1992, **10**, 896–903.
24. Meta-analysis of randomized trials testing the biochemical modulation of fluorouracil by methotrexate in metastatic colorectal cancer. Advanced Colorectal Cancer Meta-Analysis Project. *J Clin Oncol* 1994, **12**, 960–969.
25. Wils JA. High-dose fluorouracil: a new perspective in the treatment of colorectal cancer? *Semin Oncol* 1992, **19** (Suppl. 3), 126–130.
26. Köhne-Wömpner CH, Schmoll HJ, Harstrick A, Rustum YM. Chemotherapeutic strategies in metastatic colorectal cancer: an overview of curent clinical trials. *Semin Oncol* 1992, **19** (Suppl. 3), 105–125.
27. Köhne CH, Hiddemann W, Schüller J, *et al.* Failure of orally administered dipyridamole to enhance the antineoplastic activity of fluorouracil in combination with leucovorin in patients with advanced colorectal cancer: a prospective randomized trial. *J Clin Oncol* 1995, **13**, 1201–1208.
28. Schmoll HJ, Köhne-Wömpner CH, Hiddemann W, *et al.* Interferon alpha-2b, 5-fluorouracil, and folinic acid combination therapy in advanced colorectal cancer: preliminary results of a phase I/II trial. *Semin Oncol* 1992, **19** (Suppl. 3), 191–196.
29. Köhne CH, Wilke H, Hecker H, *et al.* Interferon-alpha does not improve the antineoplastic efficacy of high-dose infusional 5-fluorouracil plus folinic acid in advanced colorectal cancer. First results of a randomized multicenter study by the Association of Medical Oncology of the German Cancer Society (AIO). *Ann Oncol* 1995, **6**, 461–466.
30. Köhne CH, Schmoll HJ, Wilke H, *et al.* Weekly high dose infusional 5-fluorouracil (FU) plus leucovorin (LV) vs. FU plus alpha-interferon (IFN) vs. FU plus LV plus IFN in advanced colorectal cancer. Results of a multicentre randomizd trial. *Proc Am Soc Clin Oncol* 1995, **14**, 194 (abstract).

PII: S0959-8049(96)00395-4

Arbiter:

P.G. de Takats and D.J. Kerr[1]

University of Birmingham CRC Institute for Cancer Studies, Clinical Research Block, The Medical School, Edgbaston, Birmingham B15 2TJ, U.K.

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