

## REGIONAL PLUS SYSTEMIC CHEMOTHERAPY – AN EFFECTIVE INDUCTION THERAPY FOR INOPERABLE NON SMALL CELL LUNG CANCER STAGE III - IV

## REGIONÁLNÍ A SYSTÉMOVÁ CHEMOTERAPIE – EFEKTIVNÍ INDUKČNÍ TERAPIE U INOPERABILNÍCH NEMALOBUNĚČNÝCH KARCINOMŮ PLIC III.–IV. STÁDIÍ

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**Abstract: Purpose:** Our objective was to better define the activity, feasibility and toxicity of regional chemotherapy using an isolated thoracic perfusion (ITP) technique plus low dose systemic chemotherapy as induction chemotherapy in patients with Stage III non-small-cell lung cancer (NSCLC) followed by surgery within a pilot study. **Patients and Methods:** Twenty-two chemotherapy-naïve patients with NSCLC, median age of 57 years, Stage III - IV disease with metastases only in thoracic region, Karnofsky - Index > 60, received two cycles of regional plus systemic chemotherapy with a treatment free interval of 4 weeks. Cytostatic regimen consisted of mitomycin 10 mg/m<sup>2</sup>, navelbine 25 mg/m<sup>2</sup> and cisplatin 30 mg/m<sup>2</sup> during ITP on day 1 plus low dose systemic chemotherapy with 5-fluoruracil 250 mg/m<sup>2</sup> and cisplatin 20 mg/m<sup>2</sup> given as continuous infusion over 24 hours on day 1-4. 4 weeks after second treatment re-evaluation for response and surgery was carried out, if possible. **Results:** All 22 pts. were assessable for toxicity, response and survival. There were 19 / 22 remissions (CR 1; PR 12; MR 6) corresponding to a regression rate of 86,4 %. 16 / 22 pts. could be resected corresponding to a resectability rate of 72,7 % (13 complete resections R0, 1 R1, 2 R2). Side-effects were transient and acceptable with no treatment or surgery related death. Median survival has not been reached after an observation time of 15 months. 1-year survival rate was 67,3 %. **Conclusion:** Regional chemotherapy using an ITP application form plus low-dose systemic chemotherapy is highly active in primary advanced NSCLC stage III - IV leading to a high resectability rate with an encouraging survival outcome.

**Key words:** Non Small Cell Lung Cancer (NSCLC); Thoracic perfusion; Regional chemotherapy; Systemic chemotherapy; induction chemotherapy; Mitomycin; Navelbine, continuous CisPlatin

**Souhrn: Účel:** Naším cílem bylo lépe definovat aktivitu (činnost), proveditelnost a toxicitu regionální chemoterapie při použití techniky (metody) izolované hrudní perfuze a systémové léčby nízkými dávkami jako úvodní chemoterapie (indukční chemoterapie) u pacientů s nemalobuněčným karcinomem plic (NSCLC) III. stádia s následující chirurgií během pilotní studie. **Pacienti a metody:** Dvacet dva pacienti s nemalobuněčným karcinomem plic, u nichž nebyla prováděna chemoterapie, střední věk 57 let, III. až IV. stádium nemoci s metastázemi pouze v oblasti hrudníku, Karnofského index 60, dostávali dva cykly regionální a systémové chemoterapie se čtyřtýdenním intervalem bez léčby. Cytostatický režim se sestával z mitomycinu 10 mg/m<sup>2</sup>, navelbinu 25 mg/m<sup>2</sup>, a CisPlatinu 30 mg/m<sup>2</sup> během izolované hrudní perfuze první den a systémové chemoterapie s nízkými dávkami 5-fluoruracilu 250 mg/m<sup>2</sup> a CisPlatinu 20 mg/m<sup>2</sup> podávanými jako stálá infuze po 24 hodin první až čtvrtý den. 4 týdny po druhé léčbě bylo provedeno nové hodnocení reakce, a jestliže to bylo možné, byla provedena chirurgie. **Výsledky:** U všech 22 pacientů byla vyhodnocena toxicita, reakce a přežití. U 19/22 došlo ke zmírnění (CR 1; PR 12; MR 6) což odpovídá poměru regrese 86,4 %. Resekce mohla být provedena u 16/22 pacientů, což odpovídá poměru možností resekce 72,7 % (13 celkových resekcí R0, 1 R1, 2 R2). Průvodní jevy byly přechodné a přijatelné, bez léčení nebo úmrtí v důsledku chirurgie. Po době pozorování 15 měsíců nebylo dosaženo střední hodnoty přežití. Poměr přežití 1 rok byl 67,3 %. **Závěr:** Regionální chemoterapie využívající aplikační formy izolované hrudní perfuze (ITP) a systémové chemoterapie nízkými dávkami je vysoce činná a u prvotně pokročilých nemalobuněčných nádorů (karcinomů) plic (NSCLC) III.–IV. stádií, vede k vysokému procentu možnosti resekce s povzbudivým výsledkem přežití.

**Klíčová slova:** nemalobuněčný karcinom plic (NSCLC); hrudní perfuze, regionální chemoterapie, systémová chemoterapie, indukční chemoterapie; mitomycin, navelbine; stálá CisPlatina

Non small cell lung carcinoma (NSCLC) remains the leading cause of cancer deaths in both men and women. In 1999, approximately 171,600 people will be diagnosed with lung carcinoma, and 158,900 deaths will occur. (14) NSCLC accounts for approximately 75% of all lung carcinomas and, 35% of patients with NSCLC will present with Stage IIIA or IIIB disease (12). The majority of these patients with mediastinal involvement are not amenable to surgical resection, and primary radiation therapy alone results in 5-year survival rates of only 3-7% and median survival times of 6-11 months (9).

Because the majority of these patients ultimately die of distant metastases, recent efforts to improve their intermediate- and long-term survival have focused on neoadjuvant chemotherapy (with or without radiotherapy) as an induction regimen followed by surgical resection. The ideal trial would address the effect of chemotherapy (with or without radiotherapy) on the survival of patients with clinically visible and mediastinoscopically proven N2 disease.

The theoretical advantages of the neoadjuvant approach include systemic as well as local effects such as:

- Early control of distant micrometastatic disease
- Prevention of visible tumor seeding at surgery
- An increase in resectability of neoplastic lesions technically unresectable at diagnosis
- A reduction of tumor mass before definitive radiotherapy
- Decreased incidence of positive margins at surgery
- Possible use of less radical surgery with organ preservation
- In vivo assessment of the effects of chemotherapy and / or radiotherapy

Moreover early chemotherapy has been associated with greater efficacy and improved drug delivery to tumor cells via intact vasculature. Disadvantages of the neoadjuvant approach include morbidity and mortality related to the side effects of induction chemotherapy and an increase in surgical morbidity and mortality as well as a delay in time to definite surgery.

Because of the poor outcome of patients with unresectable Stage IIIA/B NSCLC, who are treated with thoracic radiation therapy (TRT) alone, the use of chemotherapy in combination with TRT has been evaluated. The introduction of combined modality treatment has improved the median and long term survival rates for these patients (5,11,15,26,27). Several groups have shown that this approach is feasible in patients with stage III disease, who usually have better response rates than patients with stage IV disease.(4,16) Moreover, three small randomized trials comparing surgery alone with a combined program of induction therapy followed by surgery have shown prolonged survival in the combined-modality arms. (23,24,25)

Because local control remains a substantial problem in patients with unresectable Stage III NSCLC, strategies designed to enhance local control stand to make further improvements in the long term outcome of patients with this disease. The purpose of this pilot study was to incorporate the use of isolated thoracic perfusion treatment (ITP) planning into a strategy of induction therapy followed by surgery in the treatment of patients with primarily unresectable Stage IIIA/B NSCLC (1,8,17). In order to improve activity of chemotherapy in advanced NSCLC we tried to increase regional cytostatic drug concentration in thoracic region by using a regional application form – isolated thoracic perfusion (ITP). Thoracic perfusion means the limitation of the greater circulation to the thoracic region by placing two balloon catheters in the aorta and vena cava as well as two Esmarch bandages at the roots of both arms. Pharmacokinetic studies about this application form using different cytostatic drug like doxorubicin, melphalan, FUDR, cisplatin or mitomycin have shown a 6 to 10 – times increase in loco-regional drug concentrations compared to systemic application (10, 18, 19, 22).

Aim of this study was to evaluate the toxicity profile and efficacy of a combined cytostatic regimen using regional plus systemic chemotherapy in unresectable stage III NSCLC patients. This regimen consisted of a combination of regional chemotherapy (mitomycin, navelbine and cisplatin) using an isolated thoracic perfusion technique (ITP) as application form plus systemic chemotherapy with 5-fluorouracil and cisplatin given in a low dosage continuously over 4 days (2,11). This report is the first to incorporate ITP into a inductive treatment strategy for NSCLC and describes the Phase I results of the trial.

## **Patients and Methods**

### **Patient Selection**

Eligibility criteria for study entry included the following Patients with histological or cytological confirmed unresectable or metastatic NSCLC stage III A, III B or IV with metastases defined only to thoracic region, acceptable performance status Karnofsky – index of 70 and more. Patients with severe atherosclerosis, concurrent severe cardiac, metabolic or infectious disease were excluded from this trial., and an adequate baseline Organ function defined as a WBC count of at least

3,000/NT., liver and renal function within normal limits, and acceptable spirometric values allowing general anesthesia. Patients who had previous history of chemotherapy, radiotherapy or presence of active infection were excluded from the study. All patients gave written informed consent.

### **Patient Evaluation**

A complete history, physical examination, complete blood cell count with differential, Serum biochemistry, urinalysis, spirometry, bronchoscopy, computer tomography (CT) scan of the chest and upper abdomen, and ECG were obtained at baseline. Patients were monitored throughout treatment by recording history, toxic events, and complete blood cell counts; Serum chemistry determinations were repeated just before the start of each chemotherapy cycle. Tumor response was evaluated by CT scan after two cycles of treatment. Repeated mediastinoscopy were not included in the postchemotherapy evaluation.

### **Response definition**

Definitions of response (i.e. partial or complete response), stable disease and progressive disease were based on the standardized response criteria established by the World Health Organization (WHO). Responses were assessed after second therapy cycle with CT-scan and determination of tumor marker levels, if positive. Survival and response were both determined in all enrolled patients and calculated starting from the beginning of ITP treatment.

### **Treatment plan**

Treatment plan consisted of two a combination of regional plus continuous systemic chemotherapy. For regional chemotherapy the following cytostatics mitomycin 10 mg/m<sup>2</sup>, navelbine 25 mg/m<sup>2</sup> and cisplatin 30 mg/m<sup>2</sup> were administered during ITP via central venous line on day 1. To prevent severe bone marrow dysfunction and activate immunofunction GM-CSF 300 2g was applied during ITP. As systemic chemotherapy 5-fluorouracil 250 mg/m<sup>2</sup> and cisplatin 20 mg/m<sup>2</sup> were applied as a continuous infusion over 4 days via central venous line starting after end of ITP. Treatment free interval was 4 weeks. In case of leucocytopenia or thrombocytopenia WHO grad 3 or 4 next therapy cycle was postponed until white blood cell count was > 3000 /dl and platelet count > 100.000 /dl. Granulocyte stimulating factors (G-CSF) were used, if necessary. Preoperatively antiemetic therapy has been started using Dexametason 8 mg and 3 mg Granisetron applied by iv. injection. Treatment was discontinued, if disease progression or major toxicity occurred or according to patient's and / or physician's decision.

### **Operative technique**

Under general anesthesia both femoral vessels were exposed via an inguinal approach. After systemic heparinisation with 150 I.E. Heparin / kg., both vessels were crossclamped and two three-lumen 12-french balloon catheters (PfM, Cologne, Germany) were inserted (Fig. 1). Under x-ray control both balloons were insufflated in the aorta just above the celiac axis and in the inferior caval vein below the right atrium. In order to reduce the perfusion volume Esmarch-bandages were insufflated around both roots of the arms (occlusion pressure: 250 mmHg / Mercury). Cytostatics were given via central venous line in first two minutes after start of perfusion; perfusion time was 20 minutes.

### **Statistical analysis**

Overall and progression free survival curves were generated by using the Kaplan – Meier method starting from the date of diagnosis. Both disease progression and death were considered endpoints for progression free survival.

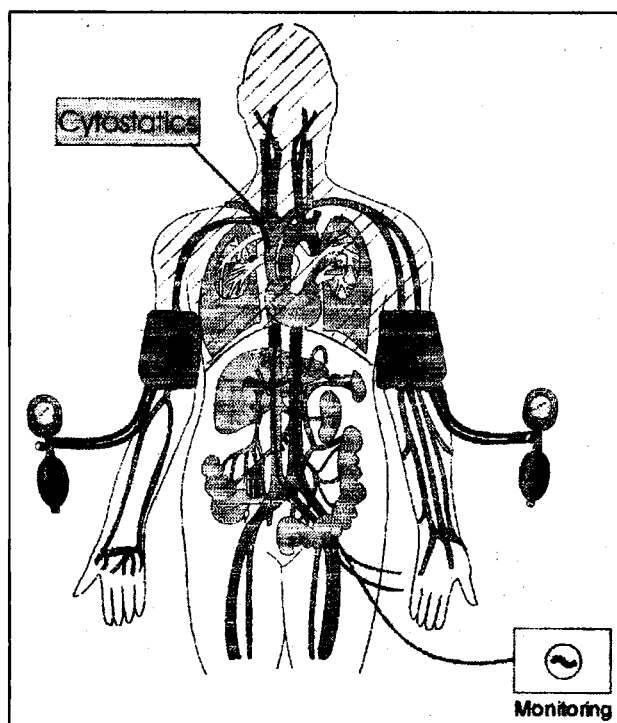


Fig. 1 Scheme of isolated thoracic perfusion

## Results

### Patient characteristics

Between March 1998 and October 2000, 22 concurrent patients could be accrued in this study. Characteristics of the 22 eligible patients (listed in Table 1) included a median age of 57 years (range, 43 to 74 years), Karnofsky -performance status of 80 and less in 59 % of the patients, and adenocarcinoma as the predominant histologic subtype (45 %). There were 10 patients in stage III A and another 11 in stage III B with 6 / 11 with T4-tumors. One patient was in stage IV because of contralateral pulmonary metastases. In one patient a third cycle of ITP plus systemic chemotherapy was added in order to reach a further shrinkage of a central located T4 tumour. In another patient with stage IIIB disease due to supraclavicular lymphnode involvement the strategy was changed to local radiotherapy plus ITP using Paclitaxel and Gemcitabine alone.

Table 1: Characteristics

Characteristics	No. of Patients	%
Total recruited	22	—
Sex		
Male	14	64
Female	8	36
Age, years		
Median	57,1	
Range	43-74	
TNM stage		
T1 N2 M0		
T2 N2 M0		
T3 N2 M0		
Histology		
Squamous Cell	5	23
Adenocarcinoma	10	45
Largecell	4	18
neuroendokrine	1	5
undifferentiated	2	9
Karnofsky - performance status		
100	3	14
90	6	27
80	10	45
70	2	9
60	1	5

## Toxicity

During 45 cycles of regional plus low-dose continuous systemic chemotherapy grade 3 leucocytopenia was observed in only 3 cases 6,7%. There was no episode of febrile neutropenia. Grade 3/4 anemia and thrombocytopenia has not been observed and there were no bleeding episodes. Due to use of single dose GM-CSF during ITP fever reactions were frequent, but not exceeding grad 1 / 2. Despite the use of Cisplatin in this regimen vomiting was manageable and not severe. Alopecia did occur in only one case. In none of all cases the operative procedure of ITP has to terminated early due to disturbance in blood pressure parameters. In none of these cases signs of pneumonitis or pulmonary fibrosis have been observed. Esophagitis grad 2 did occur only in case of radiotherapy plus second line chemotherapy – there were no sign of esophagitis in all other cases.

Table 2: Side-effects after regional plus systemic chemotherapy

WHO –	Grad 1	Grad 2	Grad 3	Grad 4
Leucocytopenia	8	5	3	—
Thrombocytopenia	3	2	—	—
Anemia	2	2	—	—
Vomitino	7	15	—	—
Fever	28	4	—	—
Alk. Phosphatase	2	—	—	—
Pain	3	10	—	—
GOT	1	—	—	—
Alopecia	—	1	—	—
Consiousness	1	—	—	—
Arrythmia	3	—	—	—

## Operative Procedures

After improvement in general condition as well as lung function parameters due to response to therapy a resection of primary tumour plus mediastinal lymphnode metastases was possible in 16 out of 22 cases. Complete pneumonectomy was carried out in 7 cases whereas in the remaining 9 cases a lobectomy or bilobectomy was necessary to resect visible tumor formations. Histologic evaluation has shown a complete resection resection (R0) in 13 cases, whereas resection was incomplete in three cases (R1 1/16, R2 2/16).

## Complications

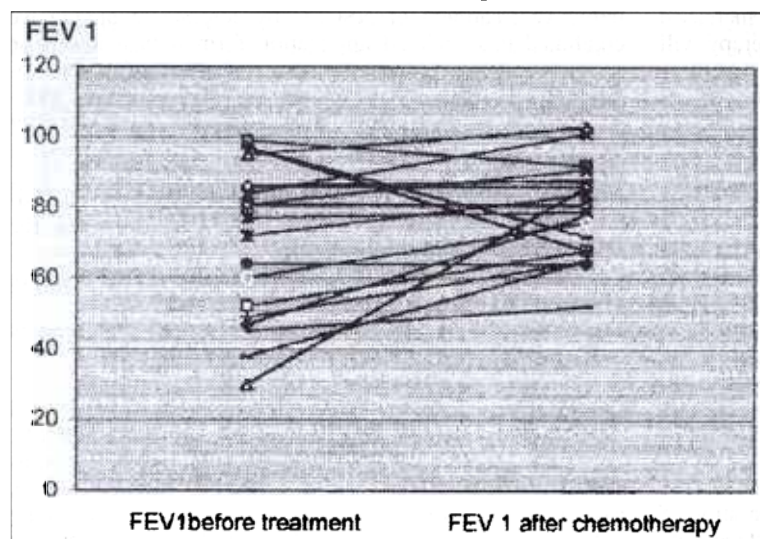
After 45 ITP procedures a superficial wound infection did occur not prolonging hospital stay. No wound infection and only one postoperative pneumonia has been observed. One early bronchial stump insufficiency did occur after right-sided pneumonectomy. In the same case a toxic lung edema with necessity for prolonged mechanical ventilation has to be treated. In another case a late bronchopleural fistulation after left-sided upper lobectomy has been observed.

## Response

The overall response rate of the 22 patients evaluable for response was 59 % (4,5 % CR and 54,5 % PR), but 6 other patients reached a minor response leading to a regression rate of 86,3 %. In this special situation we have to keep in mind that resectability will be not defined by a shrinkage of 50 % or more as defined in WHO criteria.

Looking at changes in lung function the most interesting parameter – one second Forced Expiratory Volume FEV 1 – has changed dramatically after first ITP procedure as sign of response. Nearly all patients responding to this treatment have had an increase or stabilization of FEV 1. This increase in lung function opens the way for operation and resection in this patients (fig. X / xx). For all treated patients the mean FEV 1 before chemotherapy was 69,23 % and after 74,78 %. Mean increase in FEV 1 for responding patients after the first ITP was 8,37 % (range 0 – 56 %) whereas the three patients not

#### Changes in lungfunction parameters after ITP – responder



#### Changes in lungfunction parameter after ITP – nonresponder

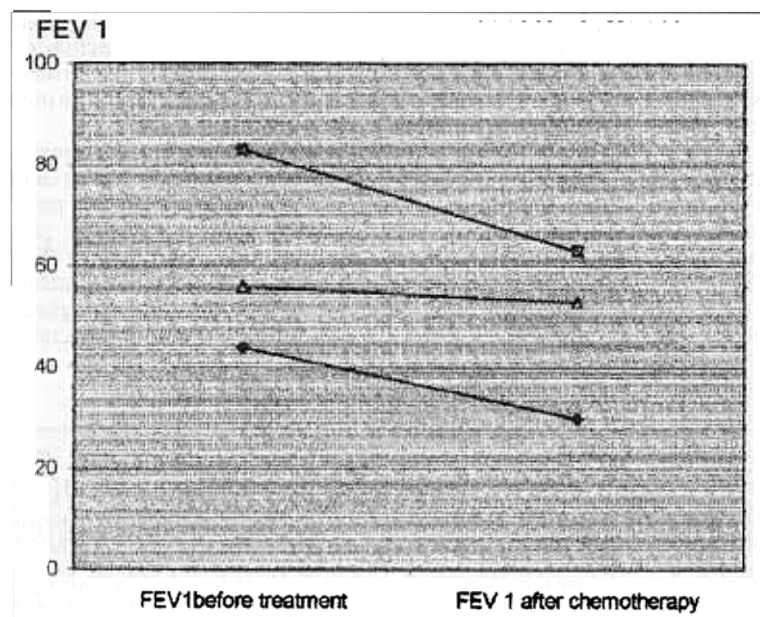
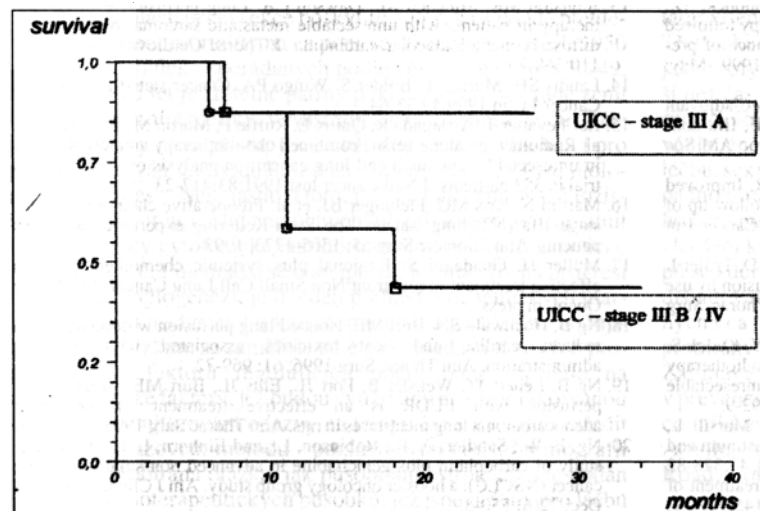


Fig. 2 Kaplan –Meier probability of survival dependent to tumor stage (UICC classification)



responding to therapy have had a drop of lung function parameters.

#### Survival

At the time of this analysis, after a median follow-up period of 15 months, 5 of the 22 patients have died. In 4 cases, the deaths were related to malignant diagnosis, whereas one died from a cardiovascular cause not related to therapy. The median duration of survival has not been reached up to now, and the estimated 1-year survival rate was 67,3 %. For 10 / 22 patients in stage III A 1-year survival rate was 87,5 %, whereas in stage III B / IV disease (12 / 22 pts.) only 58.3 % survived after one year.

#### Discussion

Combined modality therapy is now considered the standard of care for those patient with unresectable Stage IIIA/B NSCLC and a good performance status. The trial of Dillman et al.(5) was the first major random-ized trial to show that sequentially delivered chemoradiotherapy yields improved survival rates compared with radiotherapy alone. Comparing the radiotherapy arm with the combined modality arm, response rates (43 % vs. 56%, respectively;  $P = 0.092$ ), median survival (9.6 vs. 13.7 months, respectively;  $P = 0.012$ ), and 5-year survival rates (6 % vs. 17%, respectively), all favored the combined modality arm. This trial has been verified by the intergroup trial conducted by the RTOG and the ECOG, who showed similar survival advantages for the sequentially delivered combined modality arms. In addition, LeChevalier et al. (15) showed a survival advantage in a large European trial. In that trial, the combined modality arm had a statistically significant lowering of the distant metastases rate compared with radiotherapy alone.

Another possibility to improve results in NSCLC patients stage III A / B is the use of inductive chemotherapy followed by surgery. Okada et al. (21) demonstrated in his series of 51 patients an advantage in survival for all NSCLC patients with bulky nodal involvement after induction therapy and resection. These results could be confirmed by Stathopoulos et al. (29) in a larger trial with 359 patients, but there resectability rate was very low with 6,2 %. This is in contrast to the study published by De Leyn et al. (3), who reached a resectability rate of 88 % after induction chemotherapy in patients with NSCLC stage III A bulky disease.

In this study we have tried to overcome primary tumor cell resistance in NSCLC by use of high local cytostatic drug concentration (8,18,19). To reach this goal we used a simplified technique for isolation of the chest and lung compared with older application forms (6,13). As we have shown in a previous study ITP plus low dose continuous systemic chemotherapy is highly active in recurrent and progressive NSCLC defined to the thoracic region (17).

The potential benefit of regional chemotherapy is to reach high local drug concentrations in the treated area by reducing systemic side-effects (18). These high cytotoxic drug concentrations should lead to an increase in response rate



especially in case when no other negative factors such as decreased vascularity after prior radiotherapy or increased tumor cell resistance after prior chemo- or radiotherapy will diminish efficiency.

This pilot study has shown that ITP is feasible in NSCLC patients. In none of all cases ITP has to be terminated early due to disturbance in blood pressure parameters. This is in accordance to published data from Berkenstadt et al (1), by Guadagni et al. (8), who had shown that ITP does not lead to increased cardiac stress and our own prior results. Data in this study have shown an acceptable toxicity profile for these NSCLC patients who are in good to reduced general condition and performance status. There were no special side-effects related to this special application such as lymphatic fistulas in the groin, neurologic disorders or deep vein thromboses. This treatment using a cytostatic drug combination in the above mentioned dosages and application modus is combined with a very low rate of bone marrow depression. This opens the question, if an increase in dosages will lead to higher response rate.

In 1995 Johnston et al. (13) presented a special technique for isolated lung perfusion leading to an excellent separation of the lungs. Shunting rate was between 0 and 15 %, but we have to keep in mind that NSCLC is infiltrating the thoracic wall as well as the organs of the mediastinum in a high percentage of cases that an isolation of the lung does not necessarily correspond with the way of expansion in NSCLC.

In an animal model of bronchial adenocarcinoma Hendriks et al. (10) have shown that an isolated lung perfusion with melphalan can prolong survival compared with no treatment or with systemic chemotherapy of the same drug in the same dosage. Pharmacokinetic evaluations in different mouse models have shown that using thoracic as well as lung perfusion techniques cytostatic drug concentrations of melphalan, doxorubicin, cisplatin, 5-fluorouracil and mitomycin are 6 to 10 times higher compared with systemic administration (6,10,18,19).

In this trial we have chosen the cytostatics Mitomycin, CisPlatin and Navelbine for high concentrated regional

chemotherapy (2,7). Based on reported good results in the inductive treatment of NSCLC by Jeremic et al. (11) we combined this regional application form with a low dose systemic chemotherapy by use of CisPlatin and 5-Fluorouracil. This should reduce the gastrointestinal side-effects of CisPlatin usage and reduce the risk of hearing loss after high CisPlatin concentrations.

Benefit of this special therapeutic strategy is

- to reach a high rate of remissions also in advanced disease
- to reach an increase in lung function leading to the possibility for curative resection
- to open the way for an effective radiotherapy after curative resection
- to reduce the perioperative risk after induction therapy, by minimizing the radiotherapeutic tissue damage

Our data have shown the high effectivity of regional chemotherapy as induction therapy for advanced NSCLC. The treatment modality is active in bulky stage N2 disease as well as stage III B/ IV disease defined to thoracic region. Especially interesting in this study is the improvement in lung function parameters early after the first ITP which opens the way curative resection for patients in reduced condition and gives way for new diagnostic technique for response. Due to the fact that all patients responding to this treatment have had an improvement in lung function parameters lung function test can be used as a diagnostic tool of early response and in case of no improvement another cytostatic regimen should be used to break tumor cell resistance (20,28).

The high regression rate after ITP has led to an acceptable resectability rate also for stage III B / IV patients. Due to short observation time no definite conclusions can be made regarding survival after regional induction therapy plus resection, but our preliminary data are very encouraging. This means that isolated thoracic perfusion plus low dose systemic chemotherapy using the above mentioned cytostatic regimen is an very effective tool in advanced and unresectable NSCLC.

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