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Isolated hepatic perfusion with oxaliplatin combined with 100 mg melphalan in patients with metastases confined to the liver: A phase I study

L.B.J. van Iersel [a], E.M. de Leede [b], A.L. Vahrmeijer [b], F.G.J. Tijl [c], J. den Hartigh [d], P.J.K. Kuppen [b], H.H. Hartgrink [b], H. Gelderblom [a], J.W.R. Nortier [a], R.A.E.M. Tollenaar [b], C.J.H. van de Velde [b,*]

[a] *Department of Clinical Oncology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands*

[b] *Department of Surgery, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands*

[c] *Department of Extra Corporal Circulation, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands*

[d] *Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands*

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Abstract

Aim: To improve isolated hepatic perfusion (IHP), we performed a phase I dose-escalation study to determine the optimal oxaliplatin dose in combination with a fixed melphalan dose.

Methods: Between June 2007 and July 2008, 11 patients, comprising of 8 colorectal cancer and 3 uveal melanoma patients and all with isolated liver metastases, were treated with a one hour IHP with escalating doses of oxaliplatin combined with 100 mg melphalan. Samples of blood and perfusate were taken during IHP treatment for pharmacokinetic analysis of both drugs and patients were monitored for toxicity, response and survival.

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

Conclusions: 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 is not expected to improve treatment results in patients with isolated hepatic metastases.

Keywords: Isolated hepatic perfusion; Liver metastases; Melphalan; Oxaliplatin; Colorectal cancer; Uveal melanoma

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 regimens.[5–9]

Abbreviations: AUC, area under the concentration–time curve; DLT, dose limiting toxicity; HAI, hepatic artery infusion; HPLC (assay), high performance liquid chromatography; IHP, isolated hepatic perfusion; ICP-MS, Inductively Coupled Plasma-Mass Spectrometry; PHP, percutaneous hepatic perfusion; SOS, sinusoidal obstruction syndrome.

* Corresponding author. Department of Surgery, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands. Tel.: +31 71 5262309; fax: +31 71 5266750.

E-mail address: c.j.h.van_de_velde@lumc.nl (C.J.H. van de Velde).

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Nonetheless, a significant number of patients still remain unsuitable for resection. For patients with uveal melanoma, 70–90% will eventually develop metastases confined to the liver. Because disease is often multifocal, surgical resection is not an option in the majority of patients. Median survival in this group is less than 1 year and currently there is no standard systemic therapy.[24]

Isolated hepatic perfusion (IHP) is a possible therapeutic option for unresectable 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 h, therefore the drug should cause rapid irreversible tumour cell cytotoxicity. 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 antibodies 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 superiority of oxaliplatin combination therapy versus oxaliplatin monotherapy,[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 100 mg melphalan.

Patients and methods

Patient eligibility

All patients had measurable, unresectable metastases confined to the liver. Unresectability was based on the decision made by the HPB multidisciplinary team. Often this was because the tumour is multifocal, too large or positioned close to central vascular structures.

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 age over 65 years, more than 60% hepatic replacement by tumour tissue as estimated from the preoperative abdominal CT scan, evidence of extrahepatic metastatic disease or coagulation disorders (disorders affecting APTT, PT and/or INR). The interval between resection of the primary colorectal tumour and perfusion had to be at least 6 weeks.

Study design

This study is a prospective cohort study, including 11 patients with isolated liver metastases that were treated between June 2007 and July 2008. Patients were treated with IHP with escalating doses of oxaliplatin combined with 100 mg melphalan. The study protocol was approved by the medical ethical committee of the Leiden University Medical Center, was registered in the EudraCT database: number 2006-005088-25 and written informed consent was obtained from all patients.

IHP technique

All patients were treated with IHP, consisting of an extracorporeal veno-venous 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.[13,22] 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.