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ORIGINAL ARTICLE

Hepatic arterial infusion of oxaliplatin, 5-fluorouracil and leucovorin in patients with liver metastases from colorectal carcinoma

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Summary

Purpose: *Limited data are available regarding the efficacy of hepatic arterial infusion (HAI) of oxaliplatin in patients with liver metastases from colorectal carcinoma (CRC). The aim of the present study was to evaluate the results of HAI of oxaliplatin combined with 5-fluorouracil (5-FU) and leucovorin (LV) in patients with such metastases.*

Methods: *A retrospective analysis of 22 CRC patients treated with HAI of combination of oxaliplatin and 5-FU and LV was performed.*

Results: *Partial response (PR) was observed in 4 (18%) patients and stable disease (SD) in 7, with an overall disease control rate of 50%. The median progression-free (PFS) and overall survival (OS) were 7 and 11 months, respectively. Two patients treated with first-line treatment underwent subsequent liver resection. In 2 patients, HAI of oxaliplatin, 5-FU and LV was combined with systemic administration of bevacizumab.*

Conclusion: *Our data demonstrate reasonable efficacy of HAI with oxaliplatin, 5-FU and LV in patients with liver metastases from CRC.*

Key words: colorectal carcinoma, 5-fluorouracil, hepatic arterial infusion, leucovorin, oxaliplatin

Introduction

Liver represents the most common site of metastases in patients with metastatic CRC [1]. Liver involvement in CRC is often isolated, i.e. there are no extrahepatic metastases [1], and liver-directed therapeutic strategies are frequently regarded as appropriate [2]. Most patients with liver metastases present with lesions not amenable to resection. Moreover, metastases ultimately recur in the majority of patients after liver resection [3]. Patients with non-resectable liver metastases are treated with anticancer drugs. The median survival of patients with liver metastases treated with combined systemic chemotherapy (fluoropyrimidines with oxaliplatin and/or irinotecan) is between 16 and 22 months [4,5]. Although further improvement has been observed with the introduction of targeted therapies [6,7], virtually all patients will ultimately progress and die. Thus, optimal therapeutic strategy in the majority of patients with CRC metastatic to the liver still remains to be defined, and different therapeutic options should be explored.

Historically, mCRC has been known to be resistant to most cytotoxic agents. Because of a dose-response effect that is evident for many cytotoxic agents the aim in patients with metastatic disease is to administer maximum tolerated dose. However, dose escalation is limited by systemic toxicity. Because of limited inherent selectivity of cytotoxic drugs, different approaches have been explored to increase this selectivity by other manipulations, including anatomical selectivity, e.g. HAI. HAI of cytotoxic agents in patients with liver metastases has the advantage of higher intratumoral drug concentration and less systemic toxicity [8]. It has been demonstrated in clinical trials that this theoretical advantage translates into superior response rate and quality of life [9]. It was, however, more diffi-

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cult to demonstrate an improvement in survival. Only recently, a survival advantage of HAI compared to systemic chemotherapy could be demonstrated [10], but this trial was reported at the time when fluoropyrimidine monotherapy could no longer be regarded as the standard of care. Consequently, the use of HAI in CRC metastatic to the liver is still controversial. Even less is known about the use of HAI in liver metastases of non-CRC primary [11].

With improvements of systemic therapy of metastatic CRC the interest in HAI decreased markedly. Therefore, relatively limited data are available on the efficacy of HAI using oxaliplatin. Herein we present a retrospective analysis of patients with liver metastases from CRC treated with HAI of oxaliplatin and 5-FU plus LV.

Methods

A retrospective analysis was performed in patients with histologically verified CRC metastatic to the liver, treated at Charles University Medical School Teaching Hospital, Hradec Králové, Czech Republic between January 2001 and December 2009 with at least one course of HAI with oxaliplatin, 5-FU and LV. Relevant information was retrieved from the patient charts.

Chemotherapy

HAI was administered either weekly or biweekly using infusion pumps. The biweekly regimen consisted of biweekly HAI of oxaliplatin (200 mg flat dose) for 1-2 h, and weekly HAI of leucovorin (50-100 mg) administered as slow bolus and 5-FU (500-750 mg/m^2) for 2-3 h. The weekly regimen consisted of weekly HAI of oxaliplatin (100 mg flat dose) for 1-2 h, LV (50-100 mg) administered as slow bolus and 5-FU (500-750 mg/m^2) for 2-3 h.

In 2 patients HAI with oxaliplatin, 5-FU and leucovorin was combined with i.v. administration of bevacizumab, 5 mg/kg every 14 days.

Technical aspects

HAI was administered through catheters with a subcutaneous port system implanted either surgically (12 patients) or percutaneously (10 patients). Before surgical implantation of the catheter with subcutaneous port system an angiography of the arteries supplying the liver was performed. During open surgery, the hepatic artery was identified, and a intraarterial catheter was inserted via the gastroduodenal artery. The tip of the catheter was inserted into the vessel to reach the level of the junction with the common hepatic artery. The gastroduodenal artery was ligated distally, and the position of the catheter was secured with multiple ligations. The catheter was then flushed with heparin solution, thrust through the abdominal wall and, finally, connected with a subcutaneous port chamber. The port chamber was then placed subcutaneously over the lower ribs. The perfusion of liver parenchyma was verified intraoperatively by injecting methylene blue.

Percutaneous catheter was introduced by an interventional radiologist via the standard femoral approach. The 5-French visceral shape catheter was placed into the common hepatic artery, with the catheter tip close to the origin of the gastroduodenal artery. Subsequently, the exchange guide-wire was inserted into the gastroduodenal artery and diagnostic catheter was replaced with the permanent catheter that had a side-hole within 3-5 cm from the tip. The segment of the permanent catheter distally from this side-hole was stabilized in the gastroduodenal artery to expose this side-hole fully for HAI. A micro-catheter introduced through the side-hole was used to place platinum embolic microcoils along the distal segment of the catheter in the gastroduodenal artery in order to anchor the catheter tip. At the end of the procedure subcutaneous space for the port chamber was created that was connected to the catheter at the level of the common femoral artery. In case of multiple hepatic arteries, the accessory vessels were first embolized proximally to convert hepatic arterial supply to a single vessel.

Evaluation of response

Serum carcinoembryonic antigen (CEA) was determined by radioimmunoassay using a commercial kit (Immunotech; Marseille, France) [5]. Response was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST). Adverse events were graded using Common Terminology Criteria for Adverse Events version 3.0 (http://ctep.cancer.gov).

Statistical considerations

PFS was measured from the date of the first HAI course to the date of progression or death, or censored at the last follow-up in 2012. OS was measured from the date of the first HAI course to the death or censored at the last follow-up in 2012. No patient was lost to follow-up. PFS and OS were analyzed using the Kaplan-Meier method. Because of the limited number of patients included in the present retrospective study and, consequently, low statistical power, no formal statistical comparisons between the subgroups of the patients were performed, and only descriptive statistical methods were used. The statistical analyses, including survival analysis and descriptive statistics, were performed using NCSS software (Number Cruncher Statistical Systems, Kaysville, UT, USA).

Results

A total of 22 patients (11 males, 11 females, aged 62 ± 11 years, range 36-80) with isolated liver metastases from CRC were treated with at least one cycle of HAI. Eleven patients were treated by the weekly regimen, and 11 by the biweekly regimen (Table 1). Five patients received therapy as first-line, while 17 patients as second or higher-line treatment. In most of the patients treated in the first-line, the administration of chemotherapy with bevacizumab was considered problematic or even contraindicated because of comorbidities, e.g. idiopathic colitis or poor general condition. Median duration of metastatic disease at the initiation of HAI was 11 months (range 1-38). All patients treated as second –or higher– line therapy had received prior irinotecan. The median number of cycles of HAI administered was 8 (range 1-32), and the median duration of therapy was 13

Table 1. Comparison between patients treated by the weekly and biweekly regimen

Parameter	*Weekly regimen (N= 11)*	*Biweekly regimen (N= 11)*
First-line therapy (N)	4	1
Median number of HAI cycles administered (range)	9 (4-32)	7 (1-21)
Median duration of therapy, weeks (range)	13 (4-49)	20 (2-60)
Starting dose of oxaliplatin, mg/m^2 (mean ± SD; range)	56 ± 9 (46-80)	103 ± 20 (55-127)
Starting dose of 5-FU, mg/m^2 (mean ± SD; range)	597 ± 139 (385-802)	690 ± 116 (414-838)
Dose reduction (N)	2	3

SD: standard deviation, 5-FU: 5-fluorouracil, HAI: hepatic arterial infusion

weeks (range 4-49). In 5 patients who had to terminate HAI because of port system malfunction the treatment continued with systemic administration of oxaliplatin (FOLFOX7 regimen in 3 cases, combinations of oxaliplatin and raltitrexed, or oxaliplatin and capecitabine in one case each). The actual starting doses of oxaliplatin administered are shown in Table 1. The actual starting dose of 5-FU for both regimens was 644±134 mg/m^2 (range 385-838). Dose reduction was necessary in 5 patients. The best response assessed by CT or MRI was PR in 4 patients (18%) and SD in 7 (32%), with an overall disease control rate of 50%. Progression was observed in 6 (27%) patients. Response was not evaluable in 5 (23%) patients. The median PFS was 7 months (range 2-42$^+$). and the median OS survival was 11 months (range 2-54) (Figure 1). The median PFS and OS for the patients treated in the first- or second- and higher-line are shown in Table 2. Two patients treated as first-line subsequently underwent liver resection. At the time of analysis, only the patient with the comorbidity of idiopathic colitis treated in the first-line with subsequent liver resection was alive without recurrence 50 months after the start of therapy. In 2 patients treated in the second-line, HAI with oxaliplatin, 5-FU and LV was combined with systemic administration of bevacizumab (5 mg/kg every 14 days), resulting in SD and PD with OS of 8.3 and 3.5 months, respectively.

The side effects of therapy including catheter-related problems, neutropenia, anemia, thrombocytopenia, nausea or vomiting, peripheral neuropathy, diarrhea, hypersensitivity, abdominal pain and chest pain (without evidence of any cardiac event) are shown in Table 3. Serious toxicity, defined as grade 3 or higher toxicity requiring hospitalization, was observed in 5 cases, including thrombocytopenia and bleeding, diarrhea, diarrhea with dehydration and sepsis, nausea and vomiting with dehydration and pneumonia.

Baseline CEA concentrations were available for all patients, and with one exception all patients had baseline CEA concentrations above 5 μg/L. CEA concentrations were followed in 20 patients (all patients with the exception of a patient with normal baseline concentration and another patient with rapid clinical progression). CEA concentrations decreased by more than 50% in 13 patients, were stable in 4 and progressed in 3 (Figure 2). CEA surge with concentrations initially

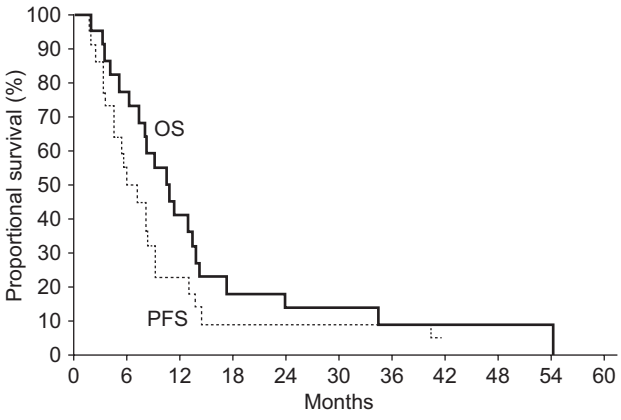

Figure 1. Progression-free survival (PFS) and overall survival (OS) of patients treated with HAI with oxaliplatin, 5-FU and leucovorin.

Table 2. Efficacy of HAI combination therapy in patients treated in the first and second or higher line of treatment

Parameter	*First-line (N = 5)*	*Second or higher line (N = 17)*
Partial response, N (%)	2 (40)	2 (12)
Stable disease, N (%)	0	7 (41)
Progressive disease, N (%)	2*(40)	6 (35)
Not evaluable, N (%)	1 (20)	2 (12)
Secondary resection, N (%)	2 (40)	0
Progression-free survival, median (range)	6 (2-50+)	7 (2-15)
Overall survival, median (range)	6 (2-54)	11 (4-35)

*early clinical progression

Table 3. Side-effects of therapy

Side-effects	*Any grade, N (%)*	*Serious (grade 3 or higher or requiring hospitalization) N (%)*
Catheter-related problems	7 (32)	0
Neutropenia	1 (5)	0
Anemia	4 (18)	0
Thrombocytopenia	11 (50)	1 (5)
Nausea/vomiting	7 (32)	1 (5)
Peripheral neuropathy	4 (18)	0
Diarrhea	5 (23)	2 (9)
Oxaliplatin hypersensitivity	1 (5)	0
Pneumonia	1 (5)	1 (5)
Abdominal pain	6 (27)	0
Chest pain	2 (9)	0

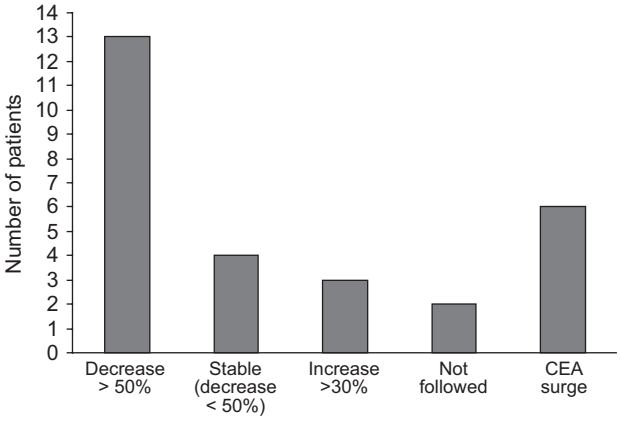

Figure 2. Response of serum CEA to therapy.

rising after the start of therapy and then decreasing was observed in 6 patients, including one patient classified as progressing (post-surge CEA increase of more than 30% compared to baseline).

Discussion

The results of the present study demonstrate the efficacy of HAI of oxaliplatin, 5-FU and LV in patients with CRC metastatic to the liver. In selected patients the therapy was effective even when administered as second- or higher- line treatment. OS and PFS rather than objective response rate were the focus of the present analysis. The PFS and OS of all patients in this study are at the lower range of values reported in earlier studies of HAI with oxaliplatin in second- and higher-line therapies, reflecting the fact that most patients were heavily pretreated. The access to oxaliplatin was restricted in the Czech Republic during the time most patients in the present series were treated, and the drug was covered by insurance plans only when other therapeutic options were exhausted. This might have created a selection bias that resulted in inclusion of patients with poor prognosis. Moreover, oxaliplatin became widely available at the time when the targeted agents were registered, and HAI with oxaliplatin, 5-FU and LV was selected for patients who were contraindicated for bevacizumab because of comorbidity or poor general condition, creating another potential negative selection bias. Specifically, this negative selection may explain the poor survival of the few patients treated in the first-line who were offered HAI because the condition of the patients limited other treatment options. Therefore, a comparison of the present cohort with prospective studies that effectively used positive patient selection is difficult. Nevertheless, the administration of HAI resulted in a significant objective response rate of 18% and an even higher proportion of patients with a more that 50% decrease of CEA concentrations. A significant proportion of patients with CEA surge illustrates the difficulties in the interpretation of CEA response.

Flat dosing was used for oxaliplatin dose calculation in the current study, similarly to HAI of some other cytotoxic agents [12]. The reason was practical as, because of difficult access to oxaliplatin, it was strived to use the whole vial of the drug. Although most studies used dosing schedules based on body surface area, there is currently no firm evidence supporting this practice against the other dosing approaches in the case of HAI. Many different cytotoxic agents have been administered as HAI in patients with liver metastases from CRC.

The last 20 years we have witnessed considerable progress in chemotherapy, the principal therapeutic modality in metastatic CRC patients. Firstly, systemic chemotherapy has been demonstrated to significantly improve survival over best supportive care in such patients [13]. Secondly, irinotecan and oxaliplatin have been introduced, and incremental survival gains have been demonstrated for the combination of fluoropyrimidines with these agents [4]. Thirdly, improvement of outcome was demonstrated for agents targeting vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR) [6,7].

Table 4. Overview of the studies of HAI with oxaliplatin in patients with metastatic colorectal cancer

Reference no.	*Study type*	*Regimen*	*Dose of oxaliplatin (mg/m^2)*	*Schedule of oxaliplatin*	*Number of patients*	*Line of therapy*	*Response rate (%)*	*Median PFS (months)*	*Median OS (months)*
18	phase I	comb. HAI FU+FA	25-150	q3w	21	1st & 2nd	59	NR (>7)	NR (>7)
19	phase II	comb. HAI FU+FA	100	BW	21	≥2nd	24	5.9	36.1
20	phase II	comb. HAI FU+FA	100	BW	11	2nd	45	7.2	18.3
21	phase II	comb. syst. FU+FA	100	BW	44	≥2nd	62	7	16
22	phase II	monotherapy	20	cont. x 5D q3w	17	≥2nd	46	10	19
23	phase II	comb. syst. FU+FA	100	BW	28	≥2nd & 1st	64	27	27
24	phase I-II	monotherapy	25-175	q3w	12	≥2nd	33*	3	13
25	phase II	comb. HAI FU+FA+MMC	130	q5w	5	1st & 2nd	80	NA	>25
26	retrospective	chronom. HAI CPT+FU	20	D2-5 q3w	29	≥2nd	35	4.5	18
27	phase II	comb. HAI CPT+ doxifluridine	100	q3w	32	1st & ≥2nd	47	7.8	17.7
28	retrospective	comb. HAI raltitrexed	130	q3w	17	≥3rd	65	10.5	27.5
29	pilot	comb. syst. FU+FA+ syst. bevacizumab	100	BW	3	≥2nd	33	4	NA
30	phase I	comb. syst. FU+FA+ syst. bevacizumab	60-175	q3w	29	≥2nd	11	NA	NA
31	pilot	comb. HAI FU+FA+ syst. cetuximab	100	BW	5	2nd	62**	8.7**	NR
Present series	retrospective	comb. HAI FU+FA	56 or 103	W or BW	22	≥2nd & 1st	18	7	11

*in the phase II part of the study at the dose of 150 mg/m^2; **in the whole group of 8 patients, including 3 patients treated with irinotecan; W: weekly, BW: biweekly, comb: combination, chronom: chronomodulated, cont: continuous, CPT: irinotecan, D: day, FA: folinic acid (leucovorin), FU: 5-fluorouracil, MMC: mitomycin C, NA: not available, NR: not reached, q3w: every 3 weeks, q5w: every 5 weeks, syst: systemic

A number of randomized studies investigated the efficacy of HAI, but significant improvement of survival against best supporting care was observed in patients treated with HAI in only 2 trials [14,15] but not in the other trials [9]. On the other hand, the objective response rate was significantly higher in many trials and a significantly better quality of life was demonstrated in patients treated with HAI [16]. Thus, before the era of targeted therapies HAI was considered treatment of choice in patients with isolated, limited, non-resectable CRC liver metastases in many centers. After the introduction of targeted agents, the use of HAI decreased markedly.

Although 5-fluoro-2'-deoxyuridine (floxuridine) has been regarded as a standard agent for hepatic arterial infusion, the results of a randomized trial indicated that 5-FU is at least as effective as floxuridine [17], and 5-FU has been widely used for HAI. Several studies have reported encouraging activity of HAI with oxaliplatin, mostly as combination therapy, in the first- or higher-line of therapy of CRC liver metastases [18-31] (Table 4). In a phase I trial the dose of oxaliplatin recommended for further study was 150 mg/m^2, administered every 3 weeks [24]. Most studies of HAI with oxaliplatin investigated the combinations with 5-FU and LV. The recommended dose of oxaliplatin in combination with 5-FU and LV from a phase I trial was 125 mg/m^2 every 3 weeks [18]. HAI with oxaliplatin at 100 mg/m^2 was also administered in combination with 5-FU and LV administered in a biweekly regimen as HAI [19,20] or systemically [21,23]. The objective response rate and median OS ranged between 24-64% and 16-27 months, respectively [19-21,23]. HAI with oxaliplatin has also been combined with HAI with raltitrexed [26]. In the present study HAI with oxaliplatin, 5-FU and LV was combined with systemic bevacizumab in 2 patients, but none of these patients had a remarkable response. Similarly to the 2 patients in the present report, the reports on HAI with oxaliplatin plus systemic bevacizumab are also limited [29,30]. HAI with oxaliplatin has been combined with systemic administration of cetuximab only in few patients [31]. The combination of systemic oxaliplatin with HAI with 5-FU resulted in a response rate of 41% [32].

The toxicities of systemic treatment, e.g. gastrointestinal toxicity induced by cytotoxic drugs [33], or skin toxicity associated with the anti-EGFR therapy [34], have profound effect on the quality of life. Abdominal pain has been reported as a peculiar side effect of HAI with oxaliplatin in a number of studies [22-24]. Although theoretically the hepatotoxicity of cytotoxic agents administered by HAI could present a serious problem, in clinical practice liver toxicity of agents administered in HAI regimens is, in general, limited. Oxaliplatin-induced liver toxicity manifests as sinusoid obstruction syndrome [35]. This toxicity may be of importance in patients undergoing liver resection after neoad-

juvant therapy [36], but it is currently unknown whether this toxicity is more prominent with HAI. So far, no warning safety signals regarding hepatic toxicity have been reported from trials using HAI with oxaliplatin.

In conclusion, the efficacy of the HAI combination of oxaliplatin, 5-FU and LV in the treatment of CRC liver metastases was confounded by possible negative selection in the present cohort. This combination may be safely administered as an adjuvant treatment before surgery for localized tumors.

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