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Technetium-99m Tetrofosmin Chest Imaging Related to P-Glycoprotein Expression for Predicting the Response with Paclitaxel-Based Chemotherapy for Non-Small Cell Lung Cancer

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Abstract. Our aim was to use technetium-99m tetrofosmin (Tc-TF) uptake in non-small cell lung cancer (NSCLC) for predicting the chemotherapeutic response of NSCLC to paclitaxel and to compare the results with the expression of multidrug resistance (MDR) - P-glycoprotein (Pgp). Twenty patients with advanced NSCLC were enrolled in this study before chemotherapy with paclitaxel. Tc-TF chest imaging was performed to calculate early and delayed tumor-to-normal lung (T/NL) count-density ratios, as well as washout indexes (WIs). Immunohistochemical analyses were performed on multiple nonconsecutive sections of the biopsy specimens to detect Pgp expression. The response to chemotherapy was evaluated by clinical and radiological methods in the third month after completion of treatment. The early and delayed T/NL count-density ratios of patients with good response were significantly higher than those of patients with poor response ($p < 0.05$). However, no significant difference in WI between the two groups of patients was found ($p > 0.05$). A significantly higher incidence of good response was found in patients with negative Pgp expression (100%) than in patients with positive Pgp expression (40%) ($p < 0.05$). Significantly higher early and delayed T/NL count-density ratios as well as decreased WIs were found in patients with negative Pgp expression than in patients with positive Pgp expression. However, other prognostic factors (age, sex, body weight loss, performance status, tumor stage,

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and tumor cell type) were not significantly different between the patients with good response and those with poor response. Because Tc-TF chest images can correctly represent the expression of Pgp in NSCLC, it can accurately predict the chemotherapeutic response to paclitaxel.

Key words: Technetium-99m tetrofosmin—Non-small cell lung cancer—Chemotherapy—Multidrug resistance —Mediated **P**—Glycoprotein

Introduction

There is recent evidence that chemotherapy does have a role in nonresectable NSCLC (stage IIIb or IV) [24, 25]. Recent papers have reported that the multidrug resistance - 1 (MDR1) gene encoding human multidrug resistance-mediated p-glycoprotein (MDR-Pgp) may play an important role in the multidrug resistance of lung cancer [9]. The ideal therapeutic goal in advanced NSCLC is to achieve the highest response with the lowest possible morbidity from the side effects of chemotherapy. Therefore, it has been suggested that the determination of MDR-Pgp at the time of diagnosis may provide valuable information for the design of treatment protocols [4, 27].

A review of the literature indicates that Pgp recognizes certain chemotherapeutic agents as substrates and prevents the accumulation of some lipophilic cationic radiopharmaceuticals such as technetium-99m tetrofosmin (Tc-TF). Some investigators have found negative and positive Tc-TF tumor uptake to be consistent with relatively high and low expressions of MDR-Pgp, respectively [1, 6, 10, 26]. In addition, recent attempts using Tc-TF to detect lung cancer have been successful [2, 3, 16]. In our previous study, we depended on this theory to successfully predict the chemotherapeutic response to cisplatin and etoposide in small cell lung cancer in humans [17].

However, in the published literature, there was only our previous study of using Tc-TF chest images to successfully predict the chemotherapeutic response to paclitaxel (Taxol; Bristol-Myers Squibb) in NSCLC patients [18]. The aim of this study was to compare Tc-TF chest imaging findings, chemotherapy response to Taxol, and the expression of MDR-Pgp detected by immunohistochemical staining.

Materials and Methods

Patients

Twenty patients (aged 43–70 years) with advanced NSCLC (stage III or IV), including eight epidermoid carcinomas and 12 adenocarcinomas, who were to undergo therapeutic chemotherapy as follows were enrolled in this study. None of the 20 patients received surgery and combination radiotherapy during the study. Informed consent was obtained from all patients. Taxol 135 mg/m^2 was given as a 3-h infusion on day 1 and cisplatin 75 mg/m^2 on day 2. The regimen was repeated every 3 to 4 weeks for up to 6 to 8 cycles unless there was evidence of tumor progression [18, 19]. The patients were required to have a complete history and physical examination. Patient enrollment criteria included no prior chemotherapy,

radiotherapy, or surgery; an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; adequate hematological (granulocyte count $\geq 1500/\mu l$, platelet count $> 100000/\mu l$), hepatic (bilirubin $\leq 1.25 \times$ the upper normal limit), and renal (serum creatinine $\leq 1.25 \times$ the upper normal limit) function; and adequate cardiac function, with no active arrhythmia or congestive heart failure. All patients were premedicated with dexamethasone (20 mg), cimetidine (300 mg), and diphenhydramine (50 mg) prior to initiation of the Taxol infusion [18, 19]. Taxol was well tolerated and none of the patients experienced an allergic reaction. Granulocytopenia was generally mild.

Evaluation of Chemotherapy Response

The response to chemotherapy was evaluated in the third month after completion of treatment. The response of NSCLC to chemotherapy was evaluated by clinical and radiological methods, and the evaluation criteria were [23]: (1) complete response = no evidence of disease; (2) partial response = $\geq$ 50% decrease in the sum of the products of the maximum perpendicular diameters of all measurable lesions, no evidence of progression in any lesion, and no new lesions; (3) no response = $<$25% increase in the sum of the products of the maximum perpendicular diameters of all measurable lesions, no evidence of progression in any lesion, and no new lesions; and (4) progressive disease = =25% increase in the sum of the products of the maximum perpendicular diameters of all measurable lesions and/or the appearance of new lesions. Because there were no complete responses in our patients, we just defined partial response as good response, and no response and progressive disease were defined as poor responses in our study.

Tc-99m TF Chest Imaging

Before chemotherapy, early and delayed Tc-99m TF chest imaging was performed on all patients. A commercial tetrofosmin preparation was obtained from Amersham International pic (Myoview). The labeling and quality control procedures were carried out according to the manufacturer's instructions. The radiochemical purity of Tc-TF used in the present study was consistently higher than 90%. The chest images were performed 10 min and 2 h after intravenous injection of 740 MBq (20 mCi) of Tc-TF. Each patient was positioned in a supine position on the imaging table with his or her chest strapped to prevent motion. The equipment consisted of a rotating, large field-of-view dual-head gamma camera (Helix HR; Elscint, Haifa, Israel) fitted with a low-energy, high-resolution collimator (LEGP, HPC 46; Elscint, Haifa, Israel). A single 20% energy window was set at 140 keV. Then, the anterior and posterior views of the chest were obtained simultaneously [15, 17, 18]. The findings from the Tc-TF chest images were evaluated quantitatively as follows. (1) The tumor-to-normal lung (T/NL) count-density ratio was obtained on early and delayed chest images. Based on chest x-ray findings, two regions of interest (ROIs) of the same size were carefully drawn over the tumor on the anterior and posterior views, respectively. Then, another two ROIs of the same size were drawn over the contralateral normal lung on both the anterior and posterior views using a mirroring technique. The T/NL count-density ratios were calculated by the following formula with geometric mean counts of the anterior and posterior counts: [(the mean counts in the ROI over the tumor in the anterior view)$^{1/2}$ $\times$ (the mean counts in the ROI over the tumor in the posterior view)$^{1/2}$] $\div$ [(the mean counts in the ROI over the contralateral normal lung in the anterior view)$^{1/2}$ $\times$ (the mean counts in the ROI over the contralateral normal lung in the posterior view)$^{1/2}$]. (2) The washout index (WI) was calculated by the following formula: [(delayed T/NL $-$ early T/NL) $\times$ 100] $\div$ early T/NL [15, 17, 18].

Analyses of Immunohistochemistry

Formalin-fixed paraffin sections (5 μm) from the biopsy specimens of the NSCLC were deparaffinized in an oven at 50°C for 40 min and hydrated with different concentrations of ethanol-water dilutions. Endogenous peroxidase was blocked by 3% hydrogen peroxide for 15 min. Antigen retrieval was performed by treatment with enzyme digestion in 0.1% trypsin in PBS for 5 min at room temperature

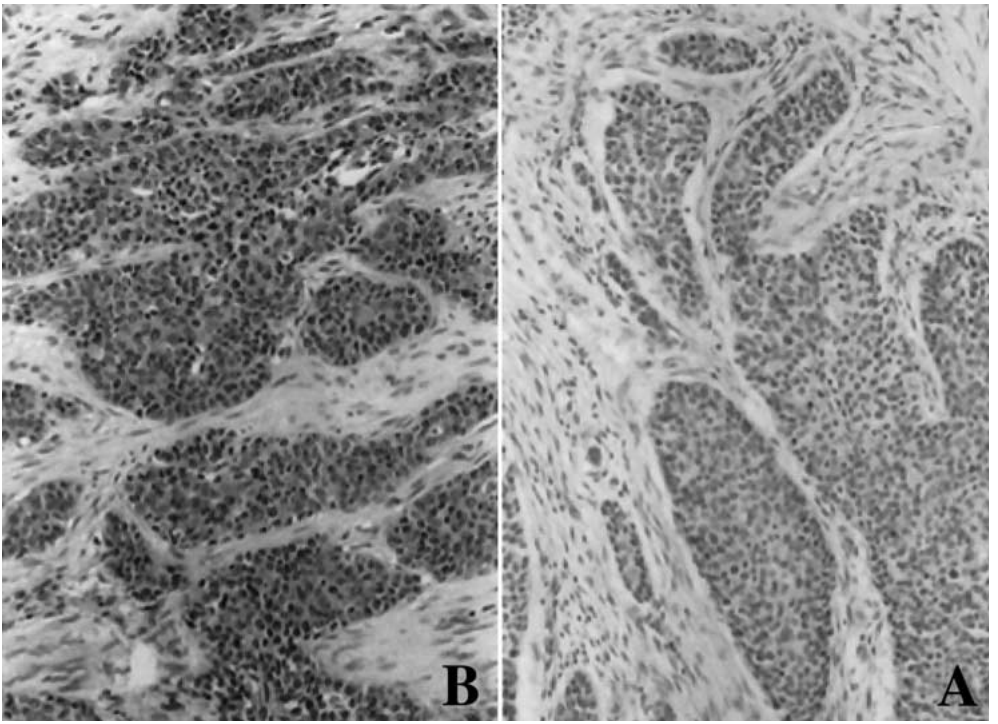

Fig. 1. Immunohistochemistry performed on sections of the whole epidermoid carcinoma specimens from two different groups reveals (A) negative and (B) positive Pgp expression NSCLC.

and inhibited with 10% skim milk in PBS for 5 min. The sections were incubated for 2 h in a moist chamber at 37°C with primary antibody JSB-1 (50 μg/ml, Boehringer Mannheim Biochemica, Germany) at a 1:50 concentration. After three 5-min washes in PBS buffer, detection of the primary antibody was performed with a link antibody according to the manufacturer's instructions (DAKO LSAB® 2 System, Peroxidase, Dako Corporation, Carpinteria, CA, USA) [20,21]. All specimen evaluations were performed on a Nikon microscope (AFX-DX) using an ocular magnification of ×20 with an eyepiece grid. Positive ceils were quantified by evaluating four randomly selected high-power fields (minimum 800 tumor cells). Pgp expression was interpreted by an experienced pathologist blinded to the clinical outcome, as follows: negative = less than 10% and positive = equal to or more than 10% stained tumor cells (Fig. 1).

Statistical Analyses

The values of early T/NL count-density ratio, delayed T/NL count-density ratio, and WI were expressed as the mean ± standard deviation (SD). To test for differences in early T/NL count-density ratio, delayed T/NL count-density ratio, and WI between patients with good vs poor response, between patients with positive vs negative Pgp expression, female vs male patients, old (60) vs young (< 60 years old) patients, patients with severe (> 5%) vs mild (≤5%) body weight loss, patients with good (0 or 1) vs poor (2) ECOG performance status, stage IIIb vs IV patients, and patients with epidermoid carcinomas vs adenocarcinomas, independent Student's t-tests were used. If the p value was < 0.05, the difference was considered significant. In addition, the differences in incidences of good and poor responses between patients with positive vs negative Pgp expression, female vs male patients, old vs young patients, patients with severe vs mild weight loss, patients with good vs poor performance

status, stage IIIb vs IV patients, and patients with epidermoid carcinomas vs adenocarcinomas were assessed by chi-square tests. If the p value was <0.05, the difference was considered significant.

Results

The detailed data of patients are shown in the Table 1. There was no significant difference in the tumor size between the good and poor response groups (by an independent Student's t-test, p value $= 0.555$). The early T/NL count-density ratio, delayed T/NL count-density ratio, and WI of the Tc-TF chest images of the patients with good response were 1.59 ± 0.25, 1.39 ± 0.21, and $-12.34 \pm 5.73\%$, respectively; those values for the patients with poor response were 1.17 ± 0.18, 1.05 ± 0.07, and $-9.13 \pm 8.98\%$, respectively. The differences in both early and delayed T/NL count-density ratios of the patients with good response vs those with poor response were significant (p values < 0.001). However, the difference in WI between the two groups of patients was not significant (p value $= 0.353$). If the delayed T/NL ratios ≥ 1.2 and 1.3, respectively, were the cut-off values of the positive Tc-TF chest imaging results, their sensitivity was 90% and 70%, specificity was 90% and 100%, accuracy was 90% and 85%, positive predictive value was 90% and 100%, and negative predictive value was 90% and 77%, respectively, to predict paclitaxel-based chemotherapy response.

The early T/NL count-density ratio, delayed T/NL count-density ratio, and WI of the Tc-TF chest images of the patients with positive Pgp expression were 1.05 ± 0.08, 1.02 ± 0.04, and $-2.90 \pm 4.50\%$, respectively; those values for the patients with negative Pgp expression were 1.52 ± 0.24, 1.31 ± 0.23, and $-14.09 \pm 5.86\%$, respectively. All values for early T/NL count-density ratio, delayed T/NL count-density ratio, and WI of the patients with positive vs negative Pgp expression were significant (p values < 0.01) (Table 2). In addition, a significantly higher incidence of good response was found in patients with negative Pgp expression (10/10, 100%) than in patients with positive Pgp expression (4/10, 40%) ($p = 0.005$) (Table 3).

No significant differences in early T/NL count-density ratio, delayed T/NL count-density ratio, or WI were found (p values > 0.05) between female vs male patients, old vs young patients, patients with severe vs mild body weight loss, patients with good vs poor performance status, stage IIIb vs IV patients, or patients with epidermoid carcinomas vs adenocarcinomas (Table 2). In addition, there were no significantly different incidences of good and poor response between female vs male patients, old vs young patients, patients with severe vs mild weight loss, patients with good vs poor performance status, stage IIIb vs IV 0.05) (Table 3).

Discussion

Taxol, that promotes polymerization of cellular microtubules and prevents mitosis, is the first taxane for treating stage IV NSCLC patients and has the highest response rates (>20%) during the past 10 years using similar study populations

Table 1. Detailed data of patients in this study

Case no	Sex	Age (years)	Body weight loss	ECOG performance status	Tumor			Tc-TF chest images			Pgp expression	Chemotherapeutic response
					Stage	Cell types	Size (cm)	Early T/NL ratio	Delayed T/NL ratio	WI%		
1	F	46	Mild	Good	IV	Epidermoid Ca	8 × 6	1.6	1.4	−12.50	Negative	Good
2	M	47	Severe	Good	IIIb	AdenoCa	5 × 6	1.8	1.5	−16.70	Negative	Good
3	M	52	Mild	Good	IV	AdenoCa	4 × 2	1.4	1.3	−7.10	Negative	Good
4	F	57	Mild	Good	IIIb	Epidermoid Ca	6 × 4.5	1.9	1.5	−21.10	Negative	Good
5	M	59	Mild	Good	IV	Epidermoid Ca	5 × 4.5	1.3	1.2	−7.70	Negative	Good
6	F	60	Severe	Poor	IIIb	Epidermoid Ca	5 × 4	1.3	1.2	−7.70	Negative	Good
7	F	62	Mild	Poor	IV	AdenoCa	5 × 3	1.5	1.3	−13.30	Negative	Good
8	M	63	Mild	Good	IV	AdenoCa	5 × 6	2	1.8	−10.00	Negative	Good
9	M	66	Mild	Good	IIIb	AdenoCa	8 × 6	1.7	1.6	−5.90	Negative	Good
10	M	67	Mild	Good	IV	AdenoCa	4 × 4	1.4	1.1	−21.40	Negative	Good
11	F	43	Mild	Poor	IV	AdenoCa	2.5 × 4	1	1	0.00	Positive	Poor
12	M	45	Mild	Good	IV	Epidermoid Ca	3 × 5	1.2	1.1	−8.30	Positive	Poor
13	F	48	Severe	Poor	IV	AdenoCa	5 × 4.5	1	1	0.00	Positive	Poor
14	F	54	Mild	Good	IV	Epidermoid Ca	3 × 3	1.3	1.1	−15.40	Negative	Poor
15	M	58	Severe	Poor	IV	AdenoCa	7 × 5	1.1	1	−9.10	Positive	Poor
16	M	61	Mild	Good	IV	AdenoCa	9 × 7	1.3	1	−23.10	Negative	Poor
17	M	65	Severe	Good	IV	AdenoCa	3.5 × 3	1.5	1.2	−20.00	Negative	Poor
18	M	65	Mild	Good	IV	AdenoCa	3.5 × 3	1	1	0.00	Positive	Poor
19	M	69	Mild	Good	IIIb	Epidermoid Ca	3 × 3	1	1	0.00	Positive	Poor
20	M	70	Mild	Good	IIIb	Epidermoid	6 × 6	1.3	1.1	−15.40	Negative	Poor

F, female; M, male; ECOG, Eastern Cooperative Oncology Group; Ca, carcinoma; Tc-TF, technetium-99m Tetrofosmin; T/NL, tumor-to-normal lung; WI, washout index; Pgp, P-glycoprotein

Table 2. Data and differences of early T/NL count-density ratio, delayed T/NL count-density ratio, and WI between different patient groups

Tc-TF Chest Images	Chemotherapeutic response			Pgp expression		
	Good	Poor	*p* value	Positive	Negative	*p* value
Early T/NL	1.59 ± 0.25	1.17 ± 0.18	<0.001	1.05 ± 0.08	1.52 ± 0.24	<0.001
Delayed T/NL	1.39 ± 0.21	1.05 ± 0.07	<0.001	1.02 ± 0.04	1.31 ± 0.23	<0.01
WI	−12.34 ± 5.73%	−9.13 ± 8.98%	0.353	−2.90 ± 4.50%	−14.09 ± 5.86%	<0.001

	Sex			Age		
	Female	Male	*p* value	Old	Young	*p* value
	1.37 ± 0.33	1.38 ± 0.30	0.929	1.40 ± 0.30	1.36 ± 0.32	0.776
	1.21 ± 0.20	1.22 ± 0.26	0.938	1.23 ± 0.27	1.21 ± 0.20	0.854
	−10.00 ± 7.90%	−11.13 ± 7.60%	0.758	−11.68 ± 8.40%	−9.79 ± 6.84%	0.588

	Body Weight loss			ECOG performance status		
	Severe	Mild	*p* value	Good	Poor	*p* value
	1.34 ± 0.32	1.39 ± 0.31	0.742	1.45 ± 0.30	1.18 ± 0.21	0.087
	1.18 ± 0.20	1.23 ± 0.25	0.670	1.26 ± 0.25	1.10 ± 0.14	0.191
	−10.70 ± 7.88%	−10.75 ± 7.68%	0.991	−12.31 ± 7.50%	−6.02 ± 5.87%	0.107

Tumor						
	Stage			Cell type		
	IIIb	IV	*p* value	Epidermoid Ca	Adenocarcinoma	*p* value
	1.50 ± 10.35	1.33 ± 10.28	0.255	1.39 ± 0.33	1.36 ± 0.27	0.839
	1.32 ± 0.25	1.18 ± 0.22	0.234	1.23 ± 0.27	1.20 ± 0.17	0.763
	−11.13 ± 7.90%	−10.56 ± 7.65%	0.882	−10.55 ± 8.42%	−11.01 ± 6.47%	0.897

Table 3. Distribution and differences in incidences of good and poor response between different patient groups

Chemotherapeutic response	Pgp expression			Sex			Age		
	Positive	Negative	*p* value	Female	Male	*p* value	Old	Young	*p* value
Good	0	10		4	6		5	5	
Poor	6	4	0.005	3	7	0.675	5	5	1.000

						Tumor					
Body weight loss			ECOG Performance status			Stage			Cell type		
Severe	Mild	*p* value	Good	Poor	*p* value	IIIb	IV	*p* value	Epidermoid Ca	Adenocarcinoma	*p* value
2	8		2	8		4	6		4	6	
3	7	0.652	3	7	0.6517	2	8	0.385	4	6	1.000

[24, 25]. However, many toxic reactions and drug resistance were encountered during chemotherapy with Taxol in lung cancers [7] and its use resulted in an unnecessary waste of the medical insurance budget. The mechanism of chemotherapy resistance to Taxol involves the expression of cell membrane energy-dependent Pgp efflux pump which has a major role in transporting chemotherapy drugs through the cell membrane to reduce the accumulation of Taxol [11, 12]. Therefore, before initiating chemotherapy with Taxol it is important to correctly understand the expression of Pgp in NSCLC, to achieve a satisfactory response to chemotherapy, to decrease unnecessary insurance cost, and to avoid lethal side effects.

In reviewing the literature we noted that Tc-TF chest images used for detecting lung cancer have shown large variations in sensitivity, specificity, and accuracy [2, 3, 16]. In addition, our previous study of using Tc-TF chest images successfully predicted the chemotherapeutic response to paclitaxel (Taxol; Bristol-Myers Squibb) in NSCLC patients [18]. The uptake of Tc-TF in cancer cells depends on the activity of the 170 kDa Pgp coded on the MDR1 gene, which functions as an ATP-dependent efflux pump for many chemotherapy drugs, therefore., one possible explanation for these variations may be differences in case selection criteria among these studies with varying Pgp expression [1, 6, 10, 26]. In our study, lower early or delayed T/NL count-density ratios on Tc-TF chest images indicated a poor response to Taxol, whereas patients with higher early or delayed T/NL count-density ratios had good chemotherapeutic responses to Taxol. Lower and higher T/NL count-density ratios have also been found to be consistent with negative and positive Pgp expressions by immunohistochemical staining (Table 2). However, other mechanisms such as multidrug resistance related protein (MRP), topoisomerase, glutathione, and lung resistant related protein may also be related to chemotherapy resistance [13,14,22]. It has recently been reported that Tc-TF can be a substrate not only for Pgp but also MRP which functions as ATP-dependent efflux pumps, and thus be extruded like chemotherapy drugs from cancer cells [10]. Therefore, negative Pgp expression could not accurately predict the response to chemotherapy in 4 of 10 NSCLC cases (40%) with poor response (Table 3). Some researchers were able to predict cisplatin resistance of lung cancers using Tc-TF imaging [8, 17]. Previous studies reported Pgp or MRP expression in cisplatin resistant cancers [5, 28]. Therefore, Tc-TF chest imaging could predict the response of combination chemotherapy with Taxol and cisplatin in our study.

Our results can explain why Tc-TF chest images could successfully predict the chemotherapeutic response to Taxol because Tc-TF chest images can well correlate with Pgp expression detected by immunohistochemical staining. We emphasize that Tc-TF chest images more accurately predict the chemotherapeutic response of Taxol than other factors such as sex, age, body weight loss, performance status, tumor stage, and tumor cell type. However, further study, including a larger number of cases is necessary to confirm our findings.

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