Pergamon

European Journal of Cancer Vol. 32A, No. 7, pp. 1117-1122, 1996

Printed in Great Britain
0959-8049/96 $15.00+0.00

PII: S0959-8049(96)00044-5

Review

Locoregional Chemotherapy for Adjuvant Treatment of Colorectal Adenocarcinoma

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Adjuvant chemotherapy with 5-fluorouracil (5-FU) and levamisole administered intravenously for 1 year has proved to be effective after curative surgical resection of Dukes' stage C colon carcinomas. Locoregional chemotherapy aims at delivering drugs directly into the abdominal cavity or the liver using either intraperitoneal or intraportal route of administration. Theoretically, these routes of administration have several advantages. The drugs can be delivered at a high dose concentration to the most common site of recurrence (i.e. peritoneum and liver) with decreased systemic toxicity. This article reviews the present status of intraportal and intraperitoneal chemotherapy as adjuvant postoperative treatment for colorectal carcinoma with special attention to the results of prospective randomised trials. Some positive results confirm that both route of administration represent promising methods for adjuvant chemotherapy. However, currently there are insufficient data on which to make a clear-cut conclusion on real benefits. New trials are currently in progress to test new modalities using different drugs or different drug combinations, using both locoregional and systemic treatments, and may prove to be more effective than systemic chemotherapy alone in the adjuvant treatment of colorectal cancers.

Key words: colorectal cancer, adjuvant treatment, chemotherapy
Eur J Cancer, Vol. 32A, No. 7, pp. 1117–1122, 1996

INTRODUCTION

COLORECTAL ADENOCARCINOMA is one of the most common malignant diseases in Western countries. In the United States, it represents the second cause of death by cancer after lung carcinoma and is diagnosed in approximately 160 000 Americans each year [1]. In recent years, there has been a shift toward earlier disease at diagnosis in screened populations [2, 3]. Recently, progress has been made in the comprehension of epidemiology and molecular mechanisms of tumour progression, but it is not known whether current measures of prevention or early diagnosis will have any impact on colorectal cancer mortality during the next decade. Currently, 75% of these patients have tumours that may be resected with curative intent, and those with Dukes' A and B1 cancer (stage I) are cured mainly by surgery alone, with survival rates of 80–95% [4–6]. Patients with B2 tumours (full thickness penetration through the bowel wall, stage II) have a 5-year survival rate ranging from 65 to 75% and those with Dukes' C (nodal involvement, stage III) from 40 to 50% [4–7]. These patients are considered at high risk of tumour recurrence and constitute the target population for current adjuvant therapy. Adjuvant treatment of colorectal carcinoma, soon after resection of all gross disease, appears attractive since micrometastases are more sensitive to a given drug because of a shorter cell cycle time, a better accessibility to drugs and a smaller chance of harbouring resistance [8, 9]. A recognition of predominant patterns of spread, especially that 50% of recurrences are hepatic metastases and that 20–50% are peritoneal [10], has provided the impetus for a series of adjuvant local-regional approaches employing portal vein infusion or intraperitoneal perfusion of 5-fluorouracil (5-FU). Here, we review the status of these adjuvant loco-regional adjuvant therapies for colorectal cancer in the light of the available, published prospective, randomised trials.

PORTAL VEIN INFUSION

Rationale

Liver is the most common site of failure following potentially curative surgical resection of primary adenocarcinoma of

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Received 25 Jul. 1995; revised 18 Jan. 1996; accepted 24 Jan. 1996

EJC(A) 32:7-C

the colon and rectum. Liver metastases will develop in 40–60% of patients who will recur [11] and are a prominent cause of death. Colorectal liver metastases reach the liver via the portal vein and such dissemination may occur during surgery [12]. Once established in the liver, micrometastases are fed by portal blood. Administration of a cytotoxic agent using the same route might be more effective than systemic administration. Operative stress and immediate postoperative decrease in immune defences have been shown, in some experimental models, to improve the survival of malignant cells and to facilitate their growth in the liver [13]. Early postoperative chemotherapy administration might be particularly beneficial, destroying suspected tumour cells in the liver before established tumour growth has taken place.

Preliminary studies

To assess these theoretical advantages, early postoperative intraportal chemotherapy has been tested in animal models. Carcinosarcoma tumour cells were injected intraportally in Walker rats, followed by a single injection of meclorethamine via the same route. A 50% reduction in liver tumour 'takes' was achieved [14]. In 1975, Almersjo and associates established the safety and the pharmacological basis of portal vein infusion [15].

Randomised trials in humans (*Table* 1)

The first positive results in humans were reported by Taylor and associates in 1985 [16]. 244 eligible patients were randomised prior to surgery to receive immediate postoperative intraportal vein infusion of 5-FU and heparin or no further treatment. Patients with primary stage A, B or C colon or rectal cancer, normal liver function tests, normal Tc-99m sulphur colloid scan and/or liver ultrasound and no evidence of metastatic disease at laparotomy were eligible. 5-FU was given at a total dose of 1 g/day in continuous infusion during the first 7 postoperative days and heparin was administered i.v. at a dose of 5000 units/day to prevent portal vein thrombosis. Only 5% of randomised patients were ineligible and excluded from analysis. Therapy was well tolerated, but mild gastrointestinal toxicity (nausea, diarrhoea) was more frequently encountered in the 5-FU group (12 versus 2%, $P = 0.002$). One patient died from leucopenia and subsequent sepsis in the intraportal 5-FU group. Hepatic recurrence was reduced in the treatment arm. After a median follow-up of 4 years, 22 of the 127 control patients (17.3%) and 5 of the 117 treated patients (4.3%) developed liver metastases. The overall survival was 77.8% in the treated group versus 57.5% in the control group ($P = 0.002$). Survival analysis indicated beneficial effects of intraportal 5-FU with a mortality rate ratio of 2.08 ($P = 0.002$). Subgroup analysis suggested beneficial effects only for Dukes' B colon cancer and Dukes' C rectal cancer. This is the only study that has demonstrated beneficial effects of portal vein infusion for both hepatic recurrence and survival. The inclusion of a large number of patients with stage A cancers, for which recurrence is unlikely, is questionable. It would be interesting to have updated results from this study in order to conclude whether the treatment really enhanced the cure rate or if it only postponed the occurence of recurrences and death.

In 1990, Wereldsma and associates published the results of a Dutch multi-institutional randomised trial [17]. 317 patients with Dukes' A, B or C colonic or rectal cancer, normal liver function test and normal radiographic studies of the liver were randomised intra-operatively after curative resection into one of three arms: no treatment (control), intraportal 5-FU plus heparin at the same dose, route and schedule as Taylor and associates [16], or urokinase 10 000 units over 24 h. Toxicity, essentially gastrointestinal and mild, was encountered in 41% of patients in the 5-FU arm. After a median follow-up of 44 months, there was a significant reduction in the incidence of liver metastases in the 5-FU arm versus control (7 versus 23%, $P = 0.01$ log rank). Multivariate analysis correcting for Dukes' stage, tumour site, age and gender showed that the chance of developing hepatic metastases following portal vein infusion of 5-FU and heparin was one third that of control ($P < 0.001$). However, despite the decrease in hepatic recurrence, there was no significant improvement in the mortality rate associated with portal vein 5-FU therapy. Why the decrease in the incidence of hepatic recurrence do not translate into an increase in survival is not clear. If portal vein

Table 1. *Portal vein infusion prospective trials*

Studies	Treatment	Eligible patients	Hepatic recurrence (%)	*P* value	5-year overall survival (%)	*P* value
Taylor and colleagues [16]	Control	127	17.3	0.001	42	0.002
	5-FU–heparin	117	4.3		72	
Wereldsma and colleagues [17]	Control	102	23	0.01	64	n.s.
	5-FU–heparin	99	7		72	
NCCTG [18]	Control	109	13	n.s.	68	n.s.
	5-FU–heparin	110	15		68	
NSABP [19]	Control	459	5.9	n.s.	71	0.03
	5-FU–heparin	442	7		76	
SAKK [21]	Control	253	14.6	n.s.	55	0.02
	5-FU–MMC–heparin	252	12.3		66	
EORTC	Control	145	Non-specified		77	
	5-FU–heparin	130			81.7	n.s.
	Heparin alone	123			72.7	
	Not entered	22			73.8	

5-FU, 5-fluorouracil; MMC, mitomycin C; n.s., not statistically significant.

infusion only acts on liver micrometastases without any beneficial effect on the progression of the disease at other sites, the efficacy of locoregional adjuvant therapies may be questioned.

The prospective randomised trial initiated by the NCCTG and Mayo Clinic included 224 patients with Dukes' B or C colorectal cancer [18]. Intra-operative randomisation was achieved after curative resection based on surgical findings and frozen section pathology. 110 patients received portal vein 5-FU at 500 mg/m^2 with 5000 units of heparin over 24 h for 1 week and 109 patients were in the placebo group, 2.2% of randomised patients were ineligible. The median follow-up was 5.5 years. Side-effects were mild and mainly represented by nausea (20%) and diarrhoea (21%). Incidence of hepatic metastases was similar in the control group (13%) and in the 5-FU group (15%). Estimated 5-year survival was identical in both groups (68%, $P = 0.61$) and subset analysis did not reveal any difference for Dukes' B or C patients. In this study, an adequate number of patients was treated to exclude a 30% reduction in the mortality rate and the major limitation of this trial was that not enough patients were studied to exclude confidently a smaller degree of therapeutic effect which would still had some therapeutic impact.

Between 1984 and 1988, the NSABP included 1158 patients in a prospective randomised trial [19]. Patients were randomised pre-operatively to receive portal vein infusion of 5-FU 600 mg/m^2/day and heparin 5000 units for 7 consecutive days or no treatment. Treatment began within 6 h of completion of surgery, and patients with Dukes' A, B or C colon cancer without evidence of metastatic disease were eligible. 217 were excluded after randomisation for Dukes' stage D cancers or benign disease, 40 others were ineligible and 3 had short follow-up. Results were given for the remaining 898 patients (458 in the no treatment arm and 440 in the 5-FU infusion arm). The follow-up was complete for more than 50% of patients at 3 years, but survival information was available for only 33% of eligible patients at 4 years. There was no significant difference in hepatic metastases as the first site of relapse between both arms. Disease-free survival improved at 4 years in the treated group (74 versus 64%, $P = 0.02$), but the overall survival difference between treated and control arms after a mean follow-up of 41.8 months was not significant (81 versus 73%, $P = 0.07$). These results were recently updated [20]. After an average time on study of 89.7 months, the 5-year disease-free survival for patients randomised to surgery alone was 60% compared to 68% for patients randomised to 5-FU ($P < 0.1$). The 5-year survival in the two arms were, respectively, 71 and 76% ($P = 0.03$). There was still no significant difference in liver metastases in the two arms. In this study, the high number of patients excluded after randomisation is questionable. However, the results are interesting in that the beneficial effects in survival cannot be attributed to a decrease in the rate of hepatic recurrence. This is in contradiction with the rationale of locoregional treatment, but may be the consequence of the systemic passage of the drug.

The results of a prospective randomised trial conducted by the Swiss Group for Clinical Cancer Research (SAKK) has been recently reported [21]. 533 patients with colorectal cancer and no evidence of metastatic disease were pre-operatively randomised to receive curative surgery alone or followed by the intraportal infusion, for 7 consecutive days, of 500 mg/m^2/day of 5-FU plus a single dose of mitomycin C 10 mg/m^2. The catheter could not be placed in 7 patients only, and 28 patients were subsequently excluded. At a mean follow-up of 8 years, adjuvant therapy reduced the risk of recurrence by 21% (hazard ratio, 0.79; 95% CI, 0.62–1.00; $P = 0.051$) and the risk of death by 26% (hazard ratio, 90.74; 95% CI, 0.57–0.97; $P = 0.026$). The risk reduction was greatest in patients with tumour-involved lymph nodes and for those with colon cancer. The treated group had fewer local recurrences or liver metastases, with or without relapse at other sites, than the control group. This well-conducted study with long follow-up showed beneficial effects on survival and decrease in hepatic recurrences, although the latter was not statistically significant. Whether these beneficial effects are due to the addition of mitomycin C to the regimen or to the early administration of the locoregional chemotherapy cannot be determined but certainly has to be taken into account for further trials.

Preliminary results from the randomised trial conducted by the EORTC, involving 398 eligible patients randomised to three treatment arms—control, portal vein infusion of heparin 5000 units for 7 days with or without 5-FU 500 mg/m^2/day—has not shown any significant survival advantage for portal vein infusion. The heparin only arm was withdrawn because of a lack of interest (B. Nordlinger, personal communication).

Conclusion

The portal vein adjuvant trials summarised above and in Table 1 have provided conflicting results. These six randomised trials, using almost an identical dose, schedule and route of administration and involving a total of over 2300 patients have attempted to establish the effectiveness of portal vein infusion of 5-FU. Treatment has generally been well tolerated without significant hepatic toxicity nor any increase in postoperative morbidity. Two studies reported a significant decrease in the incidence of hepatic recurrence compared with control [16, 17]. Three studies reported an overall survival advantage [16, 19, 21]. Most of the available trials fall short of the number of patients that may be required to demonstrate an effect of 5-FU by the portal route with sufficient statistical power on the two end-points: appearance of liver metastases and survival. The proportion of patients excluded after randomisation in some studies was unusually high, and there are conflicting results on the stage and site of tumour most likely to benefit. The current evidence from portal vein infusion trials, including estimates where full data were not available, has been recently published [22]. For all the trials studied, the ratio of deaths/number of patients entered was 240/1085 for intraportal 5-FU and 323/1116 for controls, providing a treatment effect of $2P < 0.0002$ with a test for heterogeneity of $\chi^2_5 = 9.2$ (ns). The results of another meta-analysis including nine randomised trials and a total of 3274 patients were recently presented at the ASCO meeting (Piedbois, personnal communication). Analysis was based on individual patient data and stratified by trials. Portal vein infusion of 5-FU modestly improved survival of patients with resectable colorectal cancer with an overall risk reduction of 13% ± 5%, $P = 0.01$ log rank. The risk reduction was higher for stage B and C tumours and for colon cancers. The time to liver metastases as first event was significantly longer after portal vein infusion.

In 1995, the benefit of portal vein infusion of 5-FU as adjuvant therapy for colorectal cancer seems likely, but remains to be formally proven. Therefore, it cannot be recommended in clinical practice based on all available infor-

mation at the present time. However, the possibility that portal vein infusion could confer a survival benefit, at least as great as prolonged systemic chemotherapy, cannot be excluded with a considerable human and economic advantage of a treatment completed in one week with minimal morbidity. Two important studies (EORTC and AXIS) are currently in progress. They may help in the near future to better appreciate the benefits of this therapeutic approach.

INTRAPERITONEAL CHEMOTHERAPY

Rationale

Peritoneal cavity and resection site are common sites of tumour recurrence after initial radical surgical treatment of colorectal cancer [10]. Intraperitoneal spread of tumour cells can occur prior to surgery by the dissemination of emboli, resulting from serosal penetration by cancer or leakage of malignant cells from lymphatics. It can also occur during peroperative mobilisation of the tumour and surgical dissection. Finally, fibrin entrapment of intra-abdominal tumour emboli on a traumatised peritoneal surface and tumour promotion of these entrapped cells through growth factors involved in the wound healing process may also participate in the intraperitoneal diffusion of the tumours [23].

After intraperitoneal administration, large molecular weight substances, such as chemotherapeutic agents, are confined to the abdominal cavity for long periods [24]. Intraperitoneal chemotherapy can, therefore, increase the amount and concentration of drug to the residual tumour as the peritoneal–plasma barrier increases contact duration between drug and tumour cells. It also decreases the amount of drug in plasma and reduces the risk of systemic toxicity. Immediate postoperative intraperitoneal chemotherapy can fill the abdominal cavity with a large volume of fluid that may decrease fibrin accumulation and eliminate tumour cells from the abdomen before they fix within scar tissues. The elimination of platelets, white blood cells and monocytes from the abdominal cavity may also diminish the production of tumour growth associated with the wound healing process. Another potential advantage of intraperitoneal administration is the absorption of the cytostatic drug via the lymphatics and the portal system which may be beneficial in the prevention or the treatment of hepatic micrometastases [25].

Pharmacology and physiology of intraperitoneal administration of cytotoxic drugs

Several experimental and clinical studies have been carried out to improve the understanding of the pharmacology and the physiology of intraperitoneal drug delivery in the immediate postoperative period. It has been established that the peritoneal clearance of a drug is inversely proportional to the square root of its molecular weight. Large molecules, such as many chemotherapeutic agents, take longer to clear from the peritoneal cavity than smaller ones [26]. An animal study [27] and intraperitoneal chemotherapy trials in patients with advanced intra-abdominal malignant diseases [28, 29] have demonstrated that large volumes of the drug-containing solution are necessary to ensure exposure of the entire peritoneal surface and to overcome much of the resistance to free fluid flow in the abdominal cavity. After intraperitoneal drug delivery, direct drug uptake occurs by free surface diffusion, but the depth of penetration seems to be extremely limited, from a few cell layers to a few millimetres [30–32], so tumours to be treated should, therefore, have a small volume. The major mechanism of extraction of compounds placed into the peritoneal cavity is by way of the portal circulation [33]. Drugs which are metabolised into non-toxic forms during passage through the liver will exhibit a pronounced pharmacokinetic advantage after intraperitoneal instillation, and a major portion of the drug will enter the systemic circulation in a non-toxic form. Experimental data suggest that 5-FU delivery to the liver after intraperitoneal administration equals the amount of drug entering the liver during intrahepatic artery infusion [34].

Tolerance

Intraperitoneal chemotherapy has been compared with systemic chemotherapy with regard to frequency of toxic reactions [35]. No difference in the incidence of toxicity was noted between the group of 36 patients that received intraperitoneal 5-FU and the 30 that received 5-FU intravenously with the same schedule. Toxicity of intraperitoneal therapy was limited to local complications, such as abdominal pain, mostly due to the volume of fluid instilled. Chemical peritonitis was rare and always observed after prolonged administration of the drug. Effusion of the drug into the subcutaneous tissue has been reported anecdotically [36, 37]. If intraperitoneal chemotherapy appears to be more beneficial in the immediate postoperative period (no adhesions, minimal residual disease, hepatic micrometastases), the safety for healing of colonic anastomosis had to be examined. In animal studies, some have found no difference for anastomotic spontaneous disrupture or healing strength between rats receiving intraperitoneal chemotherapy starting on days 1, 3 or 7 and controls [38], while others have found reduced early postoperative collagen synthesis [39]. Preliminary results of a prospective randomised trial in humans confirmed that early intraperitoneal chemotherapy after surgical resection of high risk colon cancers was well tolerated and not detrimental to healing of anastomosis [40]. 267 patients with stage B2 or C colon cancer were randomised to surgery alone ($n = 134$) or surgery plus 5-FU 600 mg/m^2/24 h intraperitoneally in 1.5 l of dialysis fluid for 6 days ($n = 133$). Tolerance was good in 99 patients of the 5-FU group while 16 experienced transient abdominal discomfort, pain or nausea, and 5 fever. Haematological and hepatic tolerance was good for the two groups. Overall morbidity was similar in both groups.

Results of cancer treatment

First results of intraperitoneal adjuvant therapy in animal models were promising. In a colon cancer model in rats, induced by subcutaneous administration of azoxymethane, 83 rats had isolated colon cancer. Forty-one of those with no extra-intestinal involvement were randomised after total colectomy to receive no further treatment or intraperitoneal 5-FU 5 mg/kg/day for 5 consecutive days beginning 2 weeks after surgery. At the end of the study, 30 rats were evaluable. In the control group 5/18 animals (27.7%) had peritoneal carcinomatosis and 4/18 (22.2%) had liver metastases. In the treated group, none of the 12 animals had either peritoneal carcinomatosis nor liver metastases. Survival analysis was not possible in this model as rats died because of the metabolic consequences of the total colectomy [41].

Phase 1 studies in man using 5-FU intraperitoneally demonstrated that high levels of the drug, uniformly distributed within the peritoneal cavity, were obtained providing that the treatment was administered in a large volume of fluid

(≥1500 ml). A major fraction of intraperitoneal 5-FU left the peritoneal cavity through the portal venous system, and up to 90% was extracted from the blood as it passed from portal vein into the hepatic venous system [34]. Technical considerations in the use of intraperitoneal catheter and drug delivery were also determined [42].

In 1985, Sugarbaker and associates reported the first results of a prospective randomised trial in humans [35]. 66 eligible patients with primary colon or rectal cancer and positive lymph nodes or another poor prognostic sign were randomised to receive surgery plus i.v. 5-FU ($n = 30$) or surgery plus i.p. 5-FU ($n = 36$). Intravenous 5-FU was given as a bolus dose for 5 consecutive days starting within 2 months of the large bowel resection, and given in 1 week every month for 1 year. Intraperitoneal 5-FU was administered in 2 l of solution via a Tenckhoff catheter using the same schedule and for i.v. 5-FU. Doses of 5-FU were increased each cycle until toxic side-effects occurred. No difference in disease-free survival nor in overall survival was observed. The median survival was 46.3 months in the i.v. group and 47.5 months in the i.p. group. The percentage of patients who recurred in both arms was similar (36% for i.p. treatment and 37% for i.v. treatment), but the number of patients who recurred with histologically proven peritoneal carcinomatosis was significantly lower in the intraperitoneal 5-FU arm (2/10 versus 10/11, $P = 0.003$).

In a multicentre trial conducted in Sweden from 1990 to 1992 [43], 50 patients were randomised to receive adjuvant intraperitoneal 5-FU (500 mg/m^2/day in a small volume of fluid) and intravenous leucovorin (60 mg/m^2/day), and 51 patients to receive placebo after curative resection of colorectal cancer. Treatment started on the day after surgery and continued for 6 days. Surgical complications were similar in both groups and one anastomotic dehiscence occurred in each arm. Hospital stay was identical, but the time between surgery and the first bowel motion was significantly lower in the placebo arm (4.7 versus 5.6 days, $P < 0.05$). Toxicity was not significantly different in the two groups, 13% of patients requested termination of treatment, mostly because of abdominal pain. The trial was terminated without survival data after the publication of Moertel's results of adjuvant therapy with 5-FU/levamisole [44] and a new trial comparing 5-FU/leucovorin versus 5-FU/levamisole with or without leucovorin was started.

Summary and conclusions

Available results of intraperitoneal chemotherapy as adjuvant treatment for colorectal cancer in humans reported herein are too short and preliminary to allow any definitive conclusion on this mode of treatment. However, several limited clinical trials using this therapy for other intra-abdominal malignant diseases have been reported with the suggestion of some clinical benefit [45–47]. The use of 5-FU in the early postoperative period appears to be well tolerated without detrimental effects on healing of anastomosis. As 5-fluorouracil alone has only limited activity in the adjuvant therapy of colorectal malignancies, a survival benefit was unlikely to be demonstrated. It is possible that the addition of a second drug to the intraperitoneal regimen or a treatment using both intraperitoneal and intravenous chemotherapy may be more effective than intraperitoneal 5-FU alone. A large-scale trial aiming to test the combination of locoregional and systemic chemotherapy is currently being conducted by the EORTC. The aim is to randomise postoperatively 2000 patients with Dukes' B2 or C colorectal adenocarcinoma in order to compare 6 months' intravenous therapy with 5-FU plus either levamisole or leucovorin with or without immediate postoperative loco-regional chemotherapy with 5-FU administered in the portal vein or the peritoneum for 6 days. More than 1200 patients have already been recruited (by September 1995). Six-day intraperitoneal chemotherapy may prove to be as effective as prolonged intravenous chemotherapy or add beneficial effects to standard postoperative chemotherapy with 5-FU and levamisole.

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