Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases

T G Allen-Mersh, Sally Earlam, Carol Fordy, K Abrams, Joan Houghton

Summary

Very few patients with liver metastases from colorectal cancer can be cured. We have investigated whether a treatment to slow the growth of liver metastases, hepatic-artery infusion of floxuridine, improves palliation in this setting. In a randomised study of 100 patients, we compared quality of life and survival in patients who received hepatic-artery infusion of floxuridine and in those who received conventional symptom palliation.

95% of control patient survival time was spent with normal quality-of-life scores, which suggests that the aim of treatment should be to prolong normal-quality survival rather than merely to sustain quality of life. There was a significant prolongation ($p=0.03$) in overall survival in floxuridine-treated patients compared with controls (median 405 *vs* 226 days). There were similar significant prolongations in normal-quality (ie, normal symptom scores) survival for physical symptoms ($p=0.04$), anxiety ($p=0.04$), and depression ($p=0.04$). This survival benefit was associated with significant reductions in metastasis size on computed tomography ($p=0.001$) and in serum carcinoembryonic antigen concentration ($p=0.006$) in floxuridine-treated patients. There was no evidence of treatment-related hepatotoxicity as assessed by serum aspartate aminotransferase and bilirubin measurements.

This is the first demonstration that survival can be prolonged with normal quality of life in patients with colorectal liver metastases. We conclude that hepatic-artery floxuridine infusion can be recommended for suitable patients.

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Introduction

Liver metastases develop in 40% of patients with large-bowel cancer.[1] Resection of these metastases cures no more than 3% of such patients;[2] for the remainder, tumour growth within the liver produces abdominal pain and distension, wasting, oedema, and jaundice. A treatment that slowed the growth of liver metastases might improve palliation even if it did not cure these patients.

Hepatic-artery infusion (HAI) of the fluorouracil analogue floxuridine results in a higher[3] partial response rate (50%) than has been reported (23%) for systemic fluorouracil, with folinic acid, in advanced colorectal cancer.[4] Yet HAI has not been widely adopted, for two main reasons. First, there is concern that drug-related hepatotoxicity and peptic ulceration[5] would neutralise any improvement in quality of life that resulted from better tumour control. Secondly, there is uncertainty about whether a regional liver infusion, which excludes treatment of occult extrahepatic disease, might alter the pattern of disease progression towards growth of uncontrolled extrahepatic disease without prolonging survival.[6]

To find out whether HAI has a palliative role in the management of colorectal liver metastases requires a comparison both of quality of life and of survival in HAI-treated patients and patients receiving conventional symptom palliation. In a randomised study that is what we have done.

Methods

Entry criteria and randomisation

We included patients younger than 75 years, with synchronous or metachronous colorectal liver metastases. To assess eligibility, all patients had chest radiography, abdominal computed tomography (CT) scans, and serum bilirubin estimation. Patients with fewer than four discrete resectable hepatic metastases on contrast-enhanced CT scans were excluded and treated by metastasis resection since this may lead to long-term survival.[7] We also excluded patients with very extensive metastases (>60% liver replacement by tumour), ascites, raised bilirubin, CT or radiographic evidence of disease outside the liver, or a history of systemic chemotherapy. Eligible patients were randomly assigned HAI or conventional palliation. Informed consent was obtained in all cases. The study was approved by the Riverside Ethics Committee, London.

Conventional palliation

Control patients were managed on conventional lines.[8] If the primary tumour and metastases were diagnosed synchronously, the primary tumour was resected to prevent anaemia or obstruction. Analgesics, corticosteroids, and systemic chemotherapy were permitted, the only prohibited treatment being HAI. For 39 controls the referring surgeon or oncologist, after discussion with the patient, advised delaying chemotherapy until symptoms developed. In those patients, chemotherapy was not started with onset of symptoms because the patient was then judged to be at a terminal stage of illness.

HAI

Patients randomised to HAI had an angiogram done to delineate hepatic artery anatomy, followed by surgical insertion of an Infusaid (Norwood, Massachusetts) model 400 pump with cannula into the hepatic artery via the gastroduodenal artery. The gallbladder was removed to prevent drug-induced cholecystitis,[5] and complete liver perfusion via the cannula was confirmed by methylene-blue injection. Where hepatic artery anatomy was atypical (10 patients), the non-dominant artery was ligated and the dominant one was cannulated, resulting in complete perfusion in all cases. In patients whose liver metastases and primary tumour were diagnosed synchronously, conventional radical primary tumour removal was undertaken at the same operation. All pumps were placed by one of three surgeons, inserting 46, 4, and 1.

5 days after the operation, a 14-day continuous infusion was started by filling the pump with floxuridine (0·2 mg per kg body weight per 24 h) dissolved in 50 mL saline with 5000 units heparin.

Charing Cross and Westminster Medical School (T G Allen-Mersh FRCS, S Earlam RGN, C Fordy RGN); **and Cancer Research Campaign, Clinical Trials Centre, Rayne Institute** (K Abrams PhD, J Houghton BSc), **London, UK**

Correspondence to: Mr T G Allen-Mersh, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, UK

	HAI (n=51)	Conventional palliation (n=49)
Demographic data		
Mean (SD) age (years)	55 (10)	59 (8)
M/F	34/17	29/20
No of patients		
Without weight loss	32	32
Dukes' stage (A+B/C)	9/52	15/34
Liver metastases and primary tumour diagnosed synchronously	27	21
Median (IQR)		
PHR (%)	18 (6–26)	14 (5–27)
Performance status (Karnofsky)	90 (90–100)	90 (90–100)
Anxiety score	5 (2–7)	4 (1–6)
Depression score	5 (2–8)	3 (1–5·5)
Physical score	10 (5–15)	10 (4–14)

Table 1: **Baseline characteristics**

This was followed by a 14-day "rest" with saline and heparin infusion, and the cycle was then repeated. This treatment was continued while the serum carcinoembryonic antigen remained at or below the pretreatment value or until hepatotoxicity necessitated dose reduction or omission. The dose was halved if serum aspartate aminotransferase or alkaline phosphatase rose to double the baseline value, and omitted if enzyme activity trebled or serum bilirubin doubled before the proposed treatment. Patients who needed dose omission received dexamethasone 20 mg via the pump for 2 weeks because there is evidence that this drug reduces liver parenchymal inflammation.[9] If the serum carcinoembryonic antigen rose in the absence of evidence of extrahepatic disease or if there was intrahepatic tumour progression on serial CT scans, the 24 h dose was increased to 0·3 mg/kg. All HAI patients received oral ranitidine 150 mg twice daily from the first floxuridine treatment. Additional symptom palliation was as in the control group.[8]

Quality of life

All patients completed monthly quality-of-life questionnaires[10] to assess physical symptoms (Rotterdam checklist) and anxiety and depression (Hospital Anxiety and Depression scale). In estimating normal-quality survival[11] we selected scores of 20 for physical symptoms and 8 for both anxiety and depression as the upper limit of normal.[12,13]

Other variables

Full blood count, serum alkaline phosphatase, and bilirubin were measured monthly, and chest radiography and abdominal CT scans were done 4-monthly in all patients. The liver area replaced by tumour and the total liver area on all CT slices was calculated on a Reichert-Jung MOP-2 image analyser, and division of total tumour area by total liver area and multiplication by 100 gave the percentage hepatic replacement (PHR).

Statistics

Previous reports suggested that 40% of controls[14] and 70% of HAI patients[3] would survive 1 year from randomisation. A study with 50 patients in each group would have an 80% power of revealing a true survival difference of 30% as being significant at $p < 0·05$ (log-rank test).[15] Survival curves were estimated by the Kaplan-Meier method. The significance of differences in biochemical and quality-of-life variables over time was assessed by repeated measures analysis of covariance.[16] This method assessed between-treatment effects while allowing for the possibility that observations over time on the same patient are correlated. Assuming that observations at all pairs of time points on the same patient have equal correlation, between-treatment effects may be estimated by the method of maximum likelihood.

The allocation of study arm was by minimisation[17]—a technique that takes into account pretreatment factors known to affect survival—ie, extent of liver involvement, Karnofsky performance status, and weight loss.[18,19]

Patients were recruited from April, 1988, to October, 1993, and follow-up continued until December, 1993. Patients were referred from many centres; the randomisation and surgery was done at three centres and subsequent treatment and follow-up was handled locally by travelling oncology nurse/trial coordinators.

	n	PHR (%) at liver metastasis diagnosis
Pain or mass	33	36
Routine ultrasound or CT scan	11	5
Raised serum carcinoembryonic antigen	8	14
Synchronous diagnosis with primary tumour	48	12

Table 2: **Mode of presentation with colorectal cancer metastases**

Results

Patients

100 patients were enrolled (51 HAI, 49 controls). The two groups were well matched (table 1). The mode of presentation with colorectal liver metastases is shown in table 2. Among the patients with metachronous liver metastases, 63% were diagnosed by complaints of pain or the presence of a palpable mass; this resulted in diagnosis at a median 36% PHR. 8 control patients underwent primary tumour resection because the primary tumour and liver metastases presented synchronously. 6 of the HAI group underwent primary tumour resection and hepatic artery cannulation at the same laparotomy.

Perioperative mortality and morbidity

1 control patient with extensive liver metastases (PHR 48%) died within 30 days of primary tumour resection. 2 HAI patients (PHR 45%, 55%) died within 30 days of laparotomy for hepatic artery cannulation. These patients are included in the survival analyses. The median hospital stay for insertion of the hepatic artery cannula was 12 (interquartile range 10–15) days. Perioperative complications in the HAI group were pump pocket haematoma in 2 patients, laparotomy wound infection in 2, pneumonia in 1, and transient liver failure in 1.

Floxuridine toxicity

HAI patients received a median of 12 (8–18) 14-day courses. 32 patients required one or more 14-day treatment omissions. This did not prevent subsequent treatment, and patients who required treatment omission received a median of 8 (5–15) courses.

There were no cases of treatment-induced peptic ulceration. 1 patient who drank alcohol heavily developed severe gastritis, and the cannula eroded into the duodenum in another patient. Serum aspartate aminotransferase and bilirubin were not significantly (repeated measures analysis of covariance) higher in the HAI than in the control group during the first 12 months after randomisation (figure 1), and no patient developed clinically apparent sclerosing cholangiitis.

Pump-related and catheter-related morbidity

3 patients developed pump pocket infections 40, 40, and 350 days after randomisation; in 1 case, where the catheter had also been dislodged, the pump had to be removed, but pump re-siting permitted continued treatment in 2 cases. Cannula dislodgement from the hepatic artery was detected in 5 patients a median of 100 (range 60–350) days from randomisation. In 3 cases treatment was continued by catheter re-insertion into the hepatic artery (2 patients) or portal vein (1). In 2 patients, because extrahepatic disease was detected when the arterial catheter became dislodged, it

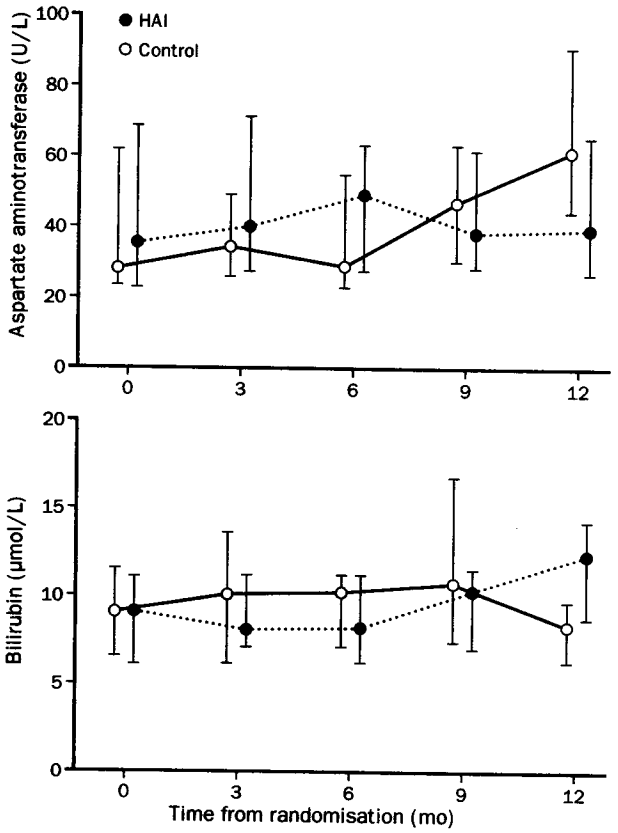

Figure 1: **Serum aspartate aminotransferase and bilirubin during first year after randomisation**
Mean and 95% CI.

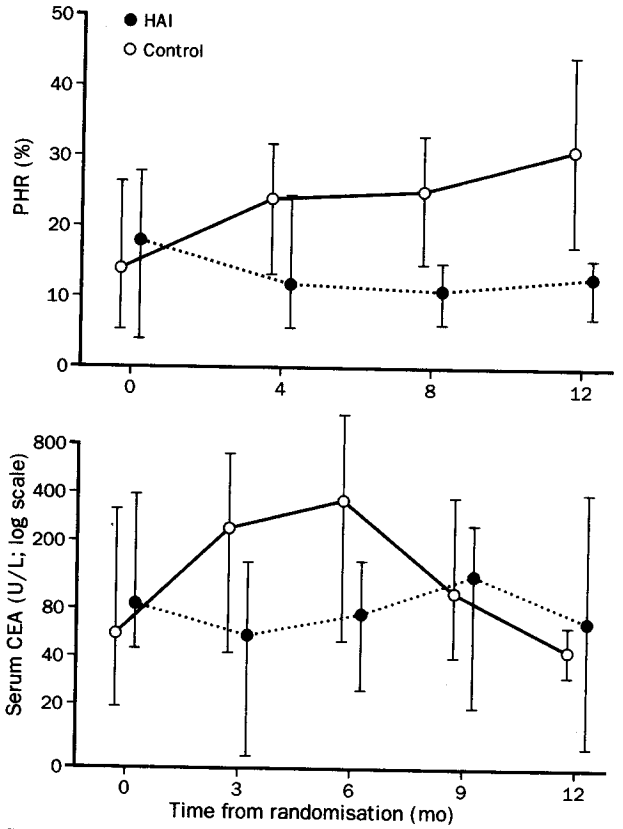

Figure 2: **Tumour shrinkage and serum carcinoembryonic antigen (CEA)**
Mean and 95% CI. Fall in serum CEA in control group at 6 months was due to deaths of patients with high values and advanced disease.

was not replaced. There were no cases of pump mechanical malfunction.

Tumour shrinkage and carcinoembryonic antigen

With allowance for baseline PHR differences, hepatic involvement was significantly reduced ($p < 0.001$) by 4 months from randomisation in the HAI group (median PHR difference at 4 months 15·9% [95% CI 8·4–23·4%]), and there was a significant reduction ($p = 0.006$), in carcinoembryonic antigen at 6 months (figure 2).

Quality of life

Quality-of-life data were collected every month for a median of 91% (74–100) of months between randomisation and death. A typical quality-of-life record for a control patient is shown in figure 3. Despite a progressive increase in PHR, deterioration in the physical symptoms score occurred late in the disease course. Control patients had a median survival of 226 (95% CI 212–241) days, of which a median of 12 (2–23) days was spent with an abnormal physical symptom score. There were no significant differences in post-randomisation symptom, anxiety, or depression scores between the HAI and control groups.

Survival

There was a significant improvement in survival ($p = 0.03$, figure 4) from a median of 226 days in the controls to 405 days in the HAI group. This was associated with a 40% (5–60) reduction in the relative risk of dying in the HAI group during the period of the study. There were also significant improvements in survival associated with normal physical, anxiety, or depression scores ($p = 0.04$ in all cases, figure 5) in HAI patients.

There was no significant association (Cox's proportional hazards regression model) between added days of survival with HAI and PHR at randomisation (stratified as 0–10%, 10–25%, >25%). Median survival was significantly ($p = 0.03$) longer in HAI patients who responded to HAI floxuridine (≥50% shrinkage of tumour) than in patients whose tumours did not respond (420 *vs* 275 days).

There was a highly significant difference (χ^2 test, $p < 0.0001$) in the proportion of patients surviving for 12 months between those who required dose omission and those who did not (6/33 *vs* 15/18).

Cause of death

Progressive liver enlargement resulted in death in 79% of control patients who died compared with only 32% ($p = 0.03$) of HAI patients, because more HAI patients died of extrahepatic disease (table 3). An HAI patient surviving

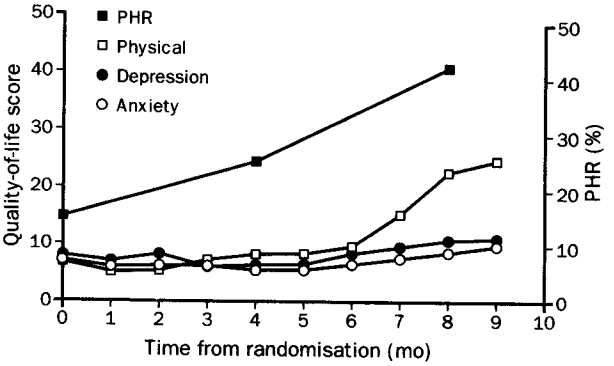

Figure 3: **Typical quality-of-life scores for conventional palliation patient during 9 months from randomisation to death**

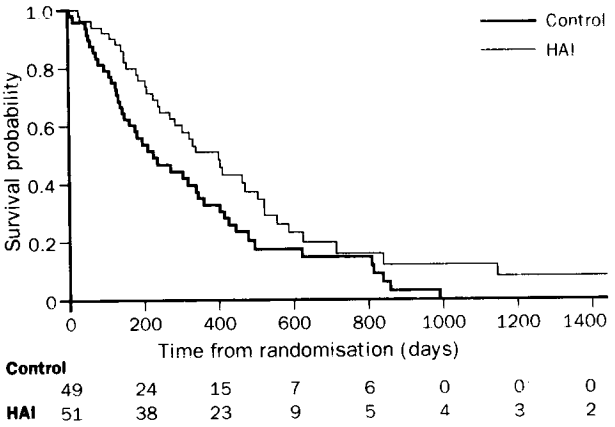

Figure 4: **Overall survival curve**

more than a year was 33% (−17 to 113) more likely to die of extrahepatic disease than one who survived for less than a year.

Hepatic-artery lymph-node involvement, primary tumour node involvement, primary tumour location (colon or rectum), and extent of liver disease at randomisation

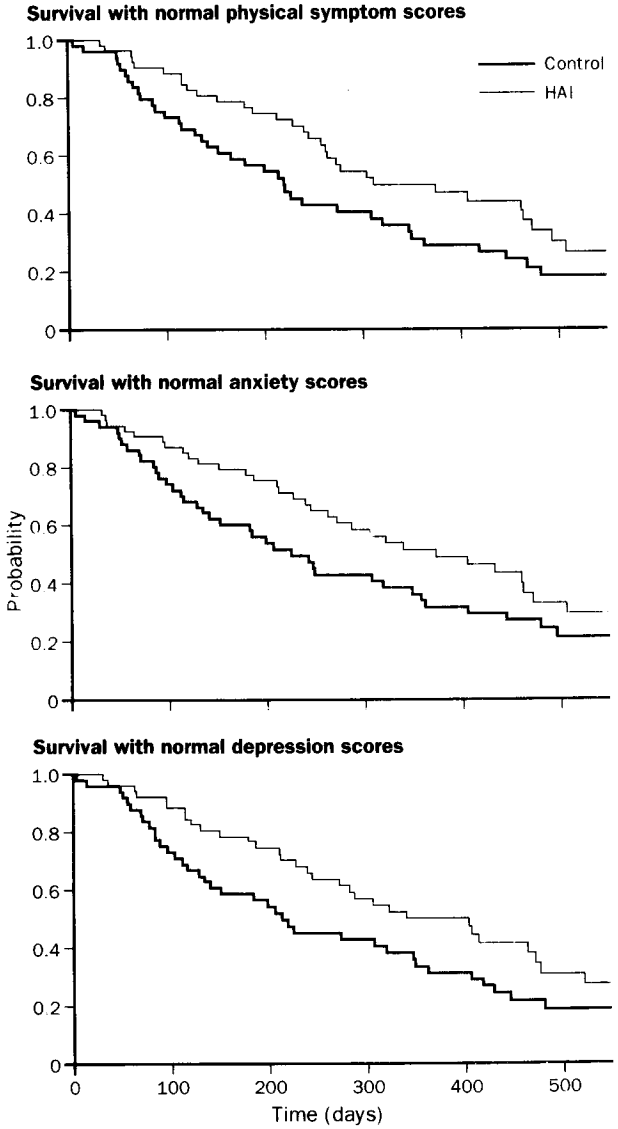

Figure 5: **Curves showing survival with normal quality-of-life scores**

Cause of death	No (%)	
	HAI (n=39)	Conventional palliation (n=46)
Liver	12 (31)	36 (78)
Lung	9 (23)	3 (7)
Locoregional	8 (20)	4 (9)
Bone	5 (13)	2 (4)
Brain	2 (5)	1 (2)
Bladder	2 (5)	..
Postoperative	2 (5)	1 (2)
Unrelated disorders	2 (5)	..

Table 3: **Site of disease causing death, by treatment group**

were not significantly associated with development of extrahepatic disease in the HAI group.

Discussion

Liver metastases were diagnosed before symptoms developed in only 37% of our patients with metachronous colorectal liver metastases (table 2) and only 22% of control patients were either advised to have or accepted systemic chemotherapy. This suggests that the fifty-one clinicians who entered patients into this study and/or their patients were uncertain about the benefit of early diagnosis and systemic chemotherapy of colorectal liver metastases over conventional symptom palliation[8] only. Although 65% of patients randomised to conventional palliation died within a year of diagnosis (figure 4), the finding that 95% of their survival after randomisation was associated with normal quality-of-life scores shows the benefit of conventional symptom palliation. Survival with this approach was unchanged from that reported for patients treated 20 years ago in the UK.[20]

Because systemic chemotherapy is frequently used to treat colorectal liver metastases it could be argued that this would have been a more suitable control than simple palliation against which to compare HAI. However, the quality-of-life consequences of systemic chemotherapy, which produces some side-effects in 80% of patients[21,22] are not clear. Simply by avoiding the risk of systemic chemotherapy side-effects, HAI might have produced a spurious quality-of-life benefit if compared with a systemic chemotherapy regimen. A Nordic group, studying patients with symptomless disseminated colorectal cancer, reported rapid deterioration in symptoms after randomisation in control patients, which was delayed by systemic chemotherapy.[23] This difference between the Nordic controls and ours may be because more than 50% of patients in the Nordic study had extrahepatic disease (including unresected primary tumours), and symptom assessment was by judgment at personal interview. Since most of our control patients' survival after diagnosis was spent with a normal quality of life, a justification for chemotherapy based solely on further sustaining quality of life[24] over that offered by conventional palliation is probably not important in improving management of colorectal liver metastases. The test of a treatment should be whether it prolongs normal-quality survival.

The HAI treatment regimen we used was associated with a less than 5% incidence of gastrointestinal side-effects and no clinically detected sclerosing cholangiitis. These complications have previously been reported[25] to affect 37% and 30%, respectively, of HAI patients receiving a higher dose of floxuridine. The method we used to compare quality-of-life variables over time allowed for the extent of liver disease. By excluding benefit from treatment-related tumour shrinkage the comparison tells us whether there are

treatment-related side-effects or placebo effects. The analysis revealed no detrimental effect of HAI on quality of life.

The partial response rate in our HAI patients (40%), involving a 64% treatment interruption rate, was similar to that (43%) reported with higher drug dosage[25] for which toxicity was greater and treatment interruption was required in 80% of patients. Thus, although the dose of fluorinated pyrimidine drugs and the response rate in colorectal cancer are related,[26] an initially higher floxuridine dose associated with more treatment interruptions and complications did not seem to improve results. Drug sensitivity requiring dose omission was associated with worse survival than that in non-sensitive HAI patients. The results would be improved by regimens that reduce liver parenchymal toxicity without reducing drug dose. The 16% incidence of catheter blockage or sepsis is similar to that reported elsewhere for HAI,[25] or for continuous systemic infusion via a portacath.[27]

This report is the first demonstration that survival in patients with colorectal liver metastases can be prolonged with normal quality of life by regional hepatic chemotherapy. The liver metastases rather than generalised disease dissemination seem to limit survival in these patients. Thus, hepatic-artery floxuridine infusion should be commended to suitable patients with colorectal liver metastases. Decisions about which patients are suitable for HAI should be made for each individual and should include an assessment of patient age, general fitness, and attitude to treatment.

Although survival with HAI treatment correlates with extent of liver disease at the start of treatment,[25] we did nor find a strong relation between HAI-added survival (ie, over survival with conventional palliation in matched controls) and extent of liver disease at randomisation. It was not only patients with minimal disease whose tumours responded and who achieved survival benefit. Survival was significantly less in HAI patients whose liver metastases did not respond than in those with a response. Tumour response to floxuridine seemed to be more important than amount of disease at randomisation in determining the extent of treatment-added survival. Therefore minimal disease should not be an HAI treatment condition. However, the 2 patients who died perioperatively after hepatic artery cannulation had extensive liver metastases, and it is preferable that HAI is reserved for patients with less than 45% PHR, in whom there was no perioperative mortality.

As previously reported,[28] we found a threefold increase in extrahepatic disease in the HAI group compared with the control group (table 3). An HAI patient who survived more than a year was 33% more likely to die of extrahepatic disease than an HAI patient who did not survive a year. Thus, patients whose liver metastases responded to floxuridine may have gained survival that allowed occult extrahepatic disease to become apparent. This raises the question of whether systemic chemotherapy might be preferable to regional hepatic chemotherapy in treating colorectal liver metastases.[6]

It is not clear whether systemic fluorouracil plus folinic acid chemotherapy confers a survival benefit in disseminated colorectal cancer.[4] Randomised comparisons between systemic fluorouracil or floxuridine and intrahepatic floxuridine suggest variously overall,[25] subgroup,[29] or non-significant[30] survival benefit in favour of HAI. Systemic chemotherapy has not been shown to be preferable to HAI for treatment of colorectal liver metastases. In the absence of wholly effective systemic chemotherapy for colorectal cancer, the limited benefits of regional hepatic and systemic chemotherapy might be complementary. Survival might have been further improved in our HAI patients who died of extrahepatic disease (54% of the group) if occult extrahepatic disease had been controlled by concurrent systemic chemotherapy. Systemic fluorouracil plus folinic acid would be expected to be more effective against occult extrahepatic disease in patients whose liver metastases responded to floxuridine than in non-responders, since the response indicates tumour sensitivity to fluorinated pyrimidines.

Since 80% of patients receiving systemic fluorouracil plus folinic acid have diarrhoea, mouth ulcers, or marrow suppression,[21,22] HAI alone would be preferable for patients who are at low risk of extrahepatic dissemination. We could not identify a useful pretreatment predictor of patients at greatest risk of developing extrahepatic disease, perhaps because all patients whose intrahepatic disease was controlled by floxuridine were at similar risk of developing symptomatic extrahepatic disease.

Thus, HAI of floxuridine prolongs both overall and normal-quality survival in patients with colorectal liver metastases. No other current treatment produces superior results, and HAI should be offered to suitable patients with colorectal liver metastases. Further prolongation in survival might be achieved by slowing the growth of occult extrahepatic disease in patients who respond to HAI with systemic chemotherapy. A trial assessing the potential benefits of this approach compared with conventional systemic chemotherapy is now under way.

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Locomotor activity in spinal man

V Dietz, G Colombo, L Jensen

Summary

We studied whether spinal locomotor centres of patients with paraplegia can be activated by external stimuli.

In patients with complete paraplegia, coordinated stepping movements were induced by weight support and standing on a moving treadmill. The pattern of leg muscle electromyographic (EMG) activity was similar to that seen in healthy subjects although EMG amplitude was smaller. With daily training the amplitude of gastrocnemius EMG activity increased during the weight-bearing phase of stepping and the degree of inappropriate tibialis anterior activity decreased. Patients with incomplete paraplegia profited from the training programme in that their walking on a stationary surface improved even when unsupported.

Our results may suggest new ways to improve mobility of patients with paraplegia.

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Paraplegic Centre, University Hospital Balgrist, CH-8008 Zürich, Switzerland (Prof V Dietz MD, G Colombo DM, L Jensen DM)

Correspondence to: Prof V Dietz

Introduction

We wanted to find out how far spinal locomotor centres can be activated by external stimuli in patients with paraplegia. Coordinated leg muscle electromyographic (EMG) activity and stepping movements have been observed in paraplegic cats on a moving treadmill.[1] The loss of stepping movements in patients with paraplegia may be due to dominance of supraspinal activity over spinal neuronal mechanisms,[2] which bring about EMG activity in leg muscles.[3] We describe the extent to which EMG activity and walking movements can be elicited and trained in leg muscles of patients with complete and incomplete paraplegia.

Patients and methods

Local ethics committee approval and patients' informed consent were obtained to make recordings from 5 patients with complete paraplegia (mean age 33; level of lesion C8 [1], C6 [4]), 4 with incomplete paraplegia (36; T5 [1], C7 [2], C6 [1]), and 5 age-matched normal subjects (33). The clinical diagnosis of complete spinal cord lesion was confirmed by electrophysiological and radiological tests. Patients with incomplete paraplegia were unable to make stepping movements on a stationary surface (Frankel class C). All patients had exaggerated patellar tendon reflexes and extensor plantar responses in both legs. Patients trained on a treadmill (approximately 300 m of walking) daily. Recordings of muscle activity and leg movements were made every week.

In patients with complete paraplegia, and at the beginning of the training in patients with incomplete paraplegia, stepping movements could be induced only with the treadmill moving at low