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

Iersel, L. van

CHAPTER 7

Isolated hepatic perfusion with oxaliplatin combined with 100 mg melphalan: a phase I study

L.B.J. van Iersel[1], A.L.Vahrmeijer[2], F.G.J. Tijl[3], J. den Hartigh[4], P.J.K. Kuppen[2], H.H. Hartgrink[2], H. Gelderblom[1], J.W.R. Nortier[1], R.A.E.M. Tollenaar[2] and C.J.H. van de Velde[2]

Department of Clinical Oncology[1], Surgery[2], Extra Corporal Circulation[3] and Clinical Pharmacy and Toxicology[4] Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

Manuscript in preparation

Abstract

To improve IHP, we performed a phase I dose-escalation study to determine oxaliplatin dose in combination with a fixed melphalan dose.

Between June 2007 and July 2008, 11 patients, consisting of 8 colorectal cancer and 3 uveal melanoma patients with isolated liver metastases, were treated with IHP with escalating doses of oxaliplatin combined with 100mg melphalan. Samples of blood and perfusate were taken for pharmacokinetic analysis and patients were monitored for toxicity, response and survival.

Dose limiting sinusoidal obstruction syndrome (SOS) occurred at 150mg oxaliplatin. The areas under the concentration-time curves (AUC) of oxaliplatin at the maximal tolerated dose (MTD) of 100mg oxaliplatin ranged from 11.9 mg/L x h to 16.5 mg/L x h. All 4 patients treated at the MTD showed progressive disease 3 months after IHP.

The MTD of oxaliplatin in combination with 100mg melphalan in IHP was reached at 100mg oxaliplatin. We think that, in view of similar and even higher doses of oxaliplatin applied in both systemic treatment and hepatic artery infusion (HAI), applying this dose in IHP will not improve treatment results in patients with isolated hepatic metastases.

Introduction

Liver metastases are diagnosed in 10-25% of colorectal cancer patients at the time of primary tumour resection, while up to 70 % of patients with colorectal cancer will at some stage of their disease develop liver metastases [1-3]. Surgical resection is considered the golden standard for isolated hepatic metastases, with 10-year survival rates as high as 17% [4]. Recently, the number of patients suitable for resection has increased to up to 60% with the introduction of new neoadjuvant systemic treatment regiments [5-9]. Nonetheless, a significant number of patients still remain unsuitable for resection. Isolated hepatic perfusion (IHP) is a possible therapeutic option for irresectable liver metastases, but recent developments in systemic treatment in colorectal cancer have limited the role of IHP [10]. For IHP to remain a treatment option response rates and overall survival need to increase, by improving both the procedure and drugs applied in IHP.

Several drugs have been applied in IHP including 5-FU [11, 12], mitomycin C [13, 14], cisplatin [11] and melphalan [11, 14-16], but in the past 10 years melphalan has been the main drug used in clinical trials [16, 17]. To improve the current standard of IHP, we considered some of the newly developed drugs for systemic treatment of colorectal cancer for application in IHP. As IHP is a regional treatment, the drug should be in the active form or easily transformed to its active agent in the liver. Preferably, this drug shows a steep dose-response curve. Moreover, IHP is a short treatment of usually 1 hour, therefore the drug should cause rapid irreversible tumor cell cytoxicity. Finally, liver toxicity should be minimal. We evaluated all registered drugs for colorectal cancer, taking into account the considerations above. Irinotecan is not an ideal candidate for IHP, since it is a pro-drug and the bioactivation to its active metabolite SN-38 is slow[18]. The monoclonal antibodie bevacizumab, cetuximab and panitumumab may not be suitable either, because they are not directly cytotoxic. Therefore oxaliplatin was selected as the most promising new candidate for IHP. Phase III trials have shown the inferiority of oxaliplatin monotherapy versus oxaliplatin combination therapy[19, 20], suggesting a role for the possible application of a combination of oxaliplatin and melphalan in IHP. In vitro results showed a synergistic schedule dependent interaction between melphalan and oxaliplatin [21].

In this report we present the results of a phase I trial with IHP with escalating doses of oxaliplatin combined with a fixed dose of 100mg melphalan.

Patients and methods

Patient Eligibility

Between June 2007 and July 2008, 11 patients with isolated liver metastases were treated with IHP with escalating doses of oxaliplatin combined with 100mg melphalan. The study protocol was approved by the medical ethical committee of the Leiden University Medical Center and informed consent was obtained from all patients. All patients had measurable, irresectable metastases confined to the liver. Standard staging studies 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 of 0 or 1, leukocyte count $\geq 3.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, minimum creatinine clearance level of 40 ml/min and maximum bilirubin level 17 µmol/L. Exclusion criteria were biological age over 65 years, more than 60% hepatic replacement by tumour tissue as estimated from the preoperative abdominal CT scan, coagulation disorders or evidence of extrahepatic metastatic disease. The interval between resection of the primary colorectal tumour and perfusion had to be at least 6 weeks.

IHP technique

All patients were treated with IHP, consisting of an extracorporeal venovenous bypass, as described previously [15].

Leakage Detection

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 [22, 23]. If no leakage was detected, oxaliplatin was administered. During the one hour treatment leakage was constantly monitored, if leakage exceeded 10% during the perfusion period, the procedure was immediately aborted and the liver flushed.

Postoperative Care

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. Patients were monitored in the intensive care unit for at least 1 day after IHP. 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.

Oxaliplatin and melphalan

Oxaliplatin (Sanofi-Aventis, Gouda, The Netherlands) was obtained as a ready-made solution and administered as a bolus in the isolated hepatic circuit. Melphalan 100mg (Alkeran®, GlaxoSmithKline, Zeist, The Netherlands) was 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. The melphalan was administered as a bolus in the isolated hepatic circuit 30 minutes after the oxaliplatin was administered.

Dose escalation

Dose escalation depended on toxicities at the prior dose level. At least 3 patients were treated at each dose level. If 1of 3 patients experienced dose limiting toxicity (DLT), 3 additional patients were entered at that dose level. DLT was defined as grade 4 thrombopenia or neutropenia for more than 7 days or febrile neutropenia or irreversible grade 3/4 liver toxicity or other grade 3/4 non-hematological toxicity other than nausea and vomiting without adequate treatment. The maximal tolerated dose (MTD) was defined as the dose level below that, which induced DLT in at least one-third of the patients. (i.e., ≥ 2 of 3 or 6 patients). Melphalan was kept at a constant dose of 100 mg, because this was considered standard treatment in several phase II trials [24-26]. Oxaliplatin was escalated with 50mg at a time. Oxaliplatin was administered 30 minutes prior to melphalan based on *in vitro* findings, suggesting a schedule dependent interaction between melphalan and oxaliplatin [21].

Toxicity

Systemic and regional toxicity were graded according to the National Cancer Institute Common Toxicicity Criteria version 3.0. Hepatic toxicities were considered melphalan-related if elevations in liver function persisted beyond 7 days after perfusion, as previously suggested [16]. Nonhepatic toxicities were defined as all toxicities that were not reversed within 24 hours after perfusion.

Melphalan and oxaliplatin pharmacokinetics

Heparinized samples of all patients were taken from the perfusion medium at hepatic inflow and outflow tracts and from the systemic circulation, at 15 different time intervals (t=0, 1, 5, 10, 15, 20, 25, 30, 31, 33, 35, 40, 45, 50, 60 minutes). Samples were stored at -80 °C until analysis. All samples were analyzed by a HPLC assay as previously described [27]. The areas under the concentration-time curves (AUC) were calculated with the trapezoidal rule.

Response evaluation

Objective tumour response measurements were obtained by follow up CT scans of the liver and remaining abdomen at 3-month intervals after treatment and at 6-month interval after 1 year. Additional imaging was performed if clinically indicated. RECIST criteria were used to determine response rates. For the RECIST criteria lesions were only considered measurable if ≥10mm. Complete response was defined as disappearance of all known disease, partial response as a reduction in the sum of maximal diameters of ≥30%, stable disease as a reduction of <30% or an increase of <20% and progressive disease as an increase of ≥20% or the appearance of new intra- or extrahepatic lesions [28]. Metastases were localized according to the Bismuth classification [29]. Serum carcinoembryonic antigen (CEA) levels were determined prior to treatment and at all follow-up visits.

Statistics

All data were analyzed using SPSS (version 12.0) software and presented as mean +/- SD or median followed by the range. All survival and disease progression analysis was performed by using Kaplan-Meier statistics.

Results

Patient characteristics

Demographics and tumour characteristics of the patient population are listed in Table 1. In total 11 patients were treated with escalating doses of oxaliplatin. The liver metastases originated from uveal melanoma in 3 patients and from colorectal cancer in the other 8 patients. Three women were treated and 8 men with a mean age of 57.9 years (range 40-64 years). One patient was included (patient no. 5) who in retrospect

Table 1. Characteristics of 11 patients treated with IHP with oxaliplatin and melphalan

Patient No.	Sex	Age (Y)	Primary tumour	Dose Melphalan (mg)	Dose Oxaliplatin (mg)	AUC Hepatic inflow Melphalan (mg/L x h)	AUC Hepatic inflow Oxaliplatin (mg/L x h)	Response	Duration response (months)	Overall survival (months)
1	F	51	Uveal melanoma	100	50	9.6	4.1	partial	7.6	22.1¤
2	M	64	Colorectal cancer	100	50	2.8	6.2	progressive	-	21.9¤
3	M	54	Uveal melanoma	100	50	7.3	6.9	progressive	-	18.7
4	M	59	Colorectal cancer	100	100	6.4	12.6	progressive	-	4.9
5+	F	40	Colorectal cancer	100	100	15.4	16.5	-	-	5.5
6	F	61	Uveal melanoma	100	100	10.3	16.5	progressive	-	7.8
7	M	63	Colorectal cancer	100	100	2.8	11.9	progressive	-	18.2¤
8	M	63	Colorectal cancer	100	150	6.7	19.6	partial	6.5	12.0¤
9	M	63	Colorectal cancer	100	150	4.8	16.7	partial	11.1	13.9¤
10*	M	57	Colorectal cancer	100	150	9.9	20.6	-	-	0.5
11*	M	62	Colorectal cancer	100	150	6.5	18.2	-	-	1.0

+ In retrospect patient showed extrahepatic metastases prior to IHP, which were immediately progressive after IHP.

* Both patients died perioperatively. Patient no. 10 due to excessive bleeding and patient no. 11 due to hepatotoxicity.

¤ Patients were still alive at the end of follow up.

showed extrahepatic disease prior to IHP. Therefore 1 extra patient was included at this dose-level.

Treatment characteristics

Treatment characteristics are shown in Table 2. Operative time, blood loss, hospital stay and hepatic artery and portal vein flow rates and pressures are similar to the previous reports [17, 30]. None of the patients showed more than 1 percent leakage during the entire procedure.

Table 2 Treatment parameters

Parameter	*Mean ± SD*	*n*
Flow rate hepatic artery (mL/min)	293.9 ± 68.1	
Flow rate portal vein (mL/min)	312.8 ± 31.3	
Pressure hepatic artery (mm/Hg)	129.4 ± 20.0	
Pressure portal vein(mm/Hg)	49.1 ± 4.0	
Percentage leakage during perfusion	0.4 ± 0.5	
Blood loss (L)	5.5 ± 5.8	
Operative time (hr)	8.4 ± 1.6	
Hospital stay (days)	16.8 ± 10.5	
Perioperative mortality		2
Major complications		4
Sinusoidal obstruction syndrome		1
Hepatic artery obstruction		1
Wound infection		1
Re-operation due to bleeding		1

Pharmacokinetics

Samples for pharmacokinetical analysis were successfully collected from each patient. Individual data of the AUC of both melphalan and oxaliplatin are shown in table 1. Escalating doses of oxaliplatin corresponded to an increasing AUC, with the maximum of 20.6 mg/L x h achieved at the highest dose level of 150mg oxaliplatin. The maximum peak concentration of oxaliplatin was 40.8 mg/L and was achieved in patient no 9, also at the highest dose level. Little difference was observed between the oxaliplatin concentrations in the hepatic inflow and outflow tract, as shown in figure 1, suggesting only limited hepatic extraction of oxaliplatin.

Toxicity and complications

Major complications occurred in 4 patients of which 2 patients died perioperatively. One perioperative death was due to massive blood loss, while the other perioperative death was due to hepatotoxicity as a result of sinusoidal obstruction syndrome (SOS). The perioperative death due to massive blood loss was attributed to the procedure and not toxicity. Therefore another patient was included at this dose-level. Toxicity levels according to dose-level are shown in Table 3. Reversible grade 3-4 hepatoxicity occurred in 7 patients. DLT consisted of irreversible grade 4 hepatotoxicity requiring hepatic-replacement therapy due to SOS and was reached at 150mg oxaliplatin combined with 100mg melphalan.

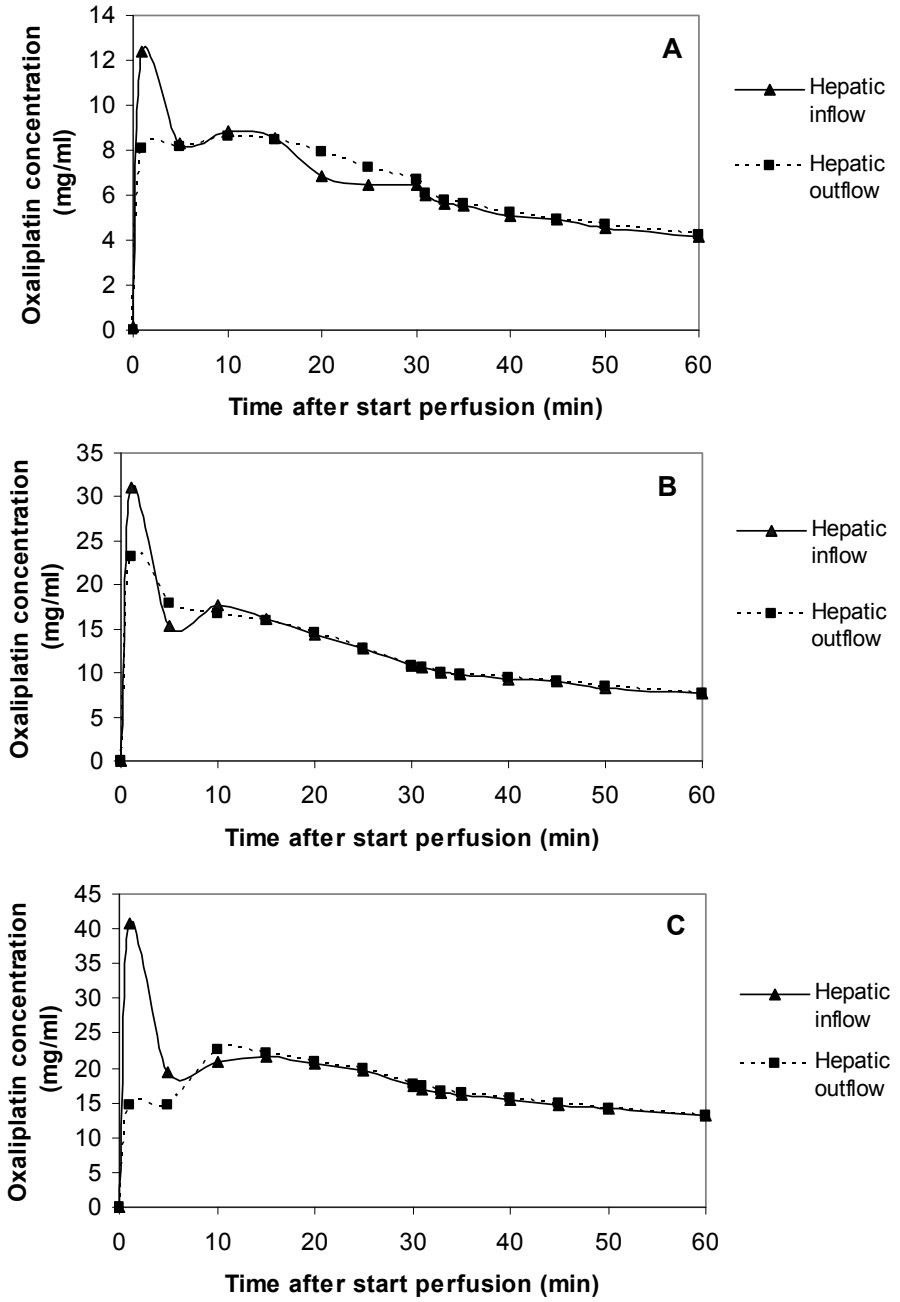

Figure 1. Typical examples of concentration time curves of oxaliplatin for each dose-level (A= 50mg oxaliplatin, B= 100mg oxaliplatin, C=150mg oxaliplatin). Increasing dose-levels show increasing peak concentrations of oxaliplatin. All concentration curves show a gradual decline over time.

Table 3 Toxicity according to National Cancer Institute Common Toxicity Criteria version 3.0 (*n=11*)

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Leukocyte nadir					
- Dose level I	3	0	0	0	0
- Dose level II	4	0	0	0	0
- Dose level III	4	0	0	0	0
Bilirubin					
- Dose level I	2	1	0	0	0
- Dose level II	2	0	0	1	1
- Dose level III	0	0	0	2	2
Alkaline phosphatase					
- Dose level I	1	2	0	0	0
- Dose level II	0	1	2	0	1
- Dose level III	0	2	2	0	0
Alanine aminotransferase (ALAT)					
- Dose level I	2	0	0	1	0
- Dose level II	1	1	1	0	1
- Dose level III	0	1	2	0	1
Asparate aminotransferase (ASAT)					
- Dose level I	0	1	2	0	0
- Dose level II	0	2	0	2	0
- Dose level III	0	1	1	1	1

Tumour response and patient survival

Of the 5 patients with colorectal cancer with an elevated CEA prior to IHP, three showed 50% or more reduction in CEA after IHP. Only 8 patients were available for response evaluation of which 3 patients showed a partial response according to the RECIST criteria. After a median follow up of only 18.2 months (95% CI; 10.5-26.0 months), median overall survival was 18.7 months (95% CI; 1.7-35.7 months) including 3 uveal melanoma patients..

Discussion

In this study we evaluated escalating doses of oxaliplatin combined with a fixed dose of 100mg melphalan in an isolated hepatic perfusion circuit for patients with metastatic

disease limited to the liver. DLT, consisting of SOS, occurred at a relatively low dose level of 150mg oxaliplatin.

In previous IHP studies DLT also consisted of SOS as one of the main limitations of IHP with melphalan [15, 16]. Nonetheless, we did not expect DLT to occur at such a low dose of oxaliplatin, especially considering the 50% reduction in melphalan compared to our previous trials[17, 31]. At the time of development of this study protocol, oxaliplatin was considered a non-hepatotoxic drug, with only limited hepatoxicity reported in both systemic and hepatic arterial infusion (HAI) trials [32-36]. This observation combined with the synergistic interaction between melphalan and oxaliplatin, as demonstrated by our previously published *in vitro* data, was the foundation of the development of this study protocol [37]. More recently however, after development of our study protocol, an increasing number of studies have reported on the hepatotoxicity, especially the risk of SOS, after treatment with oxaliplatin prior to hepatectomy of colorectal liver metastases. Incidence rates of SOS have been reported of up to 59% and oxaliplatin-based chemotherapy has been shown an independent risk factor for complications associated with hepatectomy with conflicting data concerning impact on both morbidity and mortality [38-42]. In view of the above, the addition of a cytostatic agent with a high incidence of SOS to a procedure with already a high risk of SOS, can explain the occurrence of DLT at only 150mg of oxaliplatin.

Similarly to our study, Zeh *et. al.* published a phase I study of IHP with oxaliplatin , but instead of oxaliplatin combination therapy, the perfusate consisted of oxaliplatin monotherapy, while in systemic therapy combination therapy has been shown more effective [19, 43]. Dose-limiting toxicity, also consisting of SOS, was observed at only 60 mg/m2, again indicating the high potential of inducing SOS if oxaliplatin is applied in isolated hepatic perfusion circuit, irrespective of combination with other agents. This study reported an overall response rate of 66%, but IHP was combined with HAI, complicating the interpretation of both toxicity and response rates. In our study meaningful interpretation of the response rate is complicated because of the phase I design and the inclusion of both uveal melanoma and colorectal cancer patients. Of the 8 colorectal cancer patients included, only two patients showed a partial response, both were treated at the highest dose level of 150mg oxaliplatin. All patients treated at the MTD of 100mg oxaliplatin showed progressive disease 3 months after IHP. Considering the dose of oxaliplatin used in regular systemic combination treatment in colorectal cancer patients of over 100mg/m2 per treatment cycle, conducting a phase II IHP trial based on the MTD dose of 100mg oxaliplatin seems hardly beneficial.

Although the Cmax in our study was higher than the Cmax reported after a 2-hour infusion of oxaliplatin 130mg/m2 in systemic trials, the AUC of oxaliplatin at the MTD in our study ranging from 11.9 mg/L x h to 16.5 mg/L x h was similar to the AUC reported in systemic trials[44]. A possible survival benefit for IHP over systemic treatment can only be achieved at this dose if response to oxaliplatin therapy is concentration- rather than dose-dependent. Our previous experience with melphalan showed that an increase in melphalan concentration did not increase response rates, but did increase toxicity [31]. Moreover, current HAI study protocols already apply a dose of oxaliplatin of up to 150mg/m2 [32-36]. Similarly to IHP, HAI offers the advantage of high concentrations of the cytostatic agent in the liver, but contrary to IHP, HAI is a minimally invasive procedure and is suitable for repetitive treatment, further limiting the possible role of oxaliplatin in IHP.

In conclusion, we have established the MTD of oxaliplatin in combination with 100mg melphalan in IHP at 100mg. Further escalation is limited by the occurrence of SOS. In view of similar and even higher doses of oxaliplatin applied in both systemic treatment and HAI, applying this dose in IHP will not result in further improvement of treatment of patients with isolated hepatic metastases.

Acknowledgements

We kindly thank Prof. J.H.M. Schellens of The Netherlands Cancer Institute for his advisory role during the development of this study protocol.

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