Isolated lung perfusion as additional treatment for lung metastases

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The golden standard for the treatment of lung metastases remains complete surgical resection. Prognostic factors for patients with lung metastases are histology, number of metastases and disease-free interval. However, the chance of recurrent disease in the treated lung remains high after complete resection, even in combination with systemic chemotherapy. Systemic toxicity limits the dose of the latter, resulting in only limited local pulmonary control. Therefore, new techniques are developed to deliver a high-dose of chemotherapy selectively into the lung, reducing the risk of systemic toxicity. One of these techniques is isolated lung perfusion, which is comparable with isolated limb perfusion. This experimental surgical technique allows delivery of a very high-dose of chemotherapy with or without biological response modifiers to the lung, without the risk of systemic exposure. Experimental studies with this technique have shown its superiority in achieving higher tissue concentrations of chemotherapy in the target organ as well as improved survival in comparison with systemic chemotherapy. As shown in several phase I studies, this technique is technically feasible with minimal morbidity and minimal impact on pulmonary function. In a recent phase II study, an improved local pulmonary control was found in comparison with the literature. This review discusses the current status of isolated lung perfusion as well as newer, less invasive techniques to deliver high-dose chemotherapy selectively to the lung.

(Belg J Med Oncol 2015;9(1):5-10)

Introduction

In patients with resectable lung metastases (LM), surgical excision is a widely accepted procedure and remains the golden standard of care. The largest retrospective study published to date that reports on lung metastasectomy defines several prognostic factors that have an impact on overall survival, namely: histology, number of LM and disease-free interval (DFI).[1] Patients with only one LM and a DFI longer than three years have the best prognosis, whereas patients with unresectable disease have the worst outcome.[1] However, long-term overall survival has not increased significantly over the last decades despite improved chemotherapeutic agents and better preoperative work-up.

One of the reasons that the overall-survival has not improved is the high recurrence rate of intrapulmonary metastases, even after complete resection.[1] This is especially true for LM from colorectal carcinoma (CRC) and sarcoma. These tumours have a recurrence rate inside the treated lung of 43-66%, despite complete resection.[1,2] Although reoperation for these recurrences is feasible, eventually the reduced pulmonary functional reserve will become the limiting factor resulting in medically inoperable patients.[3,4]

Patients are treated with systemic chemotherapy to prevent recurrences in the lung as well as in other potential metastatic sites. With increasing knowledge about cancer genetics, drug resistance and survival pathways, new chemotherapeutic agents are utilised for the prevention of recurrence of these metastases.

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Conflict of interest: The authors have nothing to disclose and indicate no potential conflict of interest.

Keywords: chemotherapy, combined modality treatment, isolated lung perfusion, local control, lung metastases, survival.

Table 1. Experimental studies of isolated lung perfusion.

Author	Drug	Model	Effect comment
Weksler[10]	Doxorubicin	Rat	Effective against sarcoma mets
Krueger[11]	Doxorubicin	Pig	High lung levels, heterogeneous distribution
Van Putte[12]	Gemcitabine	Rat	Effective against adenocarcinoma mets
Van Putte[13]	Gemcitabine + melphalan	Rat	More effective than gemcitabine or melphalan alone against adenocarcinoma mets
Pages[14]	Gemcitabine, cisplatin, FUDR, a.o.	Pig	In vitro gemcitabine most effective against colorectal adenocarcinoma cells; ILuP safe and reproducible with gemcitabine
Ng[15]	FUDR	Rat	Effective against carcinoma mets
Li[16]	Cisplatin	Rat	Effective against sarcoma mets
Weksler[8]	TNF-α	Rat	Effective against sarcoma mets
Hendriks[9]	Melphalan +/- TNF-α	Rat	Effective against adenocarcinoma mets, no additional effect of TNF-α
Den Hengst[17]	Melphalan	Rat	High lung levels obtained, effective against sarcoma mets

mets: metastases; ILuP: isolated lung perfusion; FUDR: 5-fluorodeoxyuridine; TNF-α: Tumour necrosis factor alpha; a.o. and others.

However, despite these advances, patients that undergo lung metastasectomy for certain tumour types in combination with systemic chemotherapy still have a poor prognosis. This is probably due to the drug resistance of these tumour types and the inability of the chemotherapeutic agents to reach a high enough concentration inside the LM to eliminate them, due to the limiting systemic toxicity. Therefore, new combined modality treatments are investigated to deliver the chemotherapeutic agents more selectively to the lung. Isolated lung perfusion (ILuP) is an experimental surgical technique that can be used as an adjuvant treatment during lung metastasectomy. With this technique the lung is isolated from the systemic circulation by clamping and cannulating the pulmonary artery and veins, resulting in a closed circuit (*Figure 1*). In this way a very high dose of chemotherapy can be selectively delivered to the lung without systemic exposure as the lung is completely isolated from the systemic circulation by central clamping of the pulmonary vessels.

In this review, we will report briefly on the history of ILuP and discuss the current status of this technique in the treatment of LM.

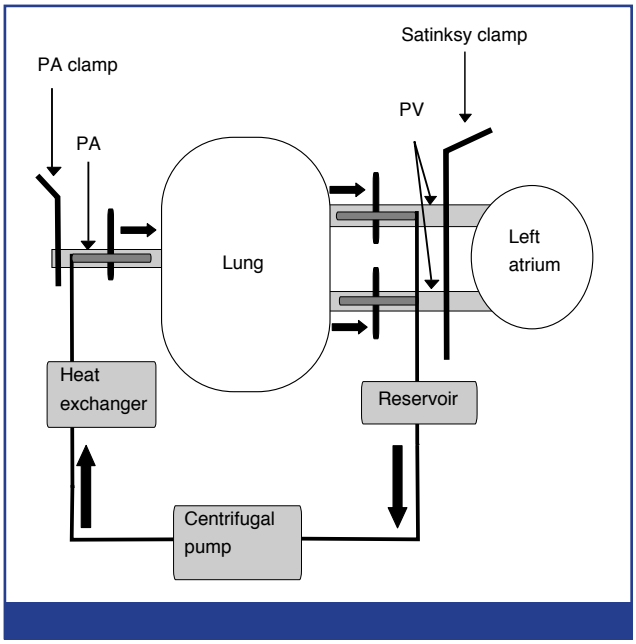

Figure 1. Isolated lung perfusion.
PA: Pulmonary artery; PV: Pulmonary vein.

History of isolated lung perfusion

In 1958, ILuP was reported for the first time but it took till 1983 before interest in ILuP started to emerge.[5] Johnston et al. showed in 1983 that the use of ILuP with doxorubicin in a dog model was safe and reproducible.[6] There was no systemic toxicity and the local pulmonary toxicity of doxorubicin was closely related to the drug concentration in the perfusate and the drug uptake in the lung.[6] In 1993, a rat model was developed to perform ILuP.[7] This resulted in an exponential increase of experimental studies in ILuP, subsequently followed by clinical trials.

Several chemotherapeutic agents were investigated in experimental studies in the following years but it is

Table 2. Clinical studies of isolated lung perfusion from 1995 onwards.

Year	Author	Drug	N	ILuP temperature (°C)	Perfusion time (min)	Resectable LM	MTD
1995	Johnston[18]	Doxorubicin/ Cisplatin	6/2	NA	45-60	No	NA
1996	Pass[19]	TNF-α and γ-interferon	15	38-39.5	90	No	6 mg
1996	Ratto[23]	Cisplatin	6	37	60	Yes	200mg/m^{2a}
2000	Burt[20]	Doxorubicin	8	37	20	No	40mg/m^2
2002	Putnam[21]	Doxorubicin	16	37	NA	No	60mg/m^2
2002	Schröder[22]	Cisplatin	4	41	21-40	Both	70mg/m^{2a}
2004	Hendriks[24]	Melphalan	16[b]	37, 42	30	Yes	45mg - 42°C
2007	Grootenboers[c 25]	Melphalan	7[d]	37, 42	30	Yes	45mg - 37°C

n: number of patients; ILuP: isolated lung perfusion; min: minutes; LM: lung metastases; MTD: maximum tolerated dose; NA: Not available; TNF-α: Tumour necrosis factor alpha.

[a]Fixed dose

[b]21 procedures (five bilateral)

[c]Extension trial of Hendriks et al[24], revision of MTD (see text)

[d]8 procedures (1 bilateral)

beyond the scope of this review to describe these studies in full detail. Besides chemotherapeutic agents, TNF-α was also investigated.[8,9] A selection of these experimental studies is summarised in *Table 1*.

The animal studies showed that it was possible to achieve high lung levels of the chemotherapeutic agent used. Gemcitabine, 5-fluorodeoxyuridine and melphalan were effective against adenocarcinoma metastases; and melphalan, cisplatin, TNF-α and doxorubicin were effective against sarcoma metastases (*Table 1*).[8-17]

Phase I studies of isolated lung perfusion

Following the promising results of the experimental studies, several phase I studies were started after 1995 (*Table 2*). These studies were used to evaluate the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) of the different chemotherapeutic agents as well as the feasibility of this procedure in patients with resectable and unresectable disease. The studies, which included resectable disease, will be discussed more in detail.

Four phase I studies were performed in patients with unresectable LM.[18-21] Of these four studies, only two were able to get a partial or complete response.[19,21] The study of Pass et al. was able to get a partial response to the treatment but after 6-9 months all patients showed progressive disease.[19] One major response in sixteen patients was found in the study of Putnam et al. with an overall median survival time of nineteen months.[21] Conclusions in these studies were that ILuP is feasible, reproducible and safe with good separation of the systemic and perfusion circuit.[18,20,21]

Schröder et al. published a pilot study including four patients with both resectable and unresectable sarcoma LM.[22] They performed a metastasectomy, followed by an ILuP with cisplatin at 41°C (hyperthermic conditions). Again, there was a good separation between the systemic circulation and the perfusion circuit, with minimal systemic expose and no systemic toxicity. All four patients developed non-cardiogenic lung oedema after the perfusion. During a mean follow-up of twelve months, three of the four patients were still alive and disease-free. One patient died thirteen months after the operation due to cerebral metastases, without any evidence of local pulmonary recurrence on autopsy.[22]

The phase I study of Ratto et al. included resectable LM from soft-tissue sarcoma.[23] DLT could not be calculated because they used a fixed dose of cisplatin of 200 mg/m^2. No patients died during or after the operation. The concentration of cisplatin in the lung was more than 40 times higher than in the systemic circulation and there was no systemic toxicity. No concentration difference was found between tumour and normal lung tissue and no histological damage was found inside the lung.[23]

In 2004, a phase I study was performed in our centre together with the Antonius Hospital in the Netherlands including a total of sixteen patients with LM from colorectal carcinoma, soft-tissue sarcoma, osteosarcoma, renal cell carcinoma and salivary gland.[24] In total, 21 ILuP procedures (five bilateral) with an increasing dose of melphalan combined with a metastasectomy were performed to determine the MTD.[24] There was no operative mortality, the operations had no technical difficulties and there was no systemic toxicity. The MTD at the end of the study was determined at 45mg melphalan perfused at a hyperthermic condition (42°C). This study was followed by an extension trial.[25] Seven patients were included, undergoing eight procedures. During this extension trial, an increased toxicity was found under the hyperthermic condition of 42°C. With these findings the MTD was set to 45mg melphalan at 37°C. In this study, a significant correlation was found between the used melphalan doses during ILuP, the perfusate area under the concentration-time curve and the melphalan lung tissue concentration.[26] No correlation was found between the melphalan dose used and the melphalan concentration in the tumour. The maximum concentration was 250 times higher and the melphalan area under the curve was ten times higher than the melphalan concentration in the systemic circulation.

The long-term follow-up of this study and the extension trial was reported in 2010.[27] After a median follow-up of 62 months, six of the total 23 patients were alive and free of recurrent disease and one patient died due to a non malignant cause. Recurrent disease was found in sixteen patients. Eleven of these sixteen patients died. Of these sixteen patients, five had a pulmonary recurrence in the perfused lung. The five-year overall survival rate was 54.8 ± 10.6% with a median disease-free survival time of nineteen months. These survival data needs to be interpreted carefully, because this is a phase I study with different dose levels and should not be generalised. Follow-up of the pulmonary function showed that both diffusion capacity as well as lung functional volumes dropped one month after the ILuP, but stabilised and recovered afterwards. No long-term toxicity was found in this study.[27]

Phase II study of isolated lung perfusion

To date, only one phase II study has recently been published under abstract form using ILuP as adjuvant treatment together with metastasectomy for LM.[28] This study performed in three thoracic surgical centres in the Netherlands and our institution, included 50 patients with resectable LM from colorectal carcinoma, osteosarcoma and soft-tissue sarcoma. They underwent a total of 62 perfusions with 45mg melphalan at 37°C, followed by complete metastasectomy. When bilateral disease was present a staged procedure was performed. The perioperative mortality was 0% and the 90-day morbidity was one grade four pulmonary toxicity. After a median follow-up of 24 months, 30 patients had recurrent disease but only seven patients (23%) had their initial recurrent disease inside the perfused lung which is lower than the 43-66% that is reported in the literature for these tumours.[1,2]

Four-year overall-survival rate in this phase II trial was 49 ± 11% and the four-year disease-free survival was 36 ± 8%.[28] Patients with LM from CRC had a significantly better survival than patients with sarcoma metastases.

Compared to the preoperative values, pulmonary function tests one month after the perfusion showed a drop of FEV1 and diffusion capacity of 21.6% and 25.8%, respectively. Twelve months after the perfusion FEV1 and diffusion capacity showed an improvement with a reduction of 10.4% and 11.3% in comparison with the preoperative values. These data suggests that the long-term pulmonary toxicity is limited.[28]

Also, a quality-of-life study was performed in one of the participating centres, showing no difference between the ILuP patients and patients that underwent a thoracotomy without ILuP.[29]

The results of this phase II trial and the quality of life study in this patient group suggests that ILuP with melphalan as additional treatment may substantially improve local pulmonary control with minimal long-term effect on lung function and quality of life.

Future

Although the results are promising with the additional use of ILuP, it is an invasive technique that can only be performed once. A possible solution is selective pulmonary artery perfusion (SPAP). This is an endovascular technique using a balloon-catheter, which is brought up from the femoral vein into the pulmonary artery, allowing a chemotherapeutic agent to be injected directly into the lung circulation. The balloon is insufflated right after the injection, resulting in blood-flow occlusion, allowing the chemotherapeutic agent to diffuse into the lung tissue. There is no control of the venous effluent, which allows the agent to reach the systemic circulation when the balloon is deflated. This

Key messages for clinical practice

1. All patients with resectable lung metastases should be considered for lung metastasectomy.
2. Isolated lung perfusion is an additional technique, in combination with lung metastasectomy, to prevent intrapulmonary recurrent disease.
3. Isolated lung perfusion data suggest no long-term pulmonary toxicity, good local pulmonary control and good quality of life.

technique can be repeated allowing several courses of locoregional chemotherapy. It has already been demonstrated that SPAS is able to reach the same concentration of chemotherapy when compared with ILuP.[17,30] SPAP was also able to achieve a superior survival in comparison with systemic chemotherapy in a rodent model.[17] These results warrant further investigation but no human phase I trials have been reported until now.

Conclusion

With the use of ILuP in combination with lung metastasectomy, it is possible to reach a better local pulmonary control when compared with systemic chemotherapy and lung metastasectomy without ILuP. There is no long-term pulmonary toxicity and no difference in quality of life. This improved local pulmonary control may result in a better prognosis for patients with resectable LM as well as a reduced number of reoperations necessary for recurrent LM. However, this remains to be confirmed in a randomised trial between metastasectomy with ILuP in comparison with metastasectomy without ILuP.

Owing to invasiveness, alternative techniques need to be investigated for ILuP. Selective pulmonary artery perfusion may be a valid alternative.

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