Pharmacologic and clinical aspects of isolated hepatic perfusion (IHP) of liver metastases of solid tumours

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CHAPTER 5

Management of isolated non-resectable liver metastases in colorectal cancer patients: a case-control study of isolated hepatic perfusion with melphalan versus systemic chemotherapy

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Abstract

To compare the median overall survival of patients with isolated non-resectable liver metastases in comparable groups of patients treated with either isolated hepatic perfusion (IHP) with melphalan or systemic chemotherapy

All patients with isolated liver metastases from colorectal cancer origin, who underwent IHP with 200mg melphalan between August 1994 and December 2004, through both the portal vein and hepatic artery, were included in this study. The control group consisted of a subgroup of colorectal cancer patients with liver metastases only, who were enrolled in the randomized CApecitabine, IRinotecan, Oxaliplatin (CAIRO) phase III study between January 2003 and December 2004.

Ninety-nine patients were treated with IHP, and 111 patients were included in the control group. All patient characteristics were comparable except for age. Median follow up was 78.1 months for IHP versus 54.7 months in the control group. Median overall survival was 25.0 (95% CI 19.4-30.6) months for IHP and 21.7 (95% CI 19.6-23.8) months for systemic treatment (P=0.29). Overall survival was not influenced by gender, age, LDH, location of primary tumor, timing of liver metastases and adjuvant treatment of the primary tumor and was only influenced by metastasectomy after study treatment (P<0.001). However, the number of patients in whom metastasectomy was performed did not differ significantly between the two groups. Treatment-related mortality was 2% for the systemic treatment and 6% for IHP (P=0.11).

Compared to a patient group with comparable characteristics treated with systemic chemotherapy, IHP does not provide a benefit in overall survival in patients with isolated non-resectable colorectal liver metastases. Currently the use of IHP cannot be advocated outside the scope of clinical studies.

Introduction

The treatment of patients with metastatic colorectal cancer is with palliative intent, and with standard cytotoxic drugs median overall survival times of approx. 17 months can be achieved, which may be further improved by the use of targeted agents [1]. Long-term survival and sometimes cure may be achieved in the subset of patients in whom a radical resection of metastases can be performed. The liver is the only site of metastatic disease in approximately 30% of colorectal cancer patients [2, 3]. Although complete surgical resection is considered the treatment of choice, with 5-year survival rates ranging from 25-51%, metastasectomy is only possible in less than 10 percent of patients, due to the number, location or size of the metastases [4-6]. The treatment of non-resectable colorectal liver metastases remains a challenge for both medical oncologists and surgeons. Down-sizing of metastases by chemotherapy may allow secondary resections in a minority of patients, but the clinical benefit is uncertain due to the lack of prospective randomized studies [1]. Regional cytotoxic treatment options can offer the potential benefit of both aggressive local treatment and limited systemic toxicity. Phase II studies involving isolated hepatic perfusion (IHP) in colorectal cancer patients have shown hepatic response rates up to 74% with a median time to hepatic progression up to 14.5 months, a median overall survival of 27 months and 5 year survival of 9%[7-11]. Currently, new techniques and agents are applied to further improve the results of IHP [12, 13].Although these results seem promising, so far the definite role of IHP has not been established. Possibly, in this selected group of patients, similar results can be achieved with systemic therapy alone. Since a randomized controlled trial comparing IHP, a complex surgical procedure with considerable mortality, with systemic treatment appears not feasible as well as possibly unethical, we performed a case-control study. In this study, we compared the overall survival after IHP treatment and systemic treatment in comparable patient groups. Our results on IHP were obtained in a time period in which targeted therapy was not yet implemented, and therefore we selected a control group that also had not been exposed to these agents. Since the overall survival of patients with metastatic colorectal cancer correlates with the exposure of patients to all three effective cytotoxic drugs (i.e. a fluoropyrimidine, oxaliplatin and irinotecan) [14], we chose our control group from a prospective study in which the use of all these drugs was a prospective part of the study design [15].

Patients and methods

IHP

Between August 1994 and December 2004, 179 patients with liver metastases were considered suitable for IHP treatment with 200mg melphalan, according to a study protocol approved by the medical ethical committee of the Leiden University Medical Center, as previously published [7, 16, 17]. Of the 105 of the 179 consecutive patients with colorectal cancer who were actually treated with IHP, 6 patients were excluded because they were treated with IHP with vena porta perfusion only, a technique which has been abandoned [17]. Therefore 99 patients were included in this analysis. The data were obtained from a prospectively collected database and analyzed retrospectively. All IHP patients had measurable, irresectable colorectal metastases confined to the liver. Standard staging procedures were performed including CT scan of the chest and abdomen. Additional MRI or PET scans were performed if clinically indicated. Eligibility criteria included a WHO performance status < 2, leukocyte count $\geq 3.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, maximum serum creatinine level 135 µmol/L, maximum serum bilirubin level 17 µmol/L and minimum serum albumin level 40 g/L. Exclusion criteria were age over 70 years, life expectancy of less than 4 months, more than 60 percent hepatic involvement of tumor tissue as estimated from the preoperative abdominal CT scan, coagulation disorders and evidence of extrahepatic metastatic disease. The interval between resection of the primary colorectal tumor and perfusion had to be at least 6 weeks.

Systemic treatment

Between January 2003 and December 2004, 803 patients were enrolled in the CApecitabine, IRinotecan, Oxaliplatin (CAIRO) study of the Dutch Colorectal Cancer Group (DCCG): a phase III randomized controlled trial comparing sequential versus combination chemotherapy with capecitabine, irinotecan and oxaliplatin in advanced colorectal cancer patients [15]. Patients aged over 18 years were eligible if they had histologically proven advanced colorectal cancer that was in an advanced stage and not amenable to curative surgery, together with measurable or assessable disease parameters, and no previous systemic treatment for advanced disease. Previous adjuvant chemotherapy was allowed provided that the last administration was given at least 6 months before randomization. Further study details have been presented [15]. The primary result of the CAIRO study showed no significant overall survival benefit for combination versus sequential treatment. Therefore patients from both treatment arms were considered eligible for the control group of this study. Exact details on percentage of liver involvement, as was necessary for IHP, were not obtained.

Comparison IHP and systemic treatment

The following patients were included from the CAIRO study for comparison with IHP patients with liver metastases only, WHO performance status < 2, age ≤ 70 years, and previous resection of the primary tumor. A total of 111 patients of the CAIRO study fulfilled these criteria and were included for the current analysis.

IHP treatment

The IHP technique was applied as described in the previously published articles [7, 16, 17]. In summary: melphalan 200mg (Alkeran®, GlaxoSmithKline, Zeist, The Netherlands) was first dissolved in 40 mL Wellcome Diluent (a 60/40 (v/v) mixture of proylene glycol containing 5.2% (v/v) ethanol and 0·068 mol/l sodium citrate), which was subsequently diluted with 60 mL sterile saline. Melphalan was administered as a bolus in the isolated hepatic circuit and in the last 30 patients through 20 minute infusion using an infusionpump (Pilote Anesthesie; Fresenius, Brezins, France) connected to the hepatic artery line of the isolated hepatic circuit. Leakage of perfusate into the systemic circuit was monitored by adding 10 MBq ^{99m}Tc-pertechnetate to the isolated circuit with subsequent measurement of the level of radioactivity in both the systemic and isolated circuit, as described previously [18, 19]. If no leakage was detected, melphalan was administered; if leakage was calculated to exceed 10% during the perfusion period, the procedure was stopped and the liver was flushed just before this level was reached. Postoperatively, all patients received a daily subcutaneous dose of 480 µg granulocyte colony-stimulating factor (G-CSF) (Filgrastim/Neupogen®; Amgen, Breda, The Netherlands) starting the day after the operation until the nadir in leukocyte count was reached and the count had risen to more than 1.0×10^9/L. Liver and renal function tests and full blood counts were carried out daily in the first week and henceforth as indicated by their respective levels. Antibiotics in a combination of cefuroxim and metronidazol were given to all patients for 5 days after IHP.

Systemic treatment

Eligible patients were randomly assigned to either sequential or combination treatment in a 1:1 ratio, as described previously [15]. All treatment cycles were administered at intervals of 3 weeks. In the sequential treatment group, first-line treatment consisted of capecitabine (1250 mg/m^2 twice daily) for 14 days, second-line treatment of irinotecan (350 mg/m^2) on day 1, and third-line treatment of capecitabine (1000 mg/m^2 twice daily) for 14 days plus oxaliplatin (130 mg/m^2) on day 1. Patients assigned to combination treatment received capecitabine (1000 mg/m^2 twice daily) for 14 days plus irinotecan

(250 mg/m^2) on day 1 as first-line treatment, and capecitabine (1000 mg/m^2) twice daily for 14 days plus oxaliplatin (130 mg/m^2) on day 1 as second-line treatment.

Statistics

All data were analyzed using SPSS (version 16.0) software and presented as mean +/- SD or median followed by the range. Survival was measured from the day of surgery or randomization until death or until the last day of follow up. Postoperative mortality was included in survival analysis. For discrete variables univariate analysis was performed with the χ^2 test. Overall survival and disease progression analysis was analyzed using Kaplan-Meier curves, the log-rank test was used to identify differences in survival between groups. All tests were two-sided and p values of less than 0.05 were deemed to be significant.

Results

Patient and treatment characteristics

In total 99 patients were treated with IHP and 111 patients were treated with systemic treatment. The median duration of follow up was significantly shorter in the systemic treatment patients compared to the IHP patients, 54.7 (95% CI 48.5-60.9) versus 78.1 (95% CI 52.1-104.2) months (P=0.004). Patient characteristics, shown in table 1, were similar in both treatment groups, except for age. The systemic treatment patients were significantly older than IHP patients (P<0.01). Serum LDH, a known prognostic factor, did not differ between both groups (P=0.43). The number of patients who received previous adjuvant chemotherapy did not differ significantly (P=0.78) from those who did not receive adjuvant treatment. Chemotherapy directed at liver metastases prior to IHP was offered to 49 patients.

Details on IHP treatment are shown in table 2. Blood loss, operative time and duration of hospital stay in the IHP group were similar to previous reports [16, 17]. Perioperative mortality was 6%, which is lower than previously published by our group, due to the exclusion of portal vein perfusions. Overall response rate in the IHP group was 47%. , and the median time to disease progression was 7.3 (95% CI 6.5-8.0) months. Sixteen IHP patients received adjuvant systemic treatment after IHP, while 72 patients received systemic treatment directed at progressive metastases after IHP. None of the patients received bevacizumab and only one patient received cetuximab as part of the treatment.

Table 1. Patient characteristics

Parameter	IHP N=99 (%)	SYSTEMIC TREATMENT CONTROL GROUP N=111(%)	P
Age			P<0.01
<50 years	26 (26)	12 (11)	
≥50-<60 years	42 (43)	38 (34)	
≥60 years	31 (31)	61 (55)	
Sex			P=0.58
male	73 (74)	78 (70)	
female	26 (26)	33 (30)	
Site of primary tumor			P=0.05
Rectum	38 (38)	26 (23)	
Rectosigmoid	8 (8)	8 (8)	
Colon	53 (54)	77 (69)	
LDH prior to start treatment			P=0.43
Normal	59 (60)	72 (65)	
Abnormal	40 (40)	39 (35)	
Liver metastases			P=0.72
Synchronous	84 (85)	94 (85)	
Metachronous	15 (15)	17 (15)	
Previous adjuvant treatment *			P=0.78
No	92 (93)	102 (92)	
Yes	7 (7)	9 (8)	

* Previous systemic treatment was only allowed in the IHP group. In total 49 patients in the IHP group received systemic treatment prior to IHP.

Details on systemic treatment in the control group of CAIRO patients are shown in table 3. Sixty patients had been randomized to combination treatment (first-line treatment capecitabine plus irinotecan and second-line capecitabine plus oxaliplatin), and 51 patients to sequential treatment (first-line treatment with capecitabine, second-line irinotecan, and third-line capecitabine plus oxaliplatin). In the combination treatment group 68% of patients received both first- and second-line treatment. In the sequential treatment group 55% of patients received all three lines of chemotherapy. Overall response rate of first-line treatment was 41%. All except four patients showed progressive disease during follow-up. The median time to disease progression upon first-line treatment was 7.9 (95% CI 6.8–8.9) months. Of the progressive patients,

26 patients showed new lesions, 44 showed an increase in preexistent lesions, 23 showed a combination of the above, 1 showed local recurrence and in 13 patients, the location of progression was unknown.

Table 2. Details of IHP treatment (N=99)

Parameter	Mean ± SD	N(%)
Blood loss (l)	5.7 ± 4.3	
Operative time (h)	9.5 ± 1.4	
Hospital stay (days)	12.7 ± 6.9	
Perioperative mortality		6 (6)
Major complications		35 (35)
Grade 3-4 toxicities		
Liver function		37 (37)
Hematological		10 (10)
Median duration of follow up (months), (95% CI)	78.1 (52.1-104.2)	
Overall response (RECIST)		
Complete		3 (3)
Partial		44 (44)
Stable		22 (22)
Progressive		24 (24)
Median time to progression (months), (95% CI)	7.3 (6.5-8.0)	

Table 3. Details of systemic treatment in control group (N=111)

Parameter	Mean ± SD	N(%)
Systemic treatment		
Combination treatment		60 (54)
First-line		60 (100)
Second-line		41 (68)
Sequential treatment		51 (46)
First-line		51 (100)
Second-line		40 (78)
Third-line		28 (55)
Median number of cycles per patients		
First-line	9.7 ± 7.4	
Second-line	7.2 ± 4.8	
Third-line	5.1 ± 2.2	
Grade 3-4 toxicities		58 (52)
Median duration of follow up (months) (95% CI)	54.7 (48.5-60.9)	
Overall response first-line (RECIST)		
Complete		9 (8)
Partial		32 (29)
Stable		45 (41)
Progressive		17 (15)
Median time to progression after first-line treatment (months) (95% CI)	7.9 (6.8-8.9)	

Overall survival

Overall survival curves are shown in figure 1. Median overall survival was 25.0 (95% CI 19.4-30.6) months for the patients who were treated with IHP and 21.7 (95% CI 19.6-23.8) months for the patients who were treated with systemic chemotherapy only. Comparison of Kaplan-Meier curves by the log-rank test showed no significant difference between the two treatment groups (P=0.29). Overall survival of both treatment groups was not influenced by gender, age, LDH, location of primary tumor, timing of liver metastases and adjuvant treatment of the primary tumor (P=0.28; P=0.31; P=0.26; P=0.88; P=0.74; P=0.36, respectively). Overall survival was only influenced by metastasectomy after study treatment. Median overall survival in the patients who underwent metastasectomy was 47.2 (95% CI 29.5-64.9) months compared to 21.5 (95% CI 19.6-23.4) months in the patients who did not undergo metastasectomy (P<0.001). Metastasectomy, however was evenly distributed over IHP and systemic treatment arms, 6 and 9 patients respectively (P=0.57). Treatment-related mortality was 2% for the systemic treatment and 6% for IHP (P=0.11).

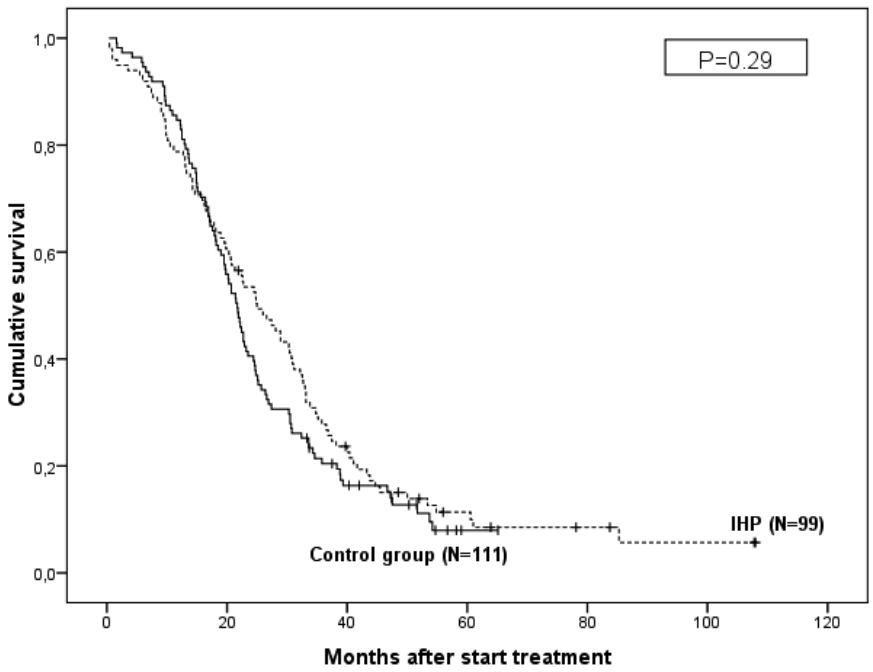

Figure 1. Overall survival curves of patients with liver metastases only treated with either IHP or systemic treatment.

A subgroup analysis was performed of the IHP patients (N=50) who received IHP as first-line treatment (figure 2), to exclude any survival disadvantage due to earlier treatment and diagnosis of liver metastases in this group of patients. Median overall survival in this subgroup increased to 28.9 (95% CI 14.2-43.6) months, but was not significantly different as compared to systemic treatment (P=0.24). As the two groups have different lengths of follow up a statistical error could arise when comparing the actuarial survival only. Therefore the actual 2-, 3- and 4-year survival rates were also calculated and compared. The 2-, 3- and 4-year survival rates for IHP patients were 53%, 28% and 14% respectively. The 2-, 3- and 4-year survival rates for the systemic treatment patients were 41%, 19% and 10% and did not differ significantly from the IHP survival rates (P=0.11; P=0.20; P=0.25, respectively). Similar to the actuarial survival, the 2-, 3- and 4-year survival rates were only influenced by metastasectomy.

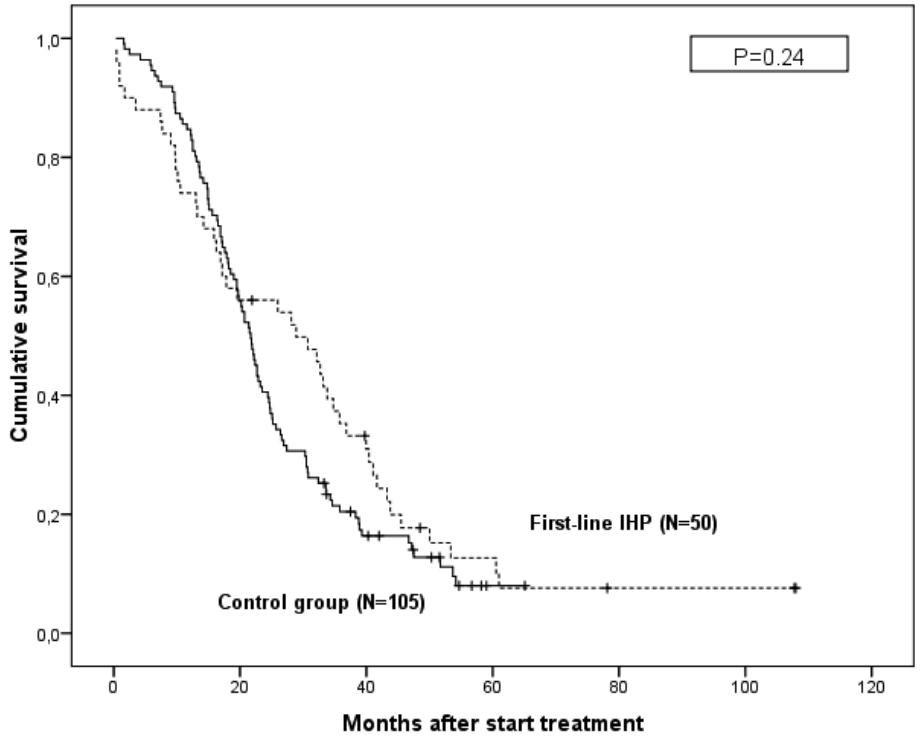

Figure 2. Overall survival of IHP patients who did not receive systemic treatment prior to IHP compared to control group.

Discussion

Over the past decade, several regional treatment options like hepatic artery infusion (HAI), radiofrequency ablation (RFA) and IHP have been studied extensively for the treatment of irresectable colorectal liver metastases. IHP has never been compared to systemic treatment and its definite role in the treatment of isolated liver metastases has not yet been established. To our knowledge this is the first attempt to compare the outcome of IHP with standard systemic treatment. Our study shows no significant survival benefit for IHP over systemic treatment with capecitabine, irinotecan and oxaliplatin.

Obviously, our study design shows several limitations. Firstly, the survival analysis is based on a nonrandomized case-control study. However, since it is hardly feasible to evaluate IHP in a prospective randomized study this approach is the best that is available. Secondly, although patient characteristics, apart from age, were evenly distributed between both groups, clinically relevant differences may still exist. In this respect it should be noted that IHP patients were more extensively evaluated by imaging for both hepatic (<60% hepatic involvement) and extrahepatic disease load. Although the serum LDH level was equally distributed between both groups, it cannot be excluded that the control group may have had extrahepatic disease upon a similar pretreatment evaluation. Thirdly, overall survival was calculated from the date of IHP or date of randomization for systemic treatment in the control group, not from the date of diagnosis of liver metastases. As IHP patients were allowed to receive systemic treatment prior to IHP, median time from diagnosis of liver metastases to start of treatment is likely to be longer. To exclude any survival disadvantage a subgroup analysis was performed of the IHP patients who received IHP as first-line treatment (N=50). Although median overall survival was increased in this subgroup to 28.9 months, this remained non-significant compared to the survival in the control group.

One of the major drawbacks of IHP is the hepatotoxicity with its associated morbidity, largely attributable to veno-occlusive disease (VOD). In the patient cohort treated at our center with IHP, VOD occurred in 9-14% of patients depending on the IHP technique which was used [7, 16, 17]. Previous phase I studies have demonstrated that VOD is the main dose limiting toxicity [11, 18]. Another factor which limits the possible application of IHP is the associated perioperative mortality. Several efforts have been undertaken to develop a minimal invasive technique to reduce mortality and increase efficacy by enabling repetition, but with only limited success. A few studies have been described involving chemofiltration under complete hepatic venous isolation after infusion of drugs, allowing administration of high doses of intrahepatic chemotherapy [20-22].

Pingpank *et al.* reported a phase I study using chemofiltration and demonstrated that treatment with highdose melphalan is feasible, but complete extraction of

melphalan by charcoal hemoperfusion is not possible, limiting the maximum tolerated dose [23]. Complete isolation of the liver using minimally invasive techniques has been demonstrated to be technically feasible, but recently carried out phase I trials have shown disappointing results [24, 25]. In our own center, we developed a minimal invasive technique using an animal model but refrained from translating this model to the clinical because of doubts about the safety of the required percutaneous catheters [26].

Another option to improve current results of IHP is to incorporate some of the newly developed drugs for systemic treatment of colorectal cancer metastases. Zeh *et. al.* published a phase I study of IHP with oxaliplatin in colorectal cancer patients [13]. Dose-limiting veno-occlusive disease was observed at 60 mg/m2. In this study, IHP was combined with HAI, thereby complicating the interpretation of both toxicity and response rates. Moreover, the perfusate consisted of oxaliplatin monotherapy, while in systemic therapy combination therapy has been shown more beneficial [27]. We are currently performing a phase I/II trial with IHP using a combination of both melphalan and oxaliplatin.

In conclusion, our study demonstrates no survival benefit for IHP with melphalan over systemic treatment with capecitabine, irinotecan and oxaliplatin. IHP should currently not be considered as standard treatment for patients with non-resectable colorectal cancer liver metastases, and should only be administered within prospective clinical studies.

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