

# Hepatic arterial floxuridine as second-line treatment for systemic fluorouracil-resistant colorectal liver metastases

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**Summary** Hepatic arterial floxuridine (HAI) in 35 patients with systemic fluorouracil/folinic acid-resistant colorectal liver metastases achieved a 14% partial response and 26% disease stabilization rate, with a median response duration of 7 months from onset of HAI.

**Keywords:** colorectal liver metastases; chemotherapy; fluorouracil resistance; hepatic arterial floxuridine

Systemic fluorouracil/folinic acid chemotherapy is the current standard treatment for unresectable colorectal liver metastases (Nordic Gastrointestinal Tumour Adjuvant Therapy Group, 1992). However, virtually all colorectal liver metastases become resistant (Advanced Colorectal Cancer Meta-analysis Project, 1992), and many patients then seek second-line treatments to prolong disease control.

There are no second-line chemotherapies of proven survival or quality of life benefit in colorectal cancer. Hepatic arterial floxuridine infusion (HAI) in patients with untreated colorectal liver metastases (Piedbois et al. 1996) produces a higher partial response rate (40%) than with bolus systemic fluorouracil/folinic acid administration (23%). Thus, HAI might be a useful second-line treatment in patients whose colorectal liver metastases have become resistant to systemic fluorouracil/folinic acid. Response to HAI has been reported in comparative studies of systemic vs hepatic arterial floxuridine (Kemeny et al. 1987; Hohn et al. 1989), in which patients allocated to the systemic control arm whose disease failed to respond were then crossed over to the hepatic arterial study arm. As a result, HAI has been recommended for treatment of patients with systemic chemotherapy-resistant liver metastases (Kemeny et al. 1993). However, the extent of benefit in patients whose colorectal liver metastases are resistant to systemic fluorouracil/folinic acid has not been established.

The purpose of this study was to determine response, toxicity, quality of life, and duration of response to hepatic arterial floxuridine, in patients with systemic fluorouracil/folinic acid-resistant colorectal liver metastases.

## MATERIALS AND METHODS

All patients had progressive disease – defined as > 25% increase in tumour size (Hayward et al. 1977) between pre- and post-treatment computerized tomography (CT) scans (Dworkin et al. 1995) – to

bolus systemic fluorouracil/folinic chemotherapy (O'Connell et al. 1989) after a minimum of three 4-weekly courses of treatment carried out as part of routine treatment in various cancer centres. Patients underwent hepatic arterial cannulation, as described in Burke et al (1995), and were treated with a 28-day regimen of continuous floxuridine (0.2 mg kg<sup>-1</sup> body weight day<sup>-1</sup>) with dexamethasone 20 mg infused for 14 days, followed by saline for a further 14 days, which was then repeated. The dose reduction for toxicity criteria has been described (Allen-Mersh et al. 1994).

All patients underwent baseline (within 1 week before hepatic arterial cannulation) and thereafter monthly estimation of serum aspartate transaminase, alkaline phosphatase, bilirubin and carcinoembryonic antigen (CEA), quality of life – Sickness Impact Profile (SIP) (Bergner et al. 1981), Rotterdam Symptom Checklist (RSC) (DeHaes et al. 1990), and Hospital Anxiety and Depression Scale (HAD) (Zigmond and Snaith, 1983) – and 4-monthly CT scan estimation of liver metastasis volume (Dworkin et al. 1995).

Criteria for complete or partial response, and stable disease were according to UICC recommendations (Hayward et al. 1977), as modified for changes between pre- and post-treatment liver CT scans (Buroker et al. 1994). Patients were recruited between October 1993 and October 1996 and followed up until October 1997. Toxicity was defined according to WHO criteria (World Health Organization, 1979).

This study was approved by the Chelsea and Westminster Hospital Ethics Committee.

## RESULTS

Thirty-five patients (M/F, 19:16; median age 56.8 years, interquartile range 48.2–62.4 years; median Karnofsky score 90%, interquartile range 90–100%) were studied. All had received bolus systemic fluorouracil/folinic acid chemotherapy (range 4–12 courses) during which liver metastasis progression had been established from CT scans before and after a minimum of three courses of treatment. No patient died within 30 days of hepatic arterial cannulation. A median of six (interquartile range 3–8.75) HAI floxuridine courses were administered.

There was a trend, which did not reach statistical significance (Wilcoxon signed-rank test,  $P = 0.14$ ), towards an overall rise in median liver metastasis volume after 4 months of hepatic arterial

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floxuridine (median 357 ml, range 101–737 ml) compared with baseline (333 ml, 82–738 ml). However, there was a significant reduction (Wilcoxon signed-rank test,  $P=0.007$ ) in serum CEA level after 4 months of hepatic arterial floxuridine (median  $126 \mu\text{g l}^{-1}$ , range 11–345  $\mu\text{g l}^{-1}$ ) compared with baseline (279  $\mu\text{g l}^{-1}$ , 62–1209  $\mu\text{g l}^{-1}$ ). Partial response (>50% reduction in liver metastasis volume) occurred in five patients, and disease stabilization (< 25% increase but < 50% reduction in liver metastasis volume) in a further nine patients. The median duration of disease stabilization (interval with CT scan liver metastasis volume < 25% greater than baseline) was 7 months (range 4–11 months). The serum CEA level initially fell below baseline level in 22 patients but subsequently rose to baseline or higher by a median of 8 months (range 3–18 months) from onset of hepatic arterial floxuridine.

Six patients were alive at completion of follow-up. Overall survival was a median of 308 days (range 179–560 days) from hepatic arterial cannulation. Thirteen of the 29 patients who died did so as a result of liver metastasis and the remainder as a result of extrahepatic disease progression. The proportion of days survived with an abnormal quality of life score (Bergner et al. 1981; Zigmund and Snaith, 1983; DeHaes et al. 1990) after hepatic arterial floxuridine was a median of 0% (range 0–4.7%) for RSC physical, 0% (0–14.5%) for RSC psychosocial, 0% (0–13.4%) for HAD depression, 0% (0–9.9%) for HAD anxiety and 30.7% (13.4–51.1%) for SIP. The proportion of survival with abnormal quality of life among patients in whom any abnormal quality of life score occurred is shown in Table 1. Toxicity necessitated temporary dose reduction in 31 and omission in 26 patients. The toxicity profile is shown in Table 2. Sclerosing cholangitis was not diagnosed in any patient.

## DISCUSSION

Although all patients had received a conventional bolus systemic fluorouracil/folinic chemotherapy regimen (O'Connell et al. 1989), this was administered as routine treatment in various oncology centres, and centre to centre variation in systemic chemotherapy treatment criteria may have been greater than between centres collaborating within a single protocol. In addition, higher (30–40%) partial response rates than with bolus systemic fluorouracil/folinic acid can be achieved with novel schedules and combinations of systemic fluorinated pyrimidines (Levi et al. 1994; Tournigand et al. 1997), and the extent of HAI response in patients whose liver metastases are resistant to these regimens is unknown. Thus, the present results relate to patients whose liver metastases were progressing during treatment with conventional bolus fluorouracil/folinic acid chemotherapy administered outside a clinical trial.

Hepatic arterial floxuridine infusion achieves a tenfold increase in liver metastasis fluorinated pyrimidine concentration compared with systemic fluorouracil infusion (Ensminger et al. 1978). The stabilization of disease in 40% of cases together with a significant fall in the serum tumour marker CEA (Allen-Mersh et al. 1987) for 7–8 months suggests that this increased fluorinated pyrimidine concentration produced an anti-tumour effect in patients with systemic fluorouracil-resistant liver metastases. However, HAI did not achieve a significant overall reduction in liver metastasis volume, and the partial response rate was only 14%. This reduced partial response rate compared with that (40%) obtained in untreated colorectal liver metastases (Piedbois et al. 1996) may

**Table 1** Proportion of survival after commencing hepatic arterial floxuridine (HAI) that was associated with abnormal quality of life (QoL) scores among patients with any abnormal QoL score during HAI treatment

QoL instrument	Abnormal QoL score (no. of patients)	Proportion (%) survival with abnormal QoL score (median, range)
RSC physical	10	17.0 (8.6–31.7)
RSC psychosocial	14	14.9 (11.6–35.6)
HAD depression	11	29.4 (15.5–44.4)
HAD anxiety	11	14.7 (11.1–35.3)
SIP	25	44.1 (28.8–52.9)

**Table 2** Number of patients experiencing toxicity, by WHO grade, after intrahepatic floxuridine in 35 patients with systemic fluorouracil-resistant colorectal liver metastases.

Toxicity	I	II	III	IV
Gastritis	9	5	3	1
Nausea/vomiting	6	7	4	1
Diarrhoea	8	5	2	3
Stomatitis	6	2	3	6

result from fluorouracil-induced up-regulation of enzymes, such as thymidylate synthase, which modulate the cytotoxic effect of floxuridine (Jenh et al. 1985). Although non-fluorinated pyrimidine cytotoxics, such as the topoisomerase inhibitor irinotecan, are more logical choices for second-line chemotherapy in fluorouracil-resistant colorectal cancer (Rothenburg et al. 1996), results currently suggest only an 18% partial response rate associated with a 1.9% incidence of fatal toxicity (Rougier et al. 1997). A higher response rate (33%) has been reported with combined intrahepatic fluorouracil and human interferon  $\alpha 2b$ , but with grade III/IV toxicity in 62% of patients (Patt et al. 1997).

The monthly RSC and HAD quality of life (QoL) assessments may have underestimated the extent of the HAI-associated QoL deficit compared with the SIP, which suggested a greater QoL abnormality. Any QoL deficit is also likely to have been underestimated at the terminal stage of disease because most patients did not complete QoL questionnaires during the month before death. HAI patients in this study received intra-arterial dexamethasone after previous studies (Kemeny et al. 1992) reporting reduced toxicity and improved response compared with floxuridine alone, and this may have influenced QoL independently of the floxuridine effect. Despite these limitations, QoL instruments suggested that quality of life was preserved in most of the previously treated patients receiving HAI. The commonest QoL deficit was depression (Table 1), which is thought to be disease rather than toxicity related (Earlam et al. 1996, 1997). Grade III or IV stomatitis affects <5% of patients receiving HAI as first-line treatment (Earlam et al. 1997), but occurred in 26% of patients in this study (Table 2). Thus, previous fluorouracil exposure may have sensitized patients to develop stomatitis with subsequent hepatic arterial floxuridine.

Eighty per cent of colorectal liver metastasis patients managed by symptom control die from liver metastasis progression (Allen-Mersh et al. 1994). It is not clear whether a similar failure pattern occurs in systemic fluorouracil-resistant liver metastasis patients subsequently managed by symptom control. However, the finding that only 45% of our patients died of liver metastasis progression

suggests that extrahepatic disease progressed while HAI slowed growth in the liver. Thus, liver metastasis patients in whom extrahepatic metastases develop slowly are likely to benefit most from HAI.

First-line chemotherapy for colorectal liver metastases should now involve either systemic (Levi et al. 1994; Tournigand et al. 1997) or regional (Piedbois et al. 1996) fluorinated pyrimidine regimens, which are capable of higher response rates than are achieved (Advanced Colorectal Cancer Meta-analysis Project, 1992) with conventional bolus systemic fluorouracil/folinic acid (O'Connell et al. 1989). Although HAI slowed liver metastasis progression in 40% of patients with systemic fluorouracil-resistant liver metastases in this study, a more effective role is in the first-line treatment of selected (Burke et al. 1995, 1997) colorectal liver metastasis patients in whom prolonged survival with sustained QoL (Allen-Mersh et al. 1994; Earlam et al. 1997) can be achieved.

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