Phase II Multicenter Clinical Trial of Pulmonary Metastasectomy and Isolated Lung Perfusion with Melphalan in Patients with Resectable Lung Metastases

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Introduction: The 5-year overall survival rate of patients undergoing complete surgical resection of pulmonary metastases (PM) from colorectal cancer (CRC) and sarcoma remains low (20–50%). Local recurrence rate is high (48–66%). Isolated lung perfusion (ILuP) allows the delivery of high-dose locoregional chemotherapy with minimal systemic leakage to improve local control.

Methods: From 2006 to 2011, 50 patients, 28 male, median age 57 years (15–76), with PM from CRC ($n = 30$) or sarcoma ($n = 20$) were included in a phase II clinical trial conducted in four cardiothoracic surgical centers. In total, 62 ILuP procedures were performed, 12 bilaterally, with 45 mg of melphalan at 37°C, followed by resection of all palpable PM. Survival was calculated according to the Kaplan–Meier method.

Results: Operative mortality was 0%, and 90-day morbidity was mainly respiratory (grade 3: 42%, grade 4: 2%). After a median follow-up of 24 months (3–63 mo), 18 patients died, two without recurrence. Thirty patients had recurrent disease. Median time to local pulmonary progression was not reached. The 3-year overall survival and disease-free survival were 57% ± 9% and 36% ± 8%, respectively. Lung function data showed a decrease in forced expiratory volume in 1 second and diffusing capacity of the alveolocapillary membrane of 21.6% and 25.8% after 1 month, and 10.4% and 11.3% after 12 months, compared with preoperative values.

Conclusion: Compared with historical series of PM resection without ILuP, favorable results are obtained in terms of local control without long-term adverse effects. These data support the further investigation of ILuP as additional treatment in patients with resectable PM from CRC or sarcoma.

Key Words: Isolated lung perfusion, Local control, Lung metastases, Survival, Combined modality treatment.

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The 5-year overall survival (OS) of patients with pulmonary metastases (PM) from colorectal carcinoma (CRC) and sarcoma remained almost the same over the last 20 years, despite improvement in systemic chemotherapy and a better preoperative selection. This ranges for CRC between 39% and 68%[1–9] and for sarcoma between 22% and 50%.[1,9–14]

One of the reasons for this rather poor survival rate is the high rate of local recurrence in the operated lung, despite complete resection, which ranges between 43% and 66% as reported in a large retrospective study[1] and also in our own institution.[15] Recurrence is a significant problem because a number of patients will not tolerate a second operation, whereas those who can will have a further decline of their lung function parameters.[16,17] Systemic chemotherapy for PM is limited by its systemic side effects and does not result in permanent control or cure of these lesions.

Isolated lung perfusion (ILuP) is a surgical technique currently evaluated as an adjuvant treatment during thoracotomy to reduce the incidence of local pulmonary recurrence. With this technique, the lung is completely isolated from the systemic circulation by cannulating the pulmonary artery and veins. The lung is subsequently perfused with high-dose chemotherapy, with minimal systemic leakage.[18] It allows the chemotherapeutic agent to reach a much higher tissue concentration compared with systemic treatment,[19,20] exploiting the steep dose–response curve. This technique proved to be safe and reproducible.[18,21]

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Melphalan is an alkylating agent. It has been used for decades in the treatment of melanoma with isolated limb perfusion.[22–24] However, it is also used in isolated limb perfusion for soft-tissue sarcoma,[25] in isolated liver perfusion for metastases of colorectal cancer,[26] and for hyperthermic intraperitoneal chemotherapy in the treatment of peritoneal carcinomatosis.[27] This makes melphalan one of the most extensively investigated chemotherapeutic agents for isolated organ perfusion, with a very well-known pharmacodynamic and pharmacokinetic profile. Because of its extensive use in isolated organ perfusion and because ILuP with melphalan yielded in an animal setting the highest efficacy for both PM of carcinoma[28] and sarcoma,[20] a clinical phase I trial was started in 2001.[21,29] In this clinical phase I trial, patients with resectable PM from a variety of cancers were treated with ILuP with melphalan followed by complete lung metastasectomy.[21,29] Patients were perfused with an increasing dose of melphalan under normothermic (37°C) or hyperthermic (42°C) conditions.[21,29] In this phase I clinical trial, followed by an extension trial, the maximum tolerated dose was set at 45 mg melphalan at a temperature of 37°C.[21,29] Recently, the long-term follow-up of this phase I trial has been reported showing no long-term pulmonary toxicity and a 5-year OS of 54.8%.[30]

Because of the results of this phase I clinical trial and the suggested feasibility of ILuP with melphalan for the improvement of local control in patients with resectable PM, a phase II clinical trial was started. This study presents the results of this multicenter phase II study of ILuP with 45 mg melphalan at 37°C for patients with resectable PM from CRC and sarcoma.

PATIENTS AND METHODS

From September 2006 until May 2011, a phase II clinical trial of ILuP with melphalan was conducted in four cardiothoracic centers in the Netherlands and Belgium: St. Antonius Hospital, Nieuwegein; Leiden University Medical Center, Leiden; Erasmus MC, Rotterdam, the Netherlands; and Antwerp University Hospital, Edegem, Belgium.

Study Protocol

The study protocol was approved by all four ethical committees of the different participating centers. Primary end-point of the study was time to progression (TTP) locally advance or metastatic. Secondary end-points were OS and pulmonary toxicity. For the inclusion and exclusion criteria, see Table 1.

Patients

A total of 50 patients with PM of osteosarcoma, soft-tissue sarcoma, or CRC were included in this study. A written informed consent was obtained from all patients.

Technique

The technique was the same as applied in our phase I clinical trial with melphalan and was reported in detail.[21] In short, patients underwent a thoracotomy. The PM were identified by bimanual palpation of the lung, and if no histological proof was present, a frozen section was performed to confirm the presence of metastatic disease. Possible other lesions were marked. Heparin was given to reach an activated clotting time of 200 seconds. The lung was isolated by cannulating the pulmonary artery and the two pulmonary veins with central clamping and snaring of the main bronchus to block the bronchial arterial circulation. This resulted in a closed circuit. Perfusion was performed with a centrifugal pump with the mean pulmonary artery pressure before clamping as maximum accepted pressure. Perfusion was performed at 37°C with 45 mg melphalan fixed dose for 30 minutes followed by a 5-minute washout. Afterward, the PM were resected followed by a systematic lymph node dissection. If bilateral disease was present, a staged bilateral thoracotomy took place within a period of 4–6 weeks. None of the patients received adjuvant systemic chemotherapy after the ILuP procedure.

TABLE 1. Inclusion and Exclusion Criteria

	Inclusion Criteria	Exclusion Criteria
1	Histologic, cytologic, or strong radiographic evidence of lung metastases from colorectal carcinoma, osteosarcoma, or soft-tissue sarcoma	Uncontrollable infectious disease
2	All metastatic diseases assessed by radiologic examination were resectable	Severe comorbidity
3	All metastatic diseases were confined to the lungs	Previous thoracotomy or pleuropulmonary diseases resulting in obliteration of the pleural space
4	Primary site has been radically treated and has no signs of recurrence	Pregnancy or lactation
5	Patients had adequate cardiac and pulmonary reserve to undergo a thoracotomy and metastasectomy	
6	No comorbid conditions are present that prevent an operation	
7	No more than 10 metastases are present in one lung	
8	No standard treatment options available, besides pulmonary metastasectomy	
9	Performance status ECOG 0–1	
10	Normal renal and liver function	
11	Adequate bone marrow reserve; absolute neutrophil count more than $2 \times 10E^9$/L and a platelet count of more than $150 \times 10E^9$/L	

ECOG, Eastern Cooperative Oncology Group.