Isolated Thoracic Perfusion with Chemofiltration (ITP-F) for Advanced and Pre-treated Non-Small-Cell Lung Cancer

24

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Substantial parts of this manuscript are from the thesis of Emir Selak.

Lung cancer is the most frequent cause of death from malignancy in men. About 500,000 patients in the northern hemisphere per year and more than 1,000,000 patients worldwide die from lung cancer every year. Non-small-cell lung cancer accounts for about 80% of all patients with lung cancer. At the time of diagnosis, most patients already have advanced disease, only some 30% are still operable, and in those, 1-year life expectancy is about 43%. The majority of patients are unsuitable for radical surgery or radiotherapy. Life expectancy with current first-line platinum-based doublets with or without additional drug combinations or targeted drugs remains unchanged at about 8–10 months. An impressive change of median overall survival has not yet been achieved, only some minor changes of prolongation of progression-free survival (PFS) of a few months. Extended survival time by a few months was achieved with dose-intense or prolonged chemotherapy but was associated with unacceptable toxicity [1–4] and a negative impact on the patient's quality of life.

In an attempt to extend survival time, improve quality of life, and administer a therapy that is less expensive than therapies already available, we initiated a technique that generates high local drug exposure by means of segmental vascular isolation of the chest, and simultaneously reduces or avoids toxic side effects by extracorporeal purification of blood.

24.1 Technique of Isolated Thoracic Perfusion with Chemofiltration

For Isolated Thoracic Perfusion with Chemofiltration (ITP-F), under general anesthesia, an arterial and venous stop-flow-three-channel balloon catheter is inserted through femoral access, and the aorta and vena cava are blocked just below the diaphragm (Fig. 24.1). By means of two additional pneumatic cuffs around the upper arms, the isolation of the

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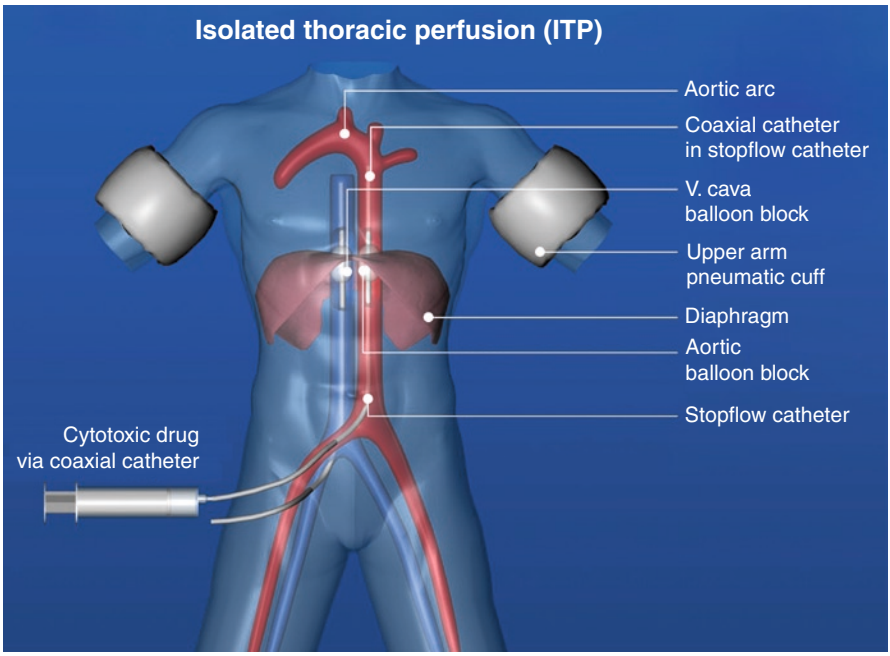

Fig. 24.1 Scheme of isolated thoracic perfusion

head-neck-chest area is completed. Chemotherapeutics are injected with high pressure against the aortic blood stream through the coaxial channel that exits at the tip of the aortic catheter. The drug can equally well be injected through the coaxial channel of the vena cava balloon catheter. After a 15 min exposure time, all blocks are released, and through the larger channels in both stop-flow catheters the arteriovenous chemofiltration is maintained over a median of 40 min at a maximal flow rate of 500 mL/min. This substantially reduces the systemic drug exposure by detoxification. It also prevents major toxicity caused by vascular leakages into the systemic blood circuit (Fig. 24.2).

At the end of chemofiltration, both catheters are removed and the femoral vessels repaired with running sutures.

24.2 Pharmacokinetics and Pharmacodynamics

In treating lung cancer, there are two aspects of how to create higher drug exposure as compared with systemic chemotherapy. First is the application of an isolated perfusion circuit showing how to generate maximum drug concentration at the target area taking benefit of the "first pass uptake." The second is the manipulation of the arterial blood flow and infusion time.

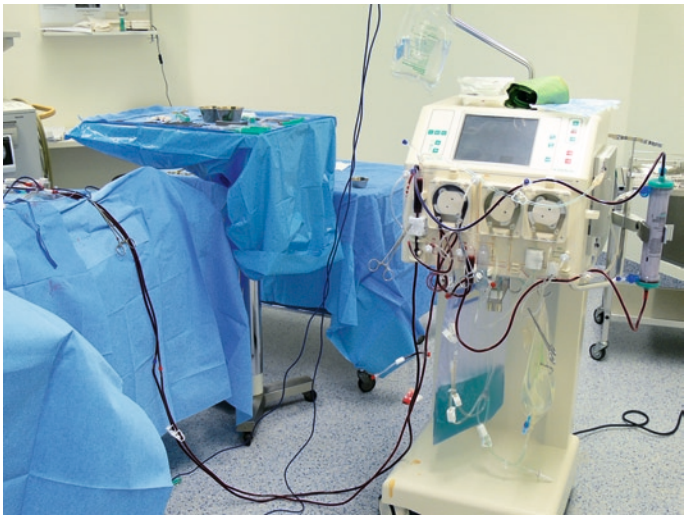

Fig. 24.2 Chemofiltration

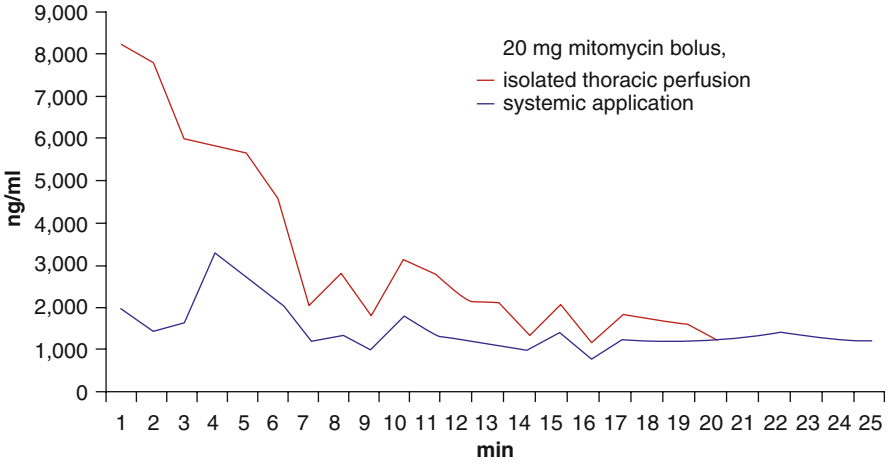

Fig. 24.3 Mitomycin plasma levels in isolated thoracic perfusion with chemofiltration versus intravenous application

First, with isolated circuit perfusion, there is the increase of drug levels and drug concentration in a closed system by reduction of the circulating blood volume. In a theoretical model, a volume reduction to one-third or one-fourth of the primary volume will increase the drug concentration by a factor three or four. Figure 24.3 shows the difference of mitomycin plasma levels when the same total dose of 20 mg is administered as an intravenous systemic bolus as compared to intra-aortic bolus infusion. The therapy had been performed in the same patient first as systemic chemotherapy, then as isolated thoracic perfusion (Fig. 24.3). The drug levels

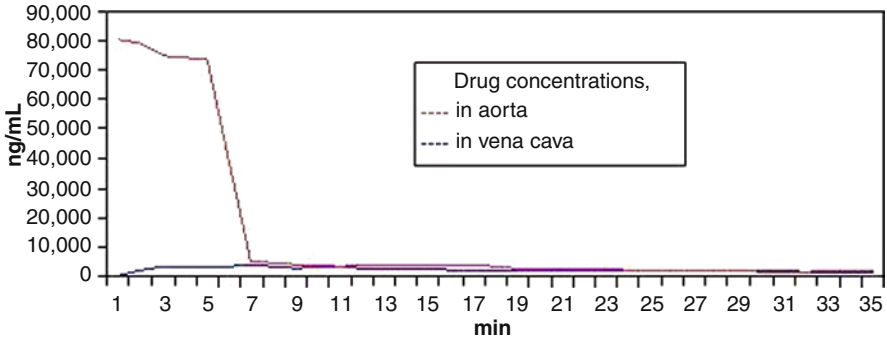

Fig. 24.4 Intra-aortic pulsatile infusion of 80 mg of cisplatin

in the isolated circuit are, in accordance with the reduced blood volumes, three to four times higher than in the entire systemic system. The advantage is reduced to twice the concentration at 6 min post-injection, most likely because of increased tissue uptake due to higher first pass concentration and equalizes with systemic drug levels after 20 min. Chemofiltration had been started at 15 min, after releasing the venous and arterial blocks of the isolated system.

A manual pulsatile jet injection through the coaxial channel of the stopflow catheter generates first pass peak concentrations of cis-platinum of about 75,000–80,000 ng/mL in the aorta while venous concentrations taken in samples from the vena cava are equivalent to those in the reduced volume model and range between 1,000 and 3,000 ng/mL maximally. This translates into a 20- to maximally 80-fold advantage of the intra-aortic application in terms of first pass effect (Fig. 24.4).

24.3 Patients and Methods

Sixty-four patients with non-small-cell lung cancer, 84% in progression after systemic platin-based chemotherapy or radiochemotherapy were assigned for isolated thoracic perfusion and chemofiltration [5]. Nineteen patients were in UICC stage III and 45 patients in UICC stage IV.

The treatment consisted of four cycles of isolated thoracic perfusion at 4 weeks intervals each. A three-drug combination of cisplatin, adriamycin, and mitomycin was administered as a pulsatile jet-bolus through the central channel of the arterial balloon catheter against the aortic blood stream. Infusion time was 3–5 min. Standard dosage in a 70 kg patient was 100 mg cisplatin, 50 mg adriamycin, and 20–30 mg mitomycin. Chemotherapeutics were administered into reduced blood volumes of the chest area, amounting to 1/3–¼ of the total body blood volume. Thus the achieved drug concentrations due to lower blood volume are increased adequately. Drug exposure time, such as total isolation of the hypoxic lower hemibody was 15 min. Average chemofiltration time was 40 min. For follow-up control a CT scan was performed after the first, the third, and the last therapy. In cases showing no concrete response within 4 weeks after the first treatment, the

administered drug combination was changed, mostly according to chemosensitivity testing. In cases showing no visible or clinical response after two courses of regional chemotherapy with different drug combinations, the treatment was discontinued. In cases showing continuous response as, for example, stepwise tumor shrinkage and improvement of respiratory parameters, the therapy was usually continued for up to four cycles, but in a few selected cases up to six cycles. One patient had resection of a responding tumor that before therapy had infiltrated the chest wall.

24.4 Results

Quality of response was noted mainly as partial remission in 56% of the patients. Possibly because of advanced stage IV cancers with mostly bulky tumors, the rate of complete remissions in CT scan was only 8% (Table 24.1). The overall response rate (CR and PR) was 64% with 28% stable disease and 8% progressive disease. Five patients had complete remissions (8%). This was already noted after the first or second isolated thoracic perfusion (Fig. 24.5a, b).

Overall survival was one of the endpoints of the study. In UICC Stage IV patients, 1-year survival was 48.9%, 2-year survival 22.2%, and 3-year survival 11.1% (Fig. 24.6). A comparison of these survival data with the American Joint Committee on Cancer (AJCC) data [6] is shown in Table 24.2.

Table 24.1 Response rates after four cycles of isolated thoracic perfusion

• CR (complete remission)	8%	Total 64%
• PR (partial remission)	56%	
• SD (stable disease)	28%	
• PD (progression)	8%	

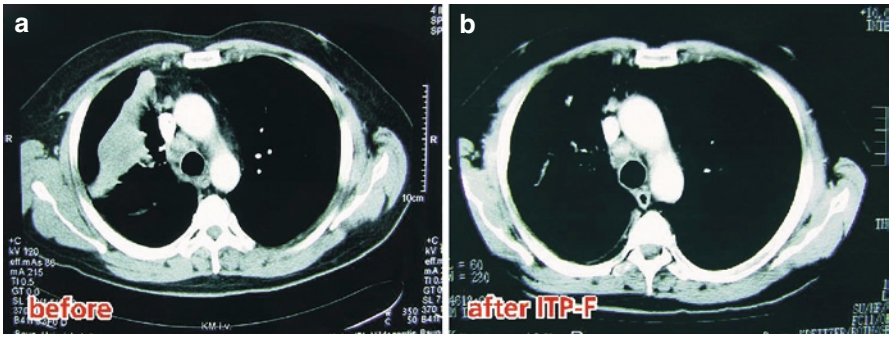

Fig. 24.5 (**a**) CT scan before isolated thoracic perfusion with chemofiltration. (**b**) CT scan 4 weeks after isolated thoracic perfusion with chemofiltration

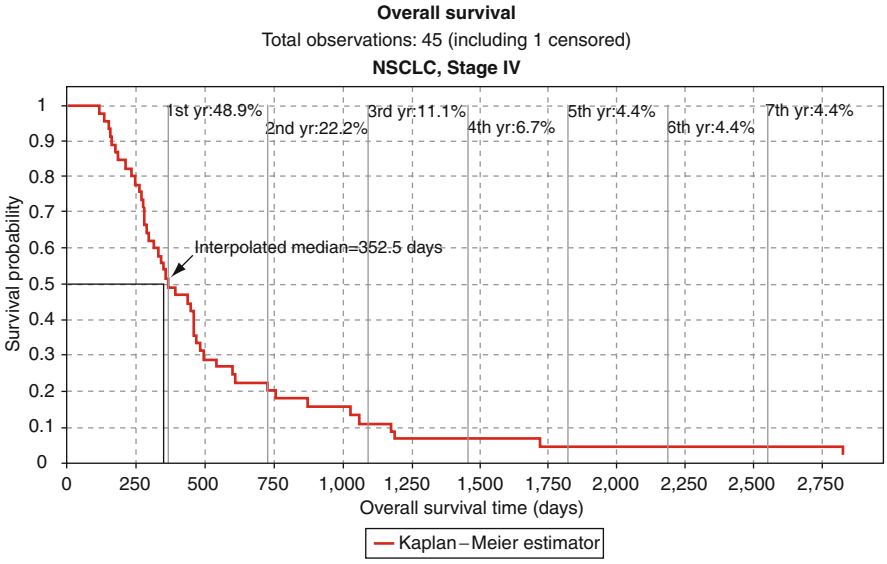

Fig. 24.6 Kaplan–Meier survival estimate $n = 45$ NSCLC stage IV patients

Table 24.2 Survival ITP-F versus cancer data base (AJCC) NSCLC stage IV

Survival years	1	2	3	4	5
ITP-F	48.9%	22.2%	11.1%	6.7%	4.4%
AJCC	16.9%	5.8%	3.1%	2.1%	1.6%

24.5 Side Effects

Hematological toxicity was low and did not exceed WHO Grade I or II. Nausea and vomiting rarely occurred. A few patients reported slight nausea. This had a clear correlation to the rate and intensity of chemofiltration. It had been observed in a former study that patients who had perfusion without chemofiltration had side effects comparable to those after systemic chemotherapy and an inpatient stay in the hospital of 10–12 days postoperatively, whereas patients who had prior chemofiltration had almost no side effects at all and were discharged on the third to fifth postoperative day.

Because of simultaneous chemotherapy of the chest, head, and neck area, more than 95% of the patients receiving isolated thoracic perfusion suffer hair loss despite the application of a cool cap. A transient symptom is facial edema (Fig. 24.7a, b) which is due to the high drug concentrations and drug exposure. It remains between 2 and 3 days and has no significant effect on the patient's quality of life or well-being. Patients with prior borderline respiratory function may need additional oxygen due to slight interstitial edema on

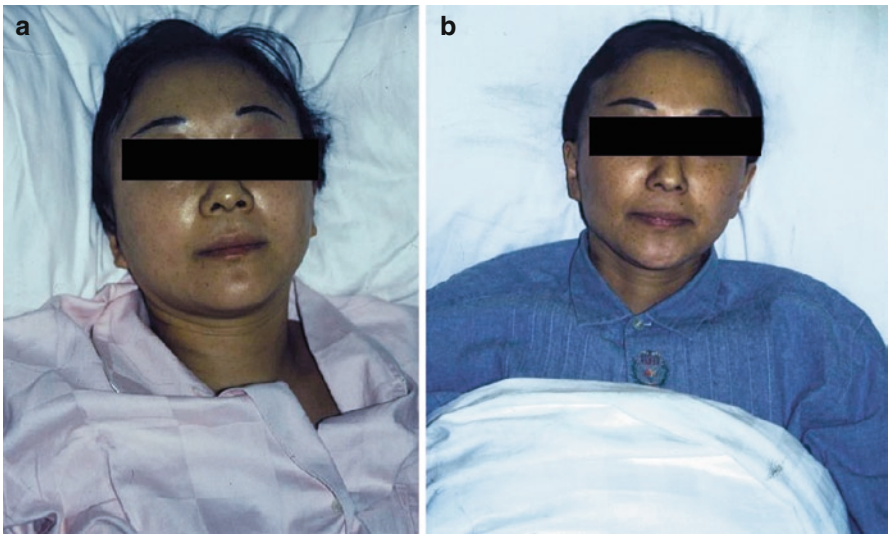

Fig. 24.7 (**a**) Facial edema directly after isolated thoracic perfusion. (**b**) Facial edema 2 days after isolated thoracic perfusion

the first 2 or 3 postoperative days. In most cases, respiratory parameters are improved by the fourth or fifth postoperative day.

Fatigue has not been observed, except in cases where isolated thoracic perfusion has led to immediate tumor necrosis within the first postoperative days. Major toxicity grade 4 or febrile neutropenia has not occurred. Toxicity from 15 min hypoxia was mainly reflected in terms of transient slight elevation of liver enzymes and serum creatinine. Permanent kidney or liver damage has not been found.

24.6 Discussion

It has been shown in this study that an increase in local drug exposure translates into an increase in response rate and overall survival. Quality of life, which was the second important endpoint of the study, could be improved impressively by means of chemofiltration, which reduces the residual drug in the systemic blood circuit. Therefore, there were no undue treatment associated side effects, which are commonly noted after dose-intense therapies, which predominantly only reveal improvements in PFS, not being accompanied by improvements in quality of life. Considering overall survival, so far there has been no substantial progress with systemic chemotherapy. Nearly all improvements in survival have been achieved in localized cancer cases. And those gains in survival are more or less the result of advances in treatment, such as better surgical techniques in general, and the higher quality of lung cancer surgery related to better imaging and pretreatment planning [6].

Data from the study published herein were compared with the relative survival rates for non-small-cell lung cancer diagnosed in the USA in 1992 and 1993 [7]. For non-small-cell lung cancer survival rates in 44,410 patients in stage IV were 16.9% at 1-year, compared with 48.9% after isolated thoracic perfusion, 5.8% after 2 years compared to 22.2% after isolated thoracic perfusion, and 3.1% after 3 years compared to 11.1% after isolated thoracic perfusion. Of course, more than 44,000 patients, representing an overall trend, can hardly be compared with 64 patients in a small study; however, those 44,000 patients indeed represent reliable data which do not change significantly despite all therapeutic endeavors [3, 4, 8–16].

24.7 Conclusion

Regional chemotherapy in terms of isolated thoracic perfusion with chemofiltration provides an advantage in such a way that dose-intense therapy can be administered to the target area and its lymphatic pathways which are predominantly invaded by cancer, without causing collateral toxicity to the entire organism. Chemofiltration plays the predominant role in this concept [17–20]. Due to isolation perfusion combined with chemofiltration, tumors can be treated more effectively without the deleterious effects of systemic treatment on the patient's quality of life.

Another important item is drug exposure. It has been shown that short-term bolus infusions induce high drug uptake in tumor tissues which consequently enhances the tumoricidal effect. Residual drug in the systemic blood pool is reduced or eliminated by subsequent chemofiltration.

A clear trend toward regional chemotherapy is obvious since patients with a poor life expectancy in progression after radiochemotherapy or chemotherapy clearly had a benefit from isolated thoracic perfusion. Taking into account that a patient with non-small-cell lung cancer at the time of diagnosis has a 1-year life expectancy of ±43% and after being in progression after intensive pretreatment with surgery, chemo- and radiotherapy, and a definitely reduced performance and a life expectancy of a few weeks, again has a 46% chance to survive 1 year, it can be concluded that isolated thoracic perfusion is effective. Nevertheless these data should be confirmed in a controlled phase III study, comparing conventional therapy in UICC stage IV patients with no therapy and regional chemotherapy focusing on the primary endpoints, overall survival, and quality of life.

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