

Regional plus systemic chemotherapy – An effective treatment in recurrent Non Small Cell Lung Cancer.

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Abstract:

Purpose: This study was undertaken to determine the activity and toxicity of regional chemotherapy using an isolated thoracic perfusion (ITP) technique as second line treatment in advanced and recurrent non small cell lung cancer (NSCLC) patients.

Patients and methods: 18 patients with relapsed NSCLC defined to thoracic region entered onto the study were to receive regional chemotherapy using ITP plus low-dose systemic chemotherapy. All 18 patients had been pretreated with some form of chemotherapy, surgery and / or radiotherapy. Cytostatic regimen consisted of a two different parts: a) regional chemotherapy using mitomycin 10 mg/m², navelbine 25 mg/m² and cisplatin 30 mg/m² during ITP on day 1; b) systemic chemotherapy with 5-floururacil 250 mg/m² plus cisplatin 20 mg/m² given as continuous infusion over 24 hours on day 1– 4.

Results: All 18 patients were assessable for toxicity, response and survival. There were 10/18 responses (CR 0; PR 10) corresponding with a response rate of 55.6 %. Side-effects were transient and acceptable. No treatment related death was observed. Median survival was 21 months. 1-year survival rate was 75 %.

Conclusion: Regional chemotherapy using an ITP application form plus low-dose systemic chemotherapy is highly active in recurrent advanced NSCLC with an encouraging survival outcome.

Key words: Non Small Cell Lung Cancer, Thoracic perfusion; Stop flow; Regional chemotherapy; Systemic chemotherapy.

Introduction

In recent years, the role of chemotherapy in the treatment of non small cell lung cancer (NSCLC) has been more evident. Some controversies still exist over the ultimate benefit of systemic chemotherapy in advanced disease, though the use of platinum based combination chemotherapy has become more established. A meta-analysis¹ using updated data on individual patients from 52 randomized clinical trials of cisplatin based chemotherapy compared with best supportive care only, showed a benefit of chemotherapy with a reduction in risk of death of 27 % and an absolute increase in one-year survival rate of 10 %. Another more recent meta-analysis² compared the effect of single-agent versus combination chemotherapy on response rate, toxicity and survival in 25 trials including 5156 patients with advanced NSCLC. Overall, combination chemotherapy produced a nearly two-fold increase in response rate compared with single – agent chemotherapy, while survival at 6 and 12 months were increased by 10 % and 22 % with combination chemotherapy, respectively.² The achievement of response to chemotherapy induce improvement of tumor associated symptoms, indicating that the use of chemotherapy, which are able to induce high response rates may have a good palliative effect, even though the benefit in terms of survival may be modest.^{3,4}

Second line chemotherapy in advanced or recurrent NSCLC is not usually indicated, as all attempts have been, until recently, almost unsuccessful.⁵ On the other hand, several meta-analyses have shown that the survival benefit obtained with first-line platinum based chemotherapy for advanced NSCLC is limited to a few weeks, and in pretreated patients with recurrent or progressive NSCLC, the rapid worsening of general conditions often contraindicates further treatment.⁶

In order to improve activity of second-line 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 to10 – times increase in loco-regional drug concentrations compared to systemic application.⁷⁻¹¹

Aim of this study was to evaluate the toxicity profile and efficacy of a combined cytostatic regimen using regional plus systemic chemotherapy in advanced NSCLC patients who have recurrent or refractory disease after one or more standard treatments. 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.

Patients and Methods

Patients with histologically or cytological confirmed unresectable or metastatic NSCLC entered this trial, provided that they had an acceptable performance status Karnofsky – index of 60 and more, a life expectancy of > 3 months, and adequate bone marrow, hepatic and renal function. Patients with severe atherosclerosis, concurrent severe cardiac, metabolic or infectious disease were excluded from this trial. Patients were eligible, if they had received one or more prior treatment such as systemic chemotherapy, radiotherapy of the chest and / or mediastinum or operative interventions. Patients in stage IV disease were enrolled only when distant metastases were located in thoracic region. Patients were eligible 6 weeks after previous treatments. In this disease-oriented study, patients were enrolled if they had at least one lesion evaluable or measurable and after giving informed consent.

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). Prior start of treatment patients were staged with total body computed tomography (CT-scan). During treatment patients were monitored with a weekly blood count. Toxicity were graded according to WHO criteria before each therapy course.

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 different parts. a) regional chemotherapy: mitomycin 10 mg/m², navelbine 25 mg/m² and cisplatin 30 mg/m² were administered during ITP via central venous line on day 1. b) systemic chemotherapy: via central venous line 5-floururacil 250 mg/m² and cisplatin 20 mg/m² were applicated as a continous infusion over 4 days 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. Granulocyt stimulating factors (G-CSF) were used when necessary. 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 3 lumen 12 french balloon catheters (PfM, Cologne, Germany) were inserted (Figure 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 mg / Mercury). For continuous arterial pressure measurement a arterial line was placed into descending aorta. Cytostatics were given via central venous line in first two minutes after start of perfusion; perfusion time was 20 minutes.

Statistical analysis

Survival analysis was assessed by the Kaplan-Meier method. All calculations were performed by SAS/STAT software.

Results

Between May 1997 and May 2000, 18 patients could be accrued in this study. Patient characteristics are listed in Table 1.

Responses were evaluated in all patients. 10 patients (55.6 %) achieved a partial response with two patients who could be re-operated for cure (Table 2). CT-scan lesions of a 53-year old patient evaluated before ITP are shown in Figures 2a and 2b. Figures 3a and 3b show a partial response two months after ITP. In addition to that there were 5 patients achieving a stable disease and in 3 cases the tumor was progressive. Responses occurred with equal frequency in all histologic subtypes, in patients with stage III disease as well as in patients with stage IV disease.

The median survival time for all patients from start of regional chemotherapy was 21 months corresponding with a 1-year survival rate of 75 % and with a 2-year survival rate of 9 % (Figure 4). There was no significant difference between stage III (median survival 17 months) and stage IV patients (median survival 21 months.).

Toxicity

In none of all cases the operative procedure of ITP has to be terminated early due to disturbance in blood pressure parameters. Toxicity was evaluated for all subjects (Table 3) giving 39 cycles for 18 patients. Hematologic toxicity was the main, but not severe side effect in this trial. 6 patients developed WHO grad 3 / 4 hematologic toxicity, but growth factors have to be administered in only 2 cases. Duration of leucocytopenia was usually brief, no infectious episodes occurred. Non hematologic toxicity consisted of mild and transient fever and Cis-Platin dependent neurotoxicity. A deep vein thrombosis occurred in two cases and a lymphatic fistula after operative placement of catheters in another 4 cases, treated conservatively.

Discussion

In recent years, the role of chemotherapy has seemed to extend to the treatment of advanced NSCLC, mainly thanks to new drugs with innovative mechanisms of action and mild toxicity profiles, which have widened the indications for chemotherapy in advanced and disseminated disease. Although there is no evidence that second –line chemotherapy can influence survival in non responding advanced NSCLC patients or in those who experience disease progression, there is some suggestion that second-line treatment may be appropriate for patients with good performance status who experience disease progression after front-line chemotherapy or for patients who responded to initial chemotherapy and then experienced a progression free interval of treatment.

The options available to patients with advanced NSCLC resistant or refractory to first-line chemotherapy are very limited. The older-generation drugs (etoposid, vindesine, epirubicin, and cisplatin) that are active against previously untreated NSCLC do not achieve a response rate greater than 10% when used in the second-line setting.¹⁹ The newer-generation agents with activity in previously untreated NSCLC include carboplatin, paclitaxel, docetaxel, vinorelbine, and gemcitabine. Although NSCLC remains relatively resistant to chemotherapy, the fact that second-line chemotherapy is being considered is tribute to the progress being made with first-line therapy.

One of the first data about second-line chemotherapy were given by Gridelli et al.¹² in 1992. In a phase II trial of 40 patients with advanced and recurrent NSCLC (Table 4) they¹² have shown that mitomycin/vindesine regimen is not active, but a combination chemotherapy using epirubicin and cisplatin lead to an objective response rate of 25 % and an amelioration of tumor-related symptoms in 35.7 % as well as an improvement in performance status in 25%. Georgoulis et al.¹³ showed in a 1997 phase II trial of 26 patients the significant activity of gemcitabine combined with paclitaxel as second-line treatment in platinum refractory NSCLC. In this study, a response rate of 29 % and a median survival rate of 8 months were achieved. Severe neurotoxicity (31 %) and fatigue (15 %) was the most interesting nonhematologic toxicity. A similar phase II – study, as reported by Fossella et al.¹⁴ in 1999, has shown the significant clinical activity of docetaxel (100 mg/m² every 21 days) as second line treatment in platin resistant NSCLC. Response rates were 22 % leading to a 1-year survival rate of 40 %. During last two years results of three different clinical trials about activity of gemcitabine were given by Crino et al.¹⁶, Gridelli et al.¹⁷ and Herrero et al..¹⁸

A pilot study done by Herrero et al.¹⁸ was stopped due to a high rate of side-effects combined with a minimal response rate of 6.25 %. In contrast to this pilot study, the results of the other two phase II – trials^{16,17} were combined with a much higher response rate of 19 and 20 %, leading to a median survival of 22 and 34 weeks. Recently Stathopoulos et al.¹⁵ have published data about a combination of cisplatin and paclitaxel in 80 recurrent NSCLC patients leading to an overall response rate of 16 % and a median survival time of 42 weeks showing that combination therapy should not be better than monotherapy.

In this study we have tried to overcome tumor cell resistance in recurrent NSCLC by using a high local cytostatic drug concentration. To reach this goal we used a simplified technique for isolation of the chest and lung compared with older application forms. In none of all cases ITP has to terminated early due to disturbance in blood pressure parameters. This is in accordance to published data from Berkenstadt et al.²⁰ and by Guadagni et al.²¹ who had shown that ITP does not lead to increased cardiac stress.

In 1995 Johnston et al.²² 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.²³ have shown in 1999 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.^{24,11,25}

Our own data in this study have shown a acceptable toxicity profile for these pretreated NSCLC patients who are in a reduced general condition and performance status. There were only two cases with special application form related side-effects such as lymphatic fistulas in the groin. In two other cases a deep vein thrombosis did occur. Systemic side-effects related to administration of cytostatic drugs were acceptable and not more frequent or more severe compared with other studies about second-line therapy in NSCLC.

Keeping in mind that this NSCLC patient population is selected to those having tumor formations defined to thoracic region only, response rates and survival rates are very

encouraging. Compared with other second-line treatment studies, response rate could be nearly doubled combined with a high percentage of patients in whom an amelioration of tumor related symptoms could be achieved (data not given).

Survival rate in our study was 21 months, which is nearly doubled compared with other studies and protocols. This means that it will be possible to reach higher response rates leading to a longer median survival in NSCLC, if we can increase the loco-regional drug concentration. Data in this study seem to support the hypothesis that isolated thoracic perfusion is an application form which increase local drug concentrations high enough to break through tumor cell resistance in NSCLC.

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Table 1: Patient characteristics.

Characteristics	
Total Number	18
Male	8
Female	10
Age	
- mean	54.4 years
- range	36 – 68
Performance Status	
- Karnofsky – Index	mean 84.4
	median 80
Stage	
- III	10
- IV	8
Histology	
- Adenocarcinoma	11
- Squamous	2
- Large cell	4
- Bronchoalveolar	1
Pretreatments	
- Radiation	8
- Chemotherapy	9
- Surgery	6

Table 2: Response to treatment.

Response	n.	%
Complete Response	0	-
Partial Response	8	44.4
Partial Response followed by curative surgery	2	11.1
Stable Disease	5	27.8
Progression	3	16.7

Table 3: WHO – toxicity (39 cycles).

	Grad 1	Grad 2	Grad 3	Grad 4
Vomitus	3	16	-	-
Fever	8	2	-	-
Hemoglobin	8	5	1	-
Platelets	1	-	2	-
Leucocytes	3	3	3	-
Peripheral neurotoxicity	1	-	1	-
Thrombosis	-	2	-	-
Pain	2	7	-	-

Table 4: Prospective trials about second line treatment in recurrent NSCLC.

Author	Year	No.pts.	Cytostatic drugs	Response %	Survival (weeks)
Gridelli ¹²	1992	28	cisplatin, epirubicin	25	-
Gridelli ¹²	1992	12	mitomycin, vindesine	0	-
Georgoulas ¹³	1997	26	gemcitabine, paclitaxel	29	32
Fossella ¹⁴	1999	88	docetaxel	17	39
Stathopoulos ¹⁵	1999	80	paclitaxel, cisplatin	16	42
Crino ¹⁶	1999	81	gemcitabine	19	34
Gridelli ¹⁷	1999	30	gemcitabine	20	22
Herrero ¹⁸	2000	16	gemcitabine, vinorelbine	6.25	25

Legends of figures

Figure 1: Scheme of Isolated Thoracic Perfusion (ITP).

Figure 2 a,b: CT-scan lesions of a 53-year old patient evaluated before Isolated Thoracic Perfusion.

Figure 3 a,b: Partial response two months after Isolated Thoracic Perfusion.

Figure 4: Overall survival time from start of Isolated Thoracic Perfusion.