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TREATMENT OF LUNG CANCER WITH BRONCHIAL ARTERY INFUSION OF CISPLATIN AND INTRAVENOUS SODIUM THIOSULFATE RESCUE

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Abstract

Forty-nine patients with primary lung cancer were treated with bronchial artery infusion of cisplatin and intravenous injection of an antidote, sodium thiosulfate. More than 50% reduction of tumor size (PR) was observed in 8 of 9 small cell carcinomas (SCLC) and in 16 of 40 non-small cell carcinomas (NSCLC). In NSCLC patients PR was obtained in 71% (12/17) after repeated infusions (≥200 mg cisplatin) and in 17% (4/23) after a single infusion (≤150 mg cisplatin). There was a significant linear relationship between cisplatin dose and tumor reduction in this group. No severe adverse effects were encountered.

Key words: Chemotherapy, intra-arterial; lung cancer, cisplatin, bronchial artery infusion, sodium thiosulfate rescue.

In recent years, many combination chemotherapy regimens have been studied in lung cancer. Despite good initial response after some drug combinations, follow-up studies or randomized trials have shown only minor benefit from the treatment in NSCLC (1, 6). Cisplatin is a cytotoxic agent against various types of solid tumor. Good effect of cisplatin has been reported, especially in cancers of urinary tract and gynecological region (4, 20). As a disadvantage of cisplatin has been considered its fast deactivation due to rapid combination with blood protein when injected into the blood stream (7, 8, 10, 17).

Regional infusion of cisplatin into the malignant lesion via a trans-arterial route may be one possibility for minimizing fast deactivation and increasing the anti-cancer effect.

Bronchial artery infusion (BAI) is known to achieve high concentration of the anticancer drug in lung cancer tissue. In our department BAI of mitomycin C and/or doxorubicin had been used for treatment of lung cancer. However, the results were not satisfactory concerning tumor regression and survival rates. Partial regression (PR) was only obtained in 9% and the median survival period for all cases after BAI and radiotherapy was 11 months (16). In a later series we therefore instead used BAI of cisplatin followed by intravenous (i.v.) administration of an antidote, sodium thiosulfate. Sodium thiosulfate is known to reduce toxicity and antitumor effect of cisplatin (10, 11).

Material and Methods

Forty-nine patients, 45 males and 4 females, aged 40 to 84 years (mean 66), with primary lung cancer without previous surgery or chemotherapy were treated in 1981–1985. Tumor histology was determined by bronchofiberscopic biopsy and brushing. The series included 9 small cell, 14 squamous cell, 21 adeno- and 5 large cell carcinomas.

The patients were staged according to the TNM classification of UICC (1978). Five patients were classified as stage I–II and 18 as stage III–IV among 23 NSCLC patients treated with one course of cisplatin infusion. One patient was classified as stage II and 16 as stage III–IV among 17 NSCLC patients who received repeated infusions. Among 9 patients with SCLC one was classified as stage II and 8 as stage III–IV (Table).

The BAI method. Normal saline solution (500 ml) was given intravenously and one or more arteries feeding the tumor were identified angiographically before infusion of cisplatin.

After catheterization of the target artery, a single dose of cisplatin (40–150 mg) was slowly infused into the bron-

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Table

Tumor response after cisplatin infusion. NC=no change, MR=minor remission, PR=partial remission

Tumor type	Cisplatin total dose (mg)	No. of patients	Response				Stage	
			NC	MR	PR	% of PR	I–II	III–IV
NSCLC		40	8	16	16	40		
Single infusion	40–150	23	7	12	4	17	5	18
Repeated infusions	200–300	17	1	4	12	71	1	16
SCLC								
1–2 infusions	50–200	9	0	1	8	89	1	8

chial artery at a rate of 8–15 ml/min for 10–20 min. The position of the tip of the catheter was checked fluoroscopically during the infusion.

Sodium thiosulfate (4–26 g) corresponding to about 0.2 g/mg cisplatin was given intravenously 10 min from the end of the cisplatin infusion. When the maximum single dose of cisplatin 150 mg was infused, 26 g of sodium thiosulfate was administered. Soon after the infusion of sodium thiosulfate, 1 500 ml of normal saline solution with sodium thiosulfate was injected intravenously for 6 h if more than 100 mg of cisplatin had been infused. Domperidone, hydrocortisone and metoclopramide were used as antemetics.

One to 3 infusions were given with intervals of 2 to 3 weeks. Of the 40 patients with NSCLC, 23 received a single infusion of cisplatin (40–150 mg). The remaining 17 were treated by 2–3 infusions (total dose of cisplatin 200–300 mg). The 9 patients with SCLC were treated by 1–2 courses (total dose of cisplatin 40–200 mg).

Clinical assessment. The evaluation of tumor response was judged from chest x-ray tomograms taken before and 2 weeks after BAI. Tumor size was mainly evaluated in anteroposterior tomograms and sometimes in lateral tomograms, by measuring and multiplying the two largest perpendicular diameters of the lesion. The tumor reduction was estimated according to the following formula: (tumor area before therapy−tumor area after therapy)× 100%/(tumor area before therapy). Reduction less than 25%, 25–50% and over 50% was defined as no change (NC), minor response (MR) and partial remission (PR) respectively. Response rate was defined as the percentage of partial remissions (PR).

Additional therapy. Approximately 2 weeks after the last cisplatin infusion 32 NSCLC patients received radiation treatment (telecobalt or x-rays from linear accelerator). 18 of these patients had received a single infusion and 14 repeated infusions. The total tumor dose ranged from 30 to 72 Gy (mean 56 Gy) after a single infusion and from 20 to 70 Gy (mean 50 Gy) after repeated infusions. Six patients with NSCLC who had received a single cisplatin infusion were given additional combination chemotherapy including mitomycin C, 5-fluorouracil, cytoarabine, peplomycin, cisplatin, cyclophosphamide, chromomycin A_3 and vincristine. One NSCLC patient who had received repeated cisplatin infusions was additionally treated with mitomycin C, cyclophosphamide, chromomycin A_3 and thio-TEPA.

The tumor radiation dose in the 9 cases of SCLC ranged from 32 to 59 Gy (mean 48 Gy). The additional chemotherapy in these cases varied widely concerning quality and intensity. All patients were followed for more than 6 months.

Results

Tumor reduction. The tumor response is shown in the Table. The response rate was in NSCLC 4/23 (17%) after a single infusion of cisplatin and 12/17 (71%) after repeated infusions. Of the 9 patients with SCLC, 8 showed partial remission (PR) and one minor remission (MR). A representative case is shown in Fig. 1.

The tumor reduction was not related to the administered dose (50–200 mg) of cisplatin in the SCLC group ($r=0.35$). In the NSCLC group, however, there was a significant correlation between cisplatin dose and tumor reduction ($r=0.61$, $p<0.01$) (Fig. 2).

Clinical course and survival. The median survival period for SCLC patients was 12 months, while for NSCLC patients with stage III–IV it was 10 months. The survival rates of NSCLC and SCLC patients did not differ statistically. In the NSCLC group (stage III–IV) the survival rates at 12 and 20 months were better after repeated infusions (≥200 mg cisplatin) than after a single infusion (≤150 mg cisplatin). They were 61 and 46% after repeated infusions and 24 and 9% after a single infusion respectively (KAPLAN & MEIER estimates (13)). The median survival was 9 months in the single infusion group, and 15 months in the repeated infusion group.

Complications. Nausea and vomiting were noted and the incidence appeared to be related to the administered dose of cisplatin. It occurred in 4 of 10 patients after 50 mg cisplatin, in 18 of 26 after 100 mg and in 22 of 33 after 150 mg. We used domperidone, hydrocortisone and metoclopramide as antemetics, and the symptoms disappeared within 3 days after the injection of cisplatin. There were no changes in liver function and peripheral blood count

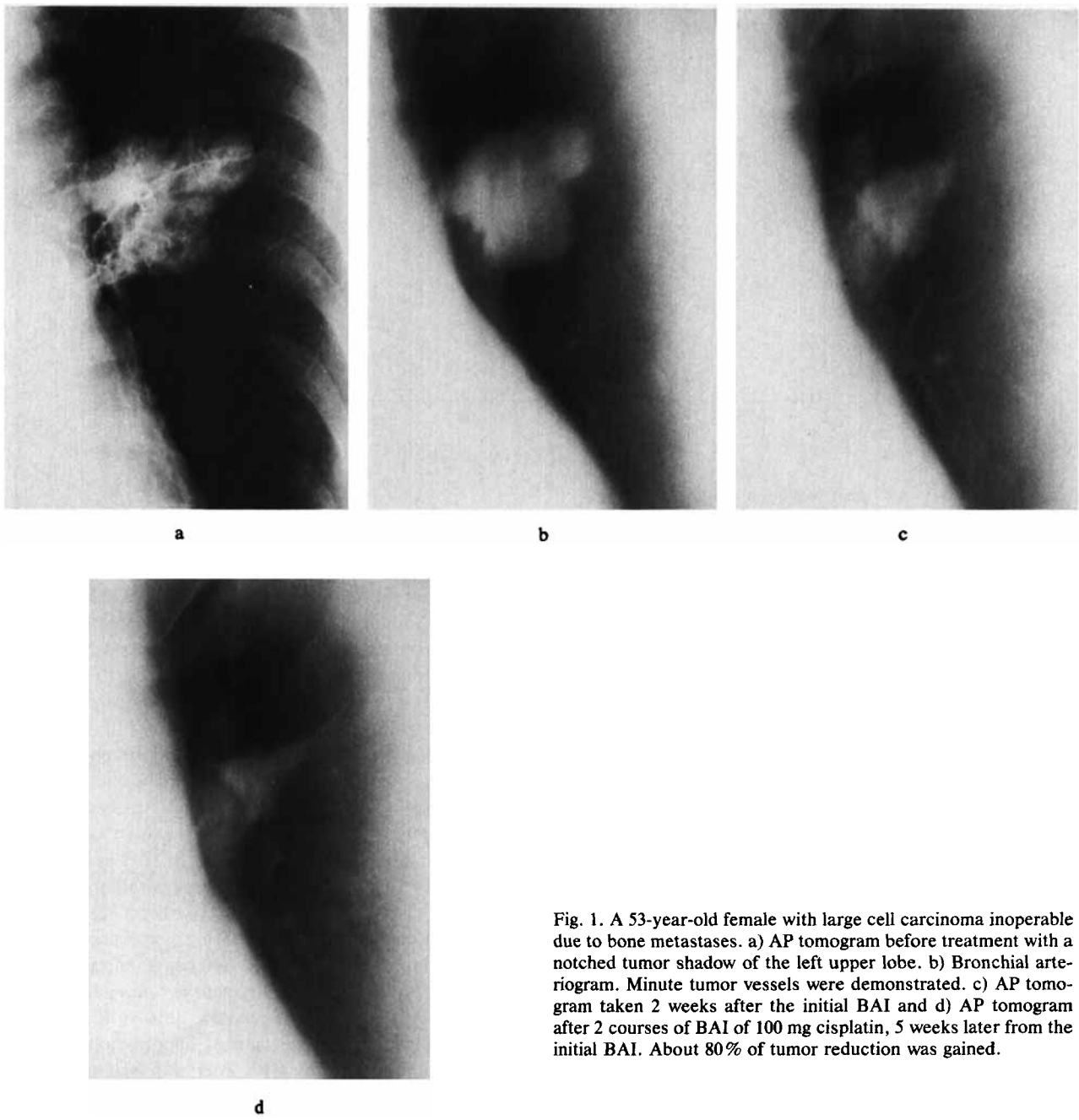

Fig. 1. A 53-year-old female with large cell carcinoma inoperable due to bone metastases. a) AP tomogram before treatment with a notched tumor shadow of the left upper lobe. b) Bronchial arteriogram. Minute tumor vessels were demonstrated. c) AP tomogram taken 2 weeks after the initial BAI and d) AP tomogram after 2 courses of BAI of 100 mg cisplatin, 5 weeks later from the initial BAI. About 80% of tumor reduction was gained.

except for one patient who had a slight elevation of serum glutamate oxaloacetate transaminase (GOT). Renal function tests showed no adverse reactions, i.e. no appreciable increase in serum creatinine and blood urea nitrogen was noted.

Discussion

Cisplatin has reduced cytotoxicity when incubated with human serum or plasma due to binding to blood protein and has therefore relatively short effective duration when injected into the blood (7, 9). The half-life of non-protein bound cisplatin is less than 30 min in vivo (8). BAI may offer a possibility to obtain high concentration of the drug in a non-protein bound form in the tumor.

Cisplatin can cause damage to kidneys, bone marrow and alimentary system (18). The dose-limiting effect of cisplatin is thought to be a damage to the renal tubular epitherium (10). In some regimens of systemic chemotherapy (2, 6, 12, 19), cisplatin had been given intravenously for two hours or more, while in our procedure cisplatin was infused intra-arterially for 10–20 min. To avoid side effects due to high blood concentrations of active cisplatin, sodium thiosulfate was given intrave-

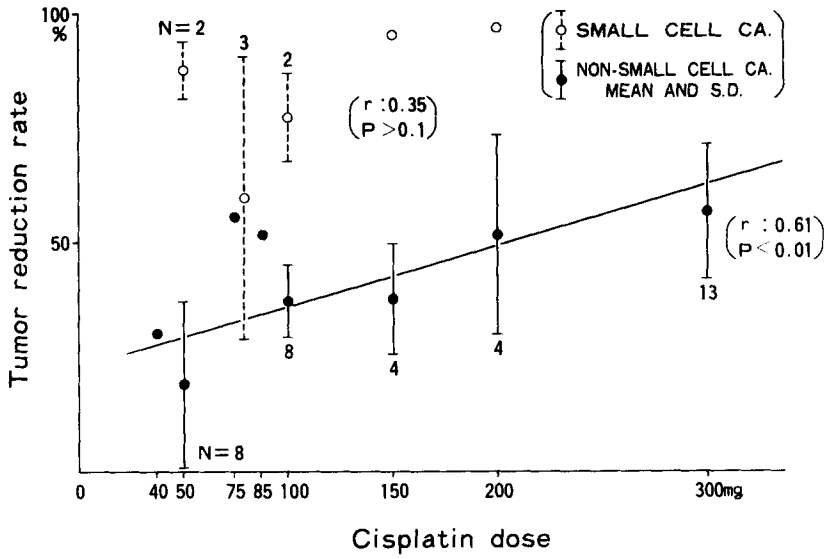

Fig. 2. Relation between tumor reduction and cisplatin dose.

nously. The effect of sodium thiosulfate on cisplatin toxicity, and its applicability in man has previously been reported (10, 11). When intra-arterial infusion of cisplatin was combined with systemic administration of sodium thiosulfate in experimental animals, excellent antitumor effect and complete protection against cisplatin toxicity was observed (18). The method has been clinically applied in the treatment of liver cancer (14).

Both branching of the bronchial artery and diameter of the arterial orifice can vary considerably (3). If sodium thiosulfate is intravenously injected prior to administration of cisplatin, blood containing sodium thiosulfate may flow into the tumor through the gap between the catheter and the walls of the vessel or by collateral circulation. Sodium thiosulfate might therefore preferably be given after completion of the cisplatin infusion. Renal protection can be achieved in mice with sodium thiosulfate injection within 1 h before or 30 min after cisplatin infusion (10).

In a previous series (21) we reported results after single BAI of cisplatin combined with intravenous sodium thiosulfate, with response rates of 24% in NSCLC and 80% in SCLC. In the present series, all NSCLC patients but one showed further reduction after a second or third cisplatin infusion (Fig. 1a). The tumor reduction was greatly influenced by the total dose of cisplatin in NSCLC patients. It is probably desirable to give as high a total dose of cisplatin as possible, in order to obtain an optimal response in these patients.

Concerning further course of the disease and survival no conclusions can be drawn from the present material due to its small size and the heterogeneity of the groups concerning tumor disease and additional treatment. The observation that the survival rate in NSCLC patients was higher after repeated infusions than after a single infusion may be of some interest but must be evaluated with great caution as the two groups were hardly comparable. As for other treatment methods of cancer the effect of cisplatin BAI on survival can only be evaluated by carefully controlled clinical trials.

Renal damage and bone marrow suppression are frequently observed during and after systemic chemotherapy using cisplatin without sodium thiosulfate. PRESTAYKO et coll. (15) reported that there were emesis in all patients, depression of white blood cell count in 27% and of platelet count in 16% after systemic administration of 60–100 mg/m^2 of cisplatin. BHUCHAR & LANZOTTI (2) observed renal dysfunction in 31% and hearing disturbances in 42% after i.v. administration of 100–140 mg/m^2 of cisplatin. In more than half of our patients, nausea and vomiting were observed but usually disappeared within 24 h. Apparent renal dysfunction or bone marrow suppression were not seen. The pretreatment with BAI of cisplatin did not prevent subsequent radiation therapy and systemic chemotherapy. Dysphagia was not observed in our series although EKHOLM et coll. (5) reported esophageal complications in 7 our of 15 patients after repeated BAI of mitomycin C.

Cisplatin BAI combined with sodium thiosulfate rescue seems to have a good potential for treatment of primary lung cancer, perhaps especially NSCLC which responds rather poorly to systemic chemotherapy. The proper combination with other treatment modalities and the tolerance level for BAI of cisplatin should, however, be explored by further clinical studies.

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