Quickly Predicting Chemotherapy Response to Paclitaxel-based Therapy in Non-Small Cell Lung Cancer by Early Technetium-99m Methoxyisobutylisonitrile Chest Single-Photon-Emission Computed Tomography

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ABSTRACT
The purpose of this study was to retrospectively predict the chemotherapy response to paclitaxel in non-small cell lung cancer (NSCLC) using technetium-99m methoxyisobutylisonitrile (Tc-99m MIBI) chest single-photon-emission computed tomography (SPECT) to detect the expression of multidrug-resistance-mediated $M_{r}$ 170,000 P-glycoprotein. Before chemotherapy with Paclitaxel (Taxol), 30 patients with stage IIIb or IV NSCLC were enrolled in this study. Early chest SPECT 10 min after i.v. injection of Tc-99m MIBI was performed to qualitatively interpret Tc-99m MIBI chest SPECT visually and quantitatively calculate early tumor:normal lung ratios (T:NL) for quick assessment of multidrug-resistant P-glycoprotein expression in NSCLC. On the basis of qualitatively visual interpretation of early Tc-99m MIBI chest SPECT, all of 15 (100%) cases with good response to chemotherapy with Taxol could be detected but 10 (67%) of 15 cases with poor response could not be detected. Early Tc-99m MIBI chest SPECT could correctly predict chemotherapy response in 25 (83%) of 30 of cases. The early T:NL were $3.30 \pm 0.19$ for 5 patients with poor response and $2.02 \pm 0.82$ for 15 patients with good response. The differences were significant ($P < 0.05$) by independent Student $t$ tests. However, no significant differences were found for other prognostic factors (age, sex, tumor size, tumor location, stage, and cell type) between good-response and poor-response patients. Early Tc-99m MIBI chest SPECT has the potential to predict chemotherapy response to Paclitaxel.

INTRODUCTION
The majority of patients with NSCLC present with disease that is beyond the scope of surgical cure. Despite few symptoms or none, 60–70% of newly diagnosed patients have locally advanced, inoperable, or distant metastatic diseases. Recently, evidence has pointed to a role for chemotherapy in unresectable NSCLC (stage IIIb or IV; Refs. 1, 2). The ideal therapeutic goal in advanced NSCLC is to achieve the highest response with the lowest possible morbidity due to chemotherapy side effects.

Taxanes are an important new class of anticancer agents that promote polymerization of cellular microtubules, preventing mitosis, which results in cell death. The ECOG and M. D. Anderson Cancer Center investigators administered paclitaxel (Taxol; Bristol-Myers Squibb), the first taxane to treat NSCLC (1, 2), to previously untreated stage IV NSCLC patients. Observed objective response rates of >20% were achieved. This represents the highest response rate against NSCLC in any drug discovery Phase II trial conducted by ECOG during the past 10 years using similar study populations (1, 3). However, leukopenia, hypersensitivity reactions, neurotoxicity, mucositis, alopecia, diarrhea, myalgias, and cardiac toxicity were encountered during clinical trials of Taxol (4–6). In addition, drug resistance will result in unnecessary expenditures.

The mechanism of acquired resistance to Taxol is conferred by MDR phenotype, which involves the amplification of membrane Pgp and reduced ability to accumulate and retain Taxol due to the energy-dependent Pgp efflux pump, which has a central role in the transport of chemotherapy drugs through the cell membrane (7–9). Therefore, before initiating chemotherapy with Taxol, it is important to understand the presence of MDR-mediated Pgp in NSCLC, to achieve satisfactory chemotherapy response, to decrease unnecessary financial waste, and to avoid lethal side effects. Although various detection methods could provide information about the Pgp expression at the mRNA (reverse transcription PCR) and protein levels (immunohistochemistry), these methods do not yield information about the dynamic function of Pgp in vivo (10, 11). Among the Tc-99m-

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3 The abbreviations used are: NSCLC, non-SCLC; SCLC, small cell lung cancer; Pgp, P-glycoprotein; MDR, multidrug resistance/resistant; ECOG, Eastern Cooperative Oncology Group; Tc-99, technetium-99m; MIBI, methoxyisobutylisonitrile; SPECT, single-photon-emission computed tomography; ROI, region of interest; T:NL (ratio/ratios), tumor:normal lung ratio/ratios.
labeled tumor-imaging agents for lung cancers, Tc-99m MIBI has been considered to have great potential (12). Some investigators have found negative and positive Tc-99m MIBI tumor uptake to be consistent with relative high and low expressions of MDR-Pgp, respectively, in lung cancers (13, 14). In addition, Tc-99m MIBI chest imaging has accurately predicted chemotherapy response in lung cancer patients in clinical trials (15–19). However, there are no studies to support similar findings in NSCLC patients receiving chemotherapy with Taxol. The aim of this study was to explore the potential role of early Tc-99m MIBI chest SPECT in quickly predicting NSCLC patient response to chemotherapy with Taxol.

**PATIENTS AND METHODS**

**Patients.** From April 1996 through March 1998, 30 patients (ages 43–70 years) with advanced NSCLC (stage IIIb or IV), including 12 epidermoid carcinomas and 18 adenocarcinomas, who were to undergo therapeutic chemotherapy were enrolled in this study. The dose of Taxol was 135 mg/m² administered on day 2. Treatment was repeated every 3–4 days to a planned maximum of six cycles. An initial tumor response assessment was conducted after two cycles of treatment. Patients with no change received a maximum of six cycles. Patients who continued to respond were permitted to receive an additional two cycles. Chemotherapy was discontinued in patients with progressive disease or in the presence of unacceptable toxicity (20) Patients were required to have a complete history taken and to undergo physical examination. Patient enrollment criteria included the following: (a) no prior chemotherapy, radiotherapy, or surgery; (b) an ECOG performance status of 0 to 2; (c) adequate hematological (granulocyte count ≥1,500/µl, platelet count >100,000/µl), hepatic (bilirubin ≤1.25 × upper normal limit), and renal functions (serum creatinine ≤1.25 × upper normal limit); and (d) adequate cardiac function, with no active arrhythmia or congestive heart failure. All of the patients were premedicated with dexamethasone (20 mg), cimetidine (300 mg), and diphenylhydramine (50 mg) before the initiation of Taxol infusion (3, 20). Taxol was well tolerated and none of the patients experienced allergic reaction.

**Fig. 1** Case 13 had a good response to Taxol. In A, an early Tc-99m MIBI chest SPECT (coronal sections) revealed Tc-99m MIBI uptake in the right upper lung and was interpreted as positive (T:NL, 4.3; arrows). In B, a chest X-ray shows an abnormal shadow in the right upper lobe of the lungs (arrow).

**Fig. 2** Case 16 had a poor response to Taxol. In A, an early Tc-99m chest SPECT (coronal sections) revealed no definitely abnormal Tc-99m MIBI uptake in the right middle lobe and was interpreted as negative. In B, a chest X-ray shows an abnormal shadow in the right middle lobe of the lungs (arrow).
Granulocytopenia was generally mild. Before chemotherapy, early Tc-99m MIBI chest SPECT was performed on all of the patients to quickly evaluate MDR-Pgp expression.

**Interpretation of Chemotherapy Response.** Chemotherapy response was evaluated in the 3rd month after completion of treatment. Response of NSCLC to chemotherapy was evaluated by clinical and radiological methods. Evaluation criteria were (21): (a) complete response = no evidence of disease; (b) partial response = $\geq 50\%$ decrease in the sum of the products of the maximum perpendicular diameters of all of the measurable lesions, no evidence of progression in any lesion, and no new lesions; (c) no response = $< 25\%$ increase in the sum of the products of the maximum perpendicular diameters of all of the measurable lesions, no evidence of progression in any lesion, and no new lesions; and (d) progressive disease = $\geq 25\%$ increase in the sum of the products of the maximum perpendicular diameters of all of the measurable lesions and/or the appearance of new lesions. Because there were no complete responses in our patients, we defined partial-response as good responses and no-response and progressive-disease as poor responses in our study.

**Tc-99m MIBI Chest Imaging.** There was a delay of 30 min from the oral intake of 500 mg perchlorate to the start of imaging procedure to prevent abnormal uptake of free Tc-99m pertechnetate. A commercial MIBI preparation (max, 5.56 Gb $150mCi$) in approximately 1 to 3 ml) was obtained from Du Pont Company (Cardiolite). The labeling and quality control procedures were carried out according to the manufacturer’s instructions. Labeling efficiencies were all higher than 95%. An early 360-degree chest SPECT was performed 10 min after i.v. injection of 740 MBq (20 mCi) Tc-99m MIBI (12, 15).**

**Data Analysis.** The findings of Tc-99m MIBI SPECT chest imaging were evaluated both qualitatively and quantitatively as follows: (a) SPECT images were visually interpreted by at least two nuclear medicine physicians. Chest SPECT was defined as positive (focal abnormal accumulation at the tumor site; Fig. 1) or negative (no abnormal focus of activity at the tumor site; Fig. 2; Refs. 12, 15); and (b) T:NL was obtained on early chest SPECT. A ROI was carefully drawn over the tumor on the one coronal section that demonstrated the lesion most clearly. On the basis of the chest computed tomographic finding, we made sure there was
no tumor on the contralateral side. Then, another ROI of the same size was drawn over the contralateral normal lung using a mirroring technique. T:NL was calculated by the following formula: (the mean counts in the ROI over the tumor) ÷ (the mean counts in the ROI over the contralateral normal lung; Ref. 17). The value of T:NL was expressed as mean ± SD. To test for differences of T:NL between patients with good response and poor response, an independent Student t test was used.

RESULTS

The detailed data of patients are shown in Table 1. On the basis of qualitatively visual interpretation of early Tc-99m MIBI chest SPECT, all (100%) of the 15 cases with good response could be detected but 10 (67%) of 15 cases with poor response could not be detected. Therefore, early Tc-99m MIBI chest SPECT could correctly predict (either positive SPECT with good response or negative SPECT with poor response) chemotherapy response in 25 (83%) of 30 cases (Table 2). The early T:NL based on Tc-99m MIBI chest SPECT were 3.30 ± 0.82 for 15 patients with good response and 2.02 ± 0.19 for 5 patients with poor response and whose lung cancers could be detected by early Tc-99m MIBI chest SPECT. Ten patients whose tumors did not show any evidence of MIBI uptake were not included. The early T:NL was significantly higher in good-response patients than in poor-response patients (Ps, <0.001).

We compared the differences in other prognostic factors, such as sex, age, tumor size, stage, and cell type, between good-response and poor-response patients. There were no significant differences in sex, age, tumor size, tumor location, stage, or cell type (all Ps, >0.05) between these two groups (Table 1).

DISCUSSION

MDR-mediated Pgp recognizes certain chemotherapeutic agents as a substrate and prevents accumulation of radionuclides such as MIBI (22). The retention of Tc-99m MIBI in cells depends on the activity of this M, 170,000 Pgp coded on the MDR1 gene, which functions as an ATP-dependent efflux pump for many cytotoxic substances, mostly lipophilic cations. Tc-99m MIBI has been reported to be a ligand for this MDR-Pgp (22) because accumulation of the complex in cells has been found to be inversely related to the level of Pgp. Other reports have also shown that verapamil and cyclosporin A, MDR-reversal agents, enhance accumulation of Tc-99m MIBI manyfold. Piwnica-Worms et al. (22) demonstrated the relationship between Tc-99m MIBI tumor uptake and MDR-Pgp and implied a potential for Tc-99m MIBI scintigraphy to be used as a noninvasive imaging test for MDR-Pgp assessment. Low and high Tc-99m MIBI tumor uptakes are thought to be consistent with relative high and low expressions of MDR-Pgp, respectively (13, 14, 22), and the mechanism of resistance to Taxol chemotherapy is thought to involve MDR-Pgp overexpression (7–9). Therefore, we used semiquantitative Tc-99m MIBI SPECT chest images to accurately predict the response to chemotherapy with Taxol. Our pervious experiences (12, 15) suggest that because of poorer resolution of radionuclide imaging, sometimes small lung cancer lesions could not be clearly shown by Tc-99m MIBI chest SPECT and were often misinterpreted as the existence of MDR-Pgp. To avoid this pitfall, we selected larger NSCLC lesions in this study. In addition, because only advanced NSCLC (stage IIIb or IV) with a higher tumor (T) stage (mmT2 stage) was included, NSCLC lesions smaller than 3 cm were excluded in this study.

Actually, an early chest image, performed 10 min after an i.v. injection of Tc-99m MIBI, was enough to correctly predict chemotherapy response in lung cancer (15, 18). After reviewing the previous related literature, similar findings to these in our study were found for lung cancer with different chemotherapy protocols. In our preliminary study, visual interpretation of early Tc-99m MIBI chest SPECT correctly predicted chemotherapy response of cisplatin and etoposide in 13 (87%) of 15 SCLC cases (15). Ceriani et al. (18) performed SPECT imaging on 19 SCLC and 12 NSCLC patients before chemotherapy with VP-16 and cisplatin, respectively. There was a significant difference in the early T:NL of Tc-99m MIBI between the patients with complete, partial, and no remission (18). In addition, a delayed chest image is not necessary to help to calculate the tumor washout rate or retention index. Tumor washout rates of Tc-99m MIBI that were calculated from early (30 min) and delayed (3 h) chest imaging did not correlate with the density of Pgp that was detected by immunohistochemical studies in lung cancer (13). Therefore, a clinical trail of Yamamoto et al. (17) in 19 SCLCs revealed that there was no significant difference in the retention index of Tc-99m MIBI that was calculated from early (15 min) and delayed (2 h) chest imaging with respect to the chemotherapy responses (cyclophosphamide, doxorubicin, vincristine, VP-16, cisplatin, mitomycin-C, and vindesine) of lung cancer (17).

In conclusion, lower T:NL in advanced NSCLCs may mean that it is not necessary to select a very expensive Taxol treatment protocol. Our results emphasize the potential of functional images, such as Tc-99m MIBI chest images, to accurately predict patients’ chemotherapy response to Taxol.

REFERENCES

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