Paclitaxel-Based Chemotherapy for Non–Small Cell Lung Cancer: Predicting the Response with ^{99m}Tc-Tetrofosmin Chest Imaging

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The purpose of this study was to retrospectively predict the chemotherapeutic response to paclitaxel for non–small cell lung cancer (NSCLC) using ^{99m}Tc-tetrofosmin (TF) uptake and to detect the expression of 170-kDa multidrug resistance–mediated P-glycoprotein (MDR-Pgp). **Methods:** Before chemotherapy with paclitaxel, 20 patients with stage IIIb or IV NSCLC were enrolled in this study to undergo early and delayed ^{99m}Tc-TF chest imaging for calculating tumor-to-normal lung ratios (T/NL) and retention indices (RI) for assessment of the MDR-Pgp in NSCLC. **Results:** The early and delayed mean T/NLs were 1.59 ± 0.25 and 1.50 ± 0.25, respectively, for 10 patients with a good response and 1.09 ± 0.09 and 1.03 ± 0.05, respectively, for 10 patients with a poor response. The differences were shown to be significant ($P < 0.001$) by independent Student t tests. However, no significant differences ($P = 0.801$) between good-response patients (−5.70% ± 3.67%) and poor-response patients (−5.23% ± 4.51%) were found in RI. In addition, other prognostic factors (age, sex, tumor size, stage, and cell type) were not significantly different between good-response patients and poor-response patients. **Conclusion:** ^{99m}Tc-TF chest images are potential tools for understanding MDR-Pgp expression in NSCLC and for predicting the chemotherapeutic response to paclitaxel.

Key Words: ^{99m}Tc-tetrofosmin; non–small cell lung cancer; chemotherapy; multidrug resistance–mediated P-glycoprotein

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The majority of patients with non–small cell lung cancer (NSCLC) present with disease that is beyond the scope of surgical cure. Despite having few or no symptoms, 60%–70% of newly diagnosed patients have locally advanced, inoperable, or distant metastatic disease. Recently, evidence has been put forward that chemotherapy does have a role in unresectable NSCLC (stage IIIb or IV) (1,2).

Recent articles 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 (3,4). 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, some investigators have suggested that determinations of MDR-Pgp at the time of diagnosis may provide valuable information for the design of treatment protocols (5–7). A review of the literature indicates that P-glycoprotein recognizes certain chemotherapeutic agents as substrates and prevents the accumulation of some lipophilic cationic radiopharmaceuticals such as ^{99m}Tc-tetrofosmin (TF). Some investigators have found negative and positive ^{99m}Tc-TF tumor uptake to be consistent with relatively high and low expressions, respectively, of MDR-Pgp (8–12). In addition, recent attempts using ^{99m}Tc-TF to detect lung cancer have been successful (13–19).

In a previous study, we depended on this theory to successfully predict the chemotherapeutic response to cisplatin and etoposide in small cell lung cancer in humans (20). However, to our knowledge, no study using ^{99m}Tc-TF chest images to predict the chemotherapeutic response to paclitaxel (Taxol; Bristol-Myers Squibb Co., Princeton, NJ) in NSCLC patients has been reported in the literature. Therefore, the aim of this study was to explore the potential role of ^{99m}Tc-TF chest imaging in predicting the NSCLC patient response to chemotherapy with paclitaxel.

MATERIALS AND METHODS

Patients

Twenty patients (13 men, 7 women; age range, 43–70 y) with advanced NSCLC (stage IIIb or IV), including eight cases of squamous cell carcinoma and 12 of adenocarcinoma, who were to undergo chemotherapy for bronchogenic carcinoma were enrolled in this study. The dose of paclitaxel was 135 mg/m² as a 3-h infusion on day 1, and 75 mg/m² cisplatin was given on day 2. The regimen was repeated every 3–4 wk for up to six to eight cycles unless tumor progression was evident (21). The patients were required to provide a complete history and undergo physical ex-

TABLE 1
Patient Data

Patient no.	Sex	Age (y)	Tumor size (cm)	Stage	Cell types	99mTc-TF chest images			Chemotherapeutic response
						Early T/NL	Delayed T/NL	RI (%)	
1	F	46	8 × 6	IV	SCC	1.60	1.40	−12.50	Good
2	M	47	5 × 6	IIIb	Adenocarcinoma	1.80	1.70	−5.56	Good
3	M	52	4 × 2	IV	Adenocarcinoma	1.40	1.30	−7.14	Good
4	F	57	6 × 4.5	IIIb	SCC	1.90	1.80	−5.26	Good
5	M	59	5 × 4.5	IV	SCC	1.30	1.30	0.00	Good
6	F	60	5 × 4	IIIb	SCC	1.30	1.20	−7.69	Good
7	F	62	5 × 3	IV	Adenocarcinoma	1.50	1.40	−6.67	Good
8	M	63	5 × 6	IV	Adenocarcinoma	2.00	1.90	−5.00	Good
9	M	66	8 × 6	IIIb	Adenocarcinoma	1.70	1.70	0.00	Good
10	M	67	4 × 4	IV	Adenocarcinoma	1.40	1.30	−7.14	Good
11	F	43	2.5 × 4	IV	Adenocarcinoma	1.00	1.00	0.00	Poor
12	M	45	3 × 5	IV	SCC	1.20	1.10	−8.33	Poor
13	F	48	4.5 × 5	IV	Adenocarcinoma	1.00	1.00	0.00	Poor
14	F	54	3 × 3	IV	SCC	1.20	1.10	−8.33	Poor
15	M	58	7 × 5	IV	Adenocarcinoma	1.10	1.00	−9.09	Poor
16	M	61	9 × 7	IV	Adenocarcinoma	1.10	1.00	−9.09	Poor
17	M	65	3.5 × 3	IV	Adenocarcinoma	1.20	1.10	−8.33	Poor
18	M	65	3.5 × 3	IV	Adenocarcinoma	1.00	1.00	0.00	Poor
19	M	69	3 × 3	IIIb	SCC	1.00	1.00	0.00	Poor
20	M	70	6 × 6	IIIb	SCC	1.10	1.00	−9.09	Poor

SCC = squamous cell carcinoma.

amination. Patient enrollment criteria included no prior chemotherapy, radiotherapy, or surgery; an Eastern Cooperative Oncology Group performance status of 0–2; adequate hematologic (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) functions; 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) before initiation of the paclitaxel infusion (21,22). Paclitaxel was well tolerated, and none of the patients experienced an allergic reaction. Granulocytopenia was generally mild. Before chemotherapy, early and delayed 99mTc-TF chest imaging was performed on all patients to evaluate MDR-Pgp.

Interpretation of Chemotherapy Response

The response of NSCLC to chemotherapy was evaluated clinically and radiologically within 4 wk after the last treatment (23). In our study, modified evaluation criteria were used (19). A good response was a 50% or greater decrease in the sum of the products of the maximum perpendicular diameters of all measurable lesions and no new lesions. A poor response was less than a 50% decrease in the sum of the products of the maximum perpendicular diameters of all measurable lesions or the appearance of new lesions.

99mTc-TF Chest Imaging

A commercial 99mTc-TF preparation was obtained (Myoview; Amersham International plc, Buckinghamshire, UK). The labeling and quality control procedures were performed according to the manufacturer's instructions. The radiochemical purity of 99mTc-TF used in this study was consistently higher than 90%. The chest images were obtained 10 min and 2 h after intravenous injection of 740 MBq (20

mCi) 99mTc-TF. Each patient was positioned supine on the imaging table with the 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 general-purpose collimator (HPC 46; Elscint). A single 20% energy window was set at 140 keV. Then, the anterior and posterior views of the chest were obtained simultaneously.

The findings from 99mTc-TF chest images were evaluated quantitatively as follows. (1) The tumor-to-normal lung (T/NL) ratio was obtained on early and delayed chest images. Based on chest radiography findings, two regions of interest (ROIs) with the same size were carefully drawn over the tumor on the anterior and posterior views. Then, another two ROIs of the same size were drawn over the contralateral normal lungs on both the anterior and posterior views using a mirroring technique. The T/NLs were calculated using 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)$^{1/2}$ × (the mean counts in the ROI over the tumor in the posterior view)$^{1/2}$]/[(the mean counts in the ROI over the contralateral normal lung in the anterior view)$^{1/2}$ × (the mean counts in the ROI over the contralateral normal lung in the posterior view)$^{1/2}$] (2) The retention index (RI) was calculated by the following formula: [(delayed T/NL − early T/NL) × 100]/early T/NL (20). The values of T/NL and RI were expressed as the mean ± SD. To test for differences between these parameters, an independent Student t test was used.

RESULTS

Detailed patient data are shown in Table 1. The mean early and delayed T/NLs of the 99mTc-TF chest images of patients
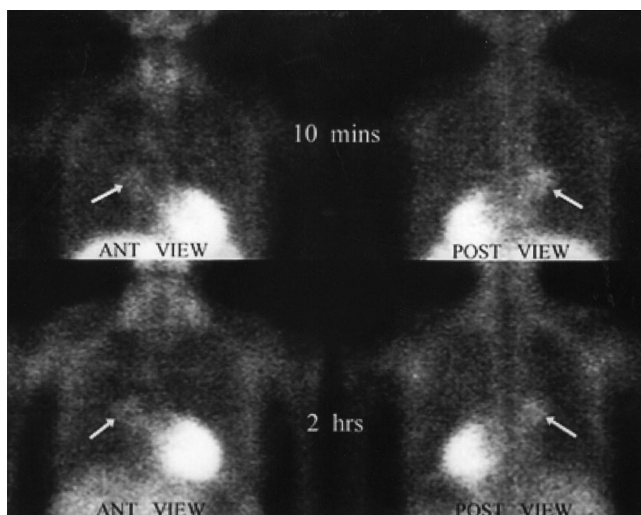
FIGURE 1. In patient 1, who had good response to paclitaxel, both early and delayed anterior and posterior ^{99m}Tc-TF chest images show significant ^{99m}Tc-TF uptake by lung cancer (arrows).

with a good response were 1.59 ± 0.25 and 1.50 ± 0.25, respectively, and those of patients with a poor response were 1.09 ± 0.09 and 1.03 ± 0.05, respectively. Both early and delayed T/NLs in good-response patients (Fig. 1) were significantly higher than those in poor-response patients (Fig. 2) ($P < 0.001$). The RI of ^{99m}Tc-TF chest images in patients with a good response was −5.70% ± 3.67%, and that in patients with a poor response was −5.23% ± 4.51%. However, the difference in RI was not significant ($P = 0.801$).

We compared the differences between other prognostic factors, including sex, age, tumor size, stage, and cell type, in the good-response and poor-response patients. No significant differences were found ($P > 0.05$ for each factor).

DISCUSSION

The taxanes are an important new class of anticancer agents that promote polymerization of cellular microtubules, preventing mitosis and resulting in cell death. Investigators from the Eastern Cooperative Oncology Group and M.D. Anderson Cancer Center, Houston, TX, administered paclitaxel, the first taxane for treating NSCLC (1,2), to previously untreated patients with stage IV NSCLC. Both groups observed objective response rates of more than 20%. These represent the highest response rates against NSCLC achieved in any drug discovery phase II trial conducted by the Eastern Cooperative Oncology Group during the past 10 y using similar study populations (1,22). However, many toxic reactions, such as leukopenia, hypersensitivity reactions, neurotoxicity, mucositis, alopecia, diarrhea, myalgias, and cardiac toxicity, were encountered during the clinical trials of paclitaxel (24,25). The mechanism of acquired resistance to paclitaxel is conferred by a multidrug-resistant phenotype that involves amplification of membrane P-glycoprotein and reduced ability to accumulate and retain pac-

litaxel because of the energy-dependent P-glycoprotein efflux pump, which has a central role in the transport of chemotherapy drugs through the cell membrane (26–28). Therefore, to achieve a satisfactory response, one must understand the presence of MDR-Pgp in NSCLC before initiating chemotherapy with paclitaxel.

In reports in the literature, ^{99m}Tc-TF chest images used for detecting lung cancer have shown large variations in sensitivity, specificity, and accuracy. Some studies dealing with ^{99m}Tc-TF chest images for the detection of lung cancer have been published (13–18). In these studies, the sensitivity has ranged from 77% to 90%. The discrepancies between the results of our recent study, which had a diagnostic sensitivity of 61% (19), and the results of these publications (13–18) are difficult to explain. One possible explanation may be differences in case selection criteria with varying MDR-Pgp expression (8–12). The retention of ^{99m}Tc-TF in cancer cells depends on the activity of the 170-kDa P-glycoprotein coded on the MDR1 gene, which functions as an adenosine triphosphate–dependent efflux pump for many chemotherapy drugs. Mostly lipophilic cations, such as ^{99m}Tc-TF, have also been reported to be ligands for this MDR-Pgp (8–12), because accumulation of the complex in cancer cells has been reported to be inversely related to the level of MDR-Pgp.

In our study, low T/NLs on ^{99m}Tc-TF chest images indicated resistance to paclitaxel and a poor response, whereas patients with high T/NLs had a good chemotherapy response to paclitaxel. Low and high T/NLs have been thought to be consistent with relatively high and low expressions of MDR-Pgp and the mechanism of resistance to paclitaxel chemotherapy because of MDR-Pgp overexpression (26–28). Therefore, we used semiquantitative ^{99m}Tc-TF chest images to accurately predict the response to chemotherapy with paclitaxel. Although quantification of
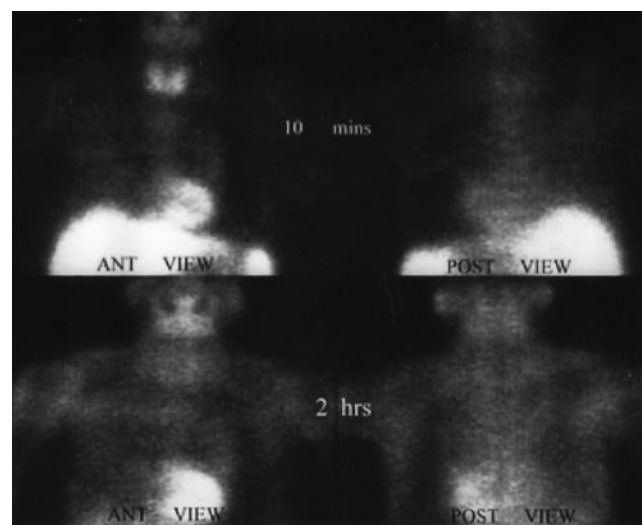

FIGURE 2. In patient 11, who had poor response to paclitaxel, both early and delayed anterior and posterior ^{99m}Tc-TF chest images show no definite ^{99m}Tc-TF uptake by lung cancer.

MDR-Pgp molecules with other conventional methods was not performed, our findings were supported by the results of previous studies in vitro (*8–12*).

In this study, we calculated T/NLs from planar chest images instead of SPECT images, because the method used has been published and can easily be practiced clinically (*20,29*). Although the advantage of SPECT is the absence of superimposition of counts of an ROI on surrounding tissue, we chose not to use SPECT because SPECT images after reconstruction have modified the real counts in ROIs and because selection of SPECT slices for summation is often difficult.

CONCLUSION

Our results emphasize the importance of pretreatment chest imaging with ^{99m}Tc-TF for predicting the chemotherapeutic response to paclitaxel more accurately than is possible through other factors, such as sex, age, tumor size, stage, and cell type. In accordance with our findings, a low T/NL in advanced NSCLC may mean that selection of an expensive paclitaxel treatment protocol is not necessary.

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REFERENCES

1. Smit EF, Postmus PE. Chemotherapy of non-small cell lung cancer. In: Carney DN, ed. *Lung Cancer*. London, UK: The Bath Press; 1995:156–172.
2. Paul DM, Johnson DH. Chemotherapy for nonsmall-cell lung cancer. In: Johnson BE, Johnson DH, eds. *Lung Cancer*. New York, NY: Wiley-Liss; 1995:247–261.
3. Goldstein LJ. MDR1 gene expression in solid tumours. *Eur J Cancer*. 1996;32A: 1039–1050.
4. Oka M, Fukuda M, Sakamoto A, et al. The clinical role of MDR1 gene expression in human lung cancer. *Anticancer Res*. 1997;17:721–724.
5. Twentyman PR. Mechanism of drug resistance in lung cancer cells. In: Carney DN, ed. *Lung Cancer*. London, UK: The Bath Press; 1995:213–233.
6. Beck W, Dalton WS. Mechanisms of drug resistance. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. Philadelphia, PA: J.B. Lippincott; 1997:498–512.
7. Volm M. Multidrug resistance and its reversal. *Anticancer Res*. 1998;18:2905–2918.
8. Tabuenca MJ, Vargas JA, Varela A, Salas C, Durantez A, Ortiz Berrocal J. Technetium-99m-tetrofosmin scintigraphy, P-glycoprotein and lung cancer. *J Nucl Med*. 1998;39:1830–1831.
9. Crankshaw CL, Marmion M, Luker GD, et al. Novel technetium (III)-Q complexes for functional imaging of multidrug resistance (MDR1) P-glycoprotein. *J Nucl Med*. 1998;39:77–86.
10. Bae KT, Piwnica Worms D. Pharmacokinetic modeling of multidrug resistance P-glycoprotein transport of gamma-emitting substrates. *Q J Nucl Med*. 1997;41: 101–110.
11. Hendrikse NH, Franssen EJ, van der Graaf WT, Vaalburg W, de Vries EG. Visualization of multidrug resistance in vivo. *Eur J Nucl Med*. 1999;26:283–293.
12. Tabuenca MJ, Vargas JA, Varela A, Salas C, Durantez A, Ortiz Berrocal J. Correlation between ^{99m}Tc-tetrofosmin uptake and P-glycoprotein expression in non-small-cell lung cancer. *Rev Esp Med Nucl*. 1998;17:427–434.
13. Basoglu T, Sahin M, Coskun C, Koparan A, Bernay I, Erkan L. Technetium-99m-tetrofosmin uptake in malignant lung tumours. *Eur J Nucl Med*. 1995;22: 687–689.
14. Novoa N, Tabuenca MJ, Varela A, Mar Cordoba M, Ortiz-Berrocal JL, Montz R. The usefulness of ^{99m}Tc-tetrofosmin in the diagnosis of pulmonary tumors: a preliminary assessment. *Arch Bronconeumol*. 1995;31:410–414.
15. Atasever T, Gokcora N, Vural G, Cetin N, Ozturk C, Unlu M. Evaluation of malignant and benign lung lesions with Tc-99m-tetrofosmin. *Nucl Med Commun*. 1996;17:557–582.
16. Basoglu T, Bernay I, Coskun C, Canbaz F, Talu A, Erkan L. Pulmonary Tc-99m tetrofosmin imaging: clinical experience with detecting malignant lesions and monitoring response to therapy. *Clin Nucl Med*. 1998;23:753–757.
17. Takekawa H, Tokaoka K, Tsukamoto E, et al. Visualization of lung cancer with ^{99m}Tc-tetrofosmin imaging: a comparison with ^{201}Tl. *Nucl Med Commun*. 1997; 18:341–345.
18. Arbab AS, Koizumi K, Toyama K, Arai T, Araki T. Detection of lung and chest tumours using ^{99m}Tc-tetrofosmin: comparison with ^{201}Tl. *Nucl Med Commun*. 1998;19:657–663.
19. Kao CH, ChangLai SP, Shen YY, Lee JK, Wang SJ. Technetium-99m tetrofosmin SPECT imaging of lung masses: a negative study. *J Nucl Med*. 1997;38: 1015–1019.
20. Kao CH, Ho YJ, Shen YY, Lee JK. Evaluate chemotherapy response in patients with small cell lung cancers using technetium-99m-tetrofosmin. *Anticancer Res*. 1999;19:2311–2315.
21. Hsu JW, Hsu JY, Chiang CD. Preliminary result of phase II study of paclitaxel and cisplatin chemotherapy for advanced non-small-cell lung cancer in Chinese patients. *Am J Clin Oncol*. 1998;21:487–490.
22. Alberola V, Rosell R, Gonzalez-Larriba JL, et al. Single agent Taxol, 3-hour infusion, in untreated advanced non-small-cell lung cancer. *Ann Oncol*. 1995; 6(suppl 3):S49–S52.
23. Yamamoto Y, Nishiyama Y, Satoh K, et al. Comparative study of technetium-99m-sestamibi and thallium-201 SPECT in predicting chemotherapeutic response in small cell lung cancer. *J Nucl Med*. 1998;39:1626–1629.
24. Arbuck SG, Dorr A, Friedman MA. Paclitaxel (Taxol) in breast cancer. *Hematol Oncol Clin North Am*. 1994;8:121–140.
25. Francis PA, Kris MG, Rigas JR, Grant SC, Miller VA. Paclitaxel (Taxol) and docetaxel (Taxotere): active chemotherapeutic agents in lung cancer. *Lung Cancer*. 1995;12(suppl 1):S163–S172.
26. van Ark Otte J, Samelis G, Rubio G, Lopez Saez JB, Pinedo HM, Giaccone G. Effects of tubulin-inhibiting agents in human lung and breast cancer cell lines with different multidrug resistance phenotypes. *Oncol Rep*. 1998;5:249–255.
27. Horwitz SB, Cohen D, Rao S, Ringel I, Shen HJ, Yang CP. Taxol: mechanism of action and resistance. *J Natl Cancer Inst Monogr*. 1993;15:55–61.
28. Horwitz SB, Lothstein I, Manfredi JJ, et al. Taxol: mechanisms of action and resistance. *Ann NY Acad Sci*. 1986;466:733–744.
29. Kao CH, ChangLai SP, Chieng PU, Yen TC. Technetium-99m methoxyisobutylisonitrile chest imaging of small cell lung carcinoma: relationship to patient prognosis and chemotherapy response—a preliminary report. *Cancer*. 1998;83: 64–68.