Technetium-99m Methoxyisobutylisonitrile Chest Imaging of Lung Cancer: Relation to Patient Prognosis and Chemotherapy Response

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Abstract

Objective: The purpose of this preliminary study was to evaluate retrospectively the relation between chemotherapy response and survival time using technetium-99m methoxyisobutylisonitrile (Tc-99m MIBI) uptake in lung cancer (small and nonsmall-cell carcinoma) and to detect the expression of multidrug resistance (mdr)-mediated P-glycoprotein (Pgp).

Design: Retrospective study on cases who have been diagnosed as lung cancer

Setting: The study group comprised 8 small-cell lung cancer (SCLC) and 6 nonsmall-cell lung cancer (NSCLC) (1 adenocarcinoma, 5 epidermoid carcinomas) cases. All cases were male, ages 49 to 68 years.

Interventions: Fourteen patients with lung cancer, prior to administration of chemotherapy (for SCLC cisplatin 60 mg/m^2, etoposide 120 mg/m^2 [3 days], for NSCLC cisplatin 50 mg/m^2, mitomycin 6 mg/m^2, Ifosfamide 3000 mg/m^2 or cisplatin 20 mg/m^2, vinorelbine 30 mg/m^2 [1st and 8th days]), were enrolled in this study to undergoTc-99m MIBI chest imaging, including single photon emission computed tomography (SPECT) and planar imaging and computed tomograhy (CT), applied just before and subsequent to the 3rd chemotherapy. Response to chemotherapy was assessed according to WHO's criteria; completed response (CR) and partial response (PR) were defined as good responses, nonresponse (NR) and progressive diseesa (PDR) were defined as poor responses. Tumor uptake ratio (TUR) was calculated from a formula taking into account total counts in the regions of interest (ROI) over the tumor and total counts in the contralateral normal lung tissue.

Measurements and results: Thirteen of the 14 (92%) cases (6 NSCLC and 7 SCLC) could be detected by visual interpretation of Tc-99m MIBI chest SPECT images. Four patients for each cancer group completed chemotherapy. One of 4 with SCLC (25%) and 3 of 4 with NSCLC (75%) were good responders to chemotherapy. There was a significant positive correlation between tumor uptake ratio (TUR) and survival time (r= 0.73, p=0.036). The value of Tc-99m MIBI in predicting response to chemotherapy could not be demonstrated statistically. This result was possibly due to the small number of patients in the series.

Conclusion: Tc-99m MIBI chest images have the potential to predict patient survival time and prognosis in patients with lung cancer.

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Key words: *Technetium-99m methoxyisobutylisonitrile, small-cell lung carcinoma, nonsmall-cell lung carcinoma, chemotherapy, multidrug resistance-mediated P-glycoprotein.*

Introduction

Small-cell lung cancer (SCLC) and non SCLC (NSCLC) show differences in their clinical response to chemotherapeutic agents, the former being more sensitive to anticancer agents than NSCLC. Resistance of malignant tumors to chemotherapeutic agents is a major cause of treatment failure. Drug-resistant cancers often recur, severely limiting the curative effect of chemotherapy. Therefore, the development of effective theurapeutic regimens for these resistant neoplasms is an urgent problem in cancer chemotherapy. Multidrug resistance (MDR) in tumor cells has

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Table 1. Patient characteristics

No	Diagnosis	Age	Perf.	Histology	Tumor location	Stage	Tumor size (cm)	Survival (days)
1	Lap. Ex.	63	1	SCLC	LUL	Extensive	7.5x5.5	210
2	FOB	52	1	Epidermoid Ca	RLL	$T_4N_3M_0$	7x6	385
3	Lap. Ex.	50	1	SCLC	RLL	Extensive	7x6	375
4	FOB	58	0	Epidermoid Ca	RUL	$T_4N_2M_0$	4x3.5	418
5	TT-FNAC	62	1	Epidermoid Ca	RUL	$T_4N_0M_0$	8.5x4	492
6	FOB	62	1	SCLC	LUL	Extensive	7x4.5	341
7	FOB	65	1	Epidermoid Ca	LUL	$T_4N_0M_1$	12x6	208
8	FOB	55	1	SCLC	LUL	Limited	7.5x6	242
9	Lap. Ex.	51	1	SCLC+VCSS	RLL	Extensive	7.5x5	27
10	TT-FNAC	45	1	SCLC+VCSS	RUL	Extensive	4x3	71
11	FOB	49	1	Epidermoid Ca.	RLL	T_4N_2M1	12x10	129
12	FOB	58	1	SCLC+VCSS	RUL	Limited	5x3	92
13	FOB	43	1	SCLC+VCSS	RUL	Extensive	5x5	47
14	Pleuvra Bx.	68	1	Adeno Ca.	RLL	$T_4N_0M_0$	8x8	Refused study

FOB: fiberoptic bronchoscopy; TT-FNAC: transthoracic fine needle aspiration cytology; Lap. Ex.: lymph node excision; Pleura Bx.: pleural biopsy; RUL: right upper lobe; RLL: right lower lobe; LUL: left lower lobe; SCLC+VCSS: small-cell lung cancer + vena cava superior syndrome; Perf: patient's performance scale (7).

Table 2. Chemotherapy regimens of the patients

Chemotherapy*	**Dose (mg/m²)**	**Introduced by**	**Days**
Mitomycine	6 (max. 10 mg)	IV 1h infusion	1
Ifosfamide	3000	IV 4h infusion	1
Mesna	3000	IV 4h infusion	1
Cisplatine	50	IV 4h infusion	1
Chemotherapy**	**Dose (mg/m²)**	**Introduced by**	**Days 1, 2, 3**
Cisplatine	60 (max. 100 mg)	IV 4h infusion	1
Etoposide	120 (max. 200 mg)	IV 2h infusion	1, 2, 3
Chemotherapy***	**Dose (mg/m²)**	**Introduced by**	**Days 1 to 8**
Vinorelbine	30	IV infusion	1 to 8
Cisplatine	20	IV 1h infusion	1, 2, 3

* for NSCLC
** for SCLC
*** for NSCLC

been correlated with overexpression of the MDR1 gene coding for P-glycoprotein (Pgp), a plasma-membrane protein that functions as an energy dependent transporter of cytotoxic lipophilic agents (1). Technetium-99m methoxyisobutyl-lisonitrile (Tc-99m MIBI) can be separated from cytosol against its concentration gradient as a suitable transport substrate by Pgp (2). Tc-99m MIBI has also been shown to be more effective than T1-201 chloride for evaluating the response to chemotherapy in patients with SCLC and NSCLC (3,4). Also, NSCLC cell lines (SW-1573/2R120) that do not over express Pgp have been identified (5). Therefore, different mechanisms may be responsible for resistance to multiple drugs.

In this study, we evaluated the prediction of chemotherapeutic effect in patients with SCLC and NSCLC using Tc-99m MIBI single photon emission computed tomography imaging (SPECT) and compared imaging findings in relation to patient survival time and chemotherapy response in both cancer groups. We also explored the potential use of Tc-99m MIBI chest imaging in these patients to predict patient response to chemotherapy and survival.

Materials and Methods Patients

Detailed data on patients are shown in Table 1. Fourteen male patients with SCLC (n=8, mean age 56.5±7.6 years, (range 45-68) and NSCLC (n=6, mean age 59.0±7.4 years, [range 49-68 years]) were included in the study. According to the guidelines of the American Committee on Cancer TNM staging (6), 2 of the 8 patients with SCLC were classified as limited and the others as extensive and all 6 patients with NSCLC (5 epidermoid cell carcinoma, 1 adeno cell carcinoma) were stage IV cases. According to Zubrod's performance scale (7), all patients scored between one and two. All patients were diagnosed by cytological or histopathological analysis of samples obtained by computed tomography (CT)-guided needle aspiration or by endoscopy. The smallest tumor diameter mass was 2 cm and the biggest was 12 cm as shown by CT scan. All patients underwent single photon emission computed tomography (SPECT) with Tc-99m MIBI. After imaging studies, 13 of the 14 patients (1 patient died before chemotherapy) received cisplatin based combination chemotherapy (Table 2). Each patient gave informed consent.

Tc-99m MIBI chest imaging

To prevent abnormal uptake of free Tc-99m pertechnetate, the imaging procedure was started 30 minutes after the oral intake of 500 mg perchlorate. A commercial MIBI preparation (a maximum amount of 5.56 Gb [150 mCi9] in approximately 1-3Ml) was used (Cardolite, obtained from Dupont). The labeling and quality control procedure were carried out accord-

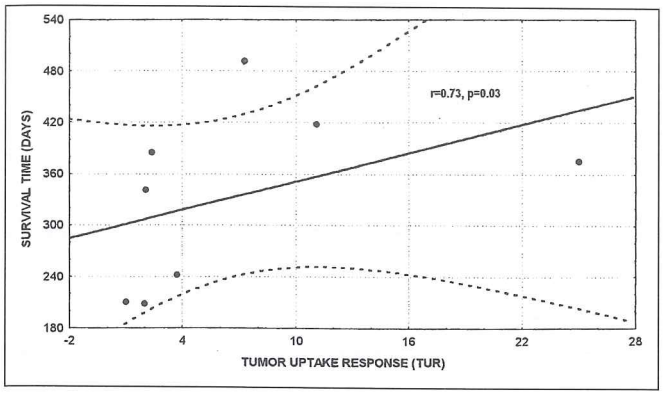

Figure 1. *The correlation between tumor uptake ratio and survival time.*

ing to the manufacturer's instructions. Labeling efficiencies were always higher than 95%. The anterior and posterior planar views, as well as 360 SPECT chest imaging, were performed 10 minutes after the intravenous injection of 740 MBq (20 mCi) Tc-99m MIBI.

The findings on the Tc-99m MIBI chest images were evaluated both qualitatively and quantitatively as follows: 1) SPECT images were interpreted by at least two specialists in the field of nuclear medicine. The images were defined as positive (focal abnormal accumulation at the tumor site) or negative (no abnormal focus of activity at the tumor site). 2) Tumor uptake ratio (TUR) was obtained on planar chest imaging. A region of interest (ROI) was carefully drawn over the tumor, then another ROI of the same size was drawn over the contralateral normal lung using a mirroring technique. The TUR was calculated by the following formula: the total count in the ROI over the tumor divided by the total counts in the same size ROI over contralateral normal lung (8). We consider a tumor with TUR ≥1.1 to be positive. If the TUR ≤1.0, it was considered negative.

Interpretation of the patient prognosis and chemotherapy response

Patient prognosis was evaluated in terms of survival time, which was defined as the period (days) from initial diagnosis to death. Response to chemotherapy was evaluated on completion of the treatment using clinical and radiological methods. Evaluation criteria were as follows: 1) complete response (CR) = no evidence of disease; 2) partial response (PR) = ≥50% decrease in the sum of the products of the maximum perpendicular diameters of all measurable lesions, with no evidence of progression of any lesion or appearance of new lesions; 3) no response (NR) = <%25 increase in the sum of the products of the maximum perpendicular diameters of all measurable lesions, with no evidence of progression of any lesion or appearance of new lesions; and 4) progressive disease (PD) = ≥25% increase in the sum of the products of the maximum perpendicular diameters of all measurable lesions and/or appearance of new lesions. In this study, CR and PR were defined as good responses and NR and PD were defined as poor responses.

Statistical analyses

Because the number of the cases was limited, we used Fisher's exact test for analysis of the positive MIBI uptake and good response to chemotherapy and negative uptake and poor response to chemotherapy in 8 cases. Correlation analysis (Spearman's Rank) was used between TUR and survival time.

Results

Detailed data on patients are shown table 3. The results showed that 92% (13 of 14) of the 14 patients (5 of 6 patients with SCLC and all 8 with NSCLC) could be detected by qualitative Tc-99m MIBI chest imaging. One patient died before chemotherapy, 4 patients died during chemotherapy, one patient refused chemotherapy and left the study after receiving two courses of chemotherapy. Response to chemotherapy could be evaluated in only 8 (4 with SCLC, 4 with NSCLC) of the 14 lung cancer patients who survived and completed their chemotherapy regimens (Table 3). Seven of these 8 cases included 4 cases with both positive SPECT and good chemotherapy response and 1 case with both negative SPECT and poor chemotherapy response. Tc-99m MIBI chest SPECT incorrectly predicted results of chemotherapy (p=0.5, Fisher's exact test). The correlation between TUR and survival time was both positive and good (correlation coefficient, r = 0.73, p=0.036) (Figure 1).

Discussion

In this study, we used Tc-99m MIBI chest imaging, including

Table 3. Patients with Tc-99m MIBI uptake

Patients	Cancer Type	Response to chemotherapy	Survival (days)	T/N■	MIBI** uptake
1	SCLC	Poor	210	0.96	-
2	SCLC	Poor	375	25	+
3	SCLC	Good	341	2.08	+
4	SCLC	Poor	242	3.75	+
5	SCLC	Ex before* Cemoth.	27	7.1	+
6	SCLC	Ex1st* Chemoth.	71	12.7	+
7	SCLC	Ex1st* Chemoth.	47	18.0	+
8	SCLC	Ex2cd* Chemoth.	92	3.0	+
9	NSCLC	Good	385	2.4	+
10	NSCLC	Good	418	11.1	+
11	NSCLC	Good	492	7.3	+
12	NSCLC	Poor	208	2.0	+
13	NSCLC	Ex 4th* Chemoth.	129	2.5	+
14	NSCLC	Incomplete* Chemoth.	80th d. refused study	6.6	+

■: T/N:tumor uptake/normal lung *. Not evaluated for chemotherapy response
**: T/N ≤1.0, MIBI uptake (-); ≥1.1 MIBI uptake (+)

SPECT and planar images, to evaluate Pgp in SCLC and NSCLC. We found a significant positive correlation between TUR and survival time (r= 0.73, p= 0.03), however we were not able to demonstrate a prediction of the response to chemotherapy by qualitative Tc-99m MIBI chest SPECT (p=0.5, Fisher's exact test) in our patients.

Response to chemotherapy is one of the most important prognostic indicators in patients with cancer. However, this is usually difficult to determine clinically or radiologically. Since 1980s an increasing number of reports have described Tc-99 MIBI uptake in several tumors, including lung tumors (9-15). Tc-99m MIBI is attached to a low molecular weight protein in the lysosomes. The cationic charge and lipophilicity of Tc-99m MIBI, the mitochondrial and plasma membrane potentials of the tumor cells, and their mitochondrial content may play important roles in the uptake of this agent by the tumor cells (16). Uptake may also be determined by indirect mechanisms such as increased tumor blood flow and capillary permeability.

Recent investigations suggest the hypothesis that Tc-99m MIBI may interact with Pgp, a cytoplasmic membrane protein encoded by the MDR1 gene, which has been shown to decrease the accumulation of cytotoxic drugs such as anthracyclines, vinca alkaloids, colchicine and actinomycin-D (2,17,18). Combinations of chemotherapy in this current study included mitomycin-ifosfamide-cisplatin or cisplatin-vinorelbine for NSCLC and cisplatin-etoposide for SCLC. Piwnica-Worms et al. (2) demonstrated the relation between Tc-99m MIBI tumor uptake and Pgp-mdr, implying the potential of Tc-99m MIBI scintigraphy as a noninvasive imaging test for Pgp-mdr assessment. We therefore used Tc-99m MIBI chest imaging, including SPECT and planar images, to evaluate Pgp in lung cancer in our study. However, one limitation of our study was the small number of the patients and we believe that for this reason we were not able to demonstrate statistically the value of this method in predicting response to chemotherapy (p=0.5 Fisher's exact test). Chia-Hung Kao et al. (19) who conducted a similar study on 15 patients with SCLC, found thatTc-99m MIBI accurately predicted the response to chemotherapy in 13 of 15 cases (%87), including 10 cases with both positive SPECT and good chemotherapy response and 3 cases with both negative response and poor chemotherapy response (p=0.022, Fisher's exact test) (19). Negative Tc-99m MIBI tumor uptake and positive Tc-99m MIBI tumor uptake are thought to be consistent with relatively high and and low expression of Pgp, respectively (20-22).

We found a significant positive correlation between survival time and TUR (r=0.73, p=0.036, Figure 1.). Similar findings have been reported after clinical Tc-99m MIBI tumor imaging in human breast carcinoma (22), metastatic renal cell carcinoma (21) and small-cell lung carcinoma (19,22). In this study we calculated TURs from planar chest images instead of SPECT images, because this method appears in publications and also because it is easy to apply clinically (8).

In conclusion, our results support previous reports and indicate that the positive Tc-99m MIBI chest SPECT findings or higher TUR have the potential to predict response to chemotherapy and patient prognosis in lung cancer.

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