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The role of Tc-99m sestamibi imaging in predicting clinical response to chemotherapy in lung cancer

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Multidrug resistance (MDR) is a major problem in lung cancer. Tc-99m methoxyisobutyl isonitrile (MIBI) has been demonstrated to be a non-invasive marker to diagnose MDR1 related P-glycoprotein (Pgp) and multidrug resistance-associated protein (MRP) expression in various solid tumors. The aim of this study was to evaluate the relationship between the degree of Tc-99m MIBI uptake and its retention on delayed images and the response to chemotherapy in lung cancer. Twenty-three patients (1 woman and 22 men, age range 40–67 years) with lung cancer (9 small cell and 14 non-small cell) were examined with Tc-99m MIBI imaging before chemotherapy. After i.v. administration of 740 MBq Tc-99m MIBI, planar and SPECT imaging at 30 minutes and 2 hours was performed. Tumor to normal lung uptake ratio (T/N) and percent retention were measured. Response to chemotherapy was evaluated according to follow-up CT and grouped as complete responders (CR), partial responders (PR) and non-responders (NR). Clinical follow-up and CT evaluation revealed that 12 patients had partial remission, 4 patients had complete remission and 7 patients had no-remission after chemotherapy. Statistically, there was no significant correlation between early (30 min), delayed (2 hr) T/N ratios and percent retention of Tc-99m MIBI with chemotherapeutic response of the lung cancer among the three groups ($p > 0.05$). Results of the current study imply that Tc-99m MIBI uptake and the retention index may not correlate with chemotherapy response in lung cancer, so that the accuracy of this method needs to be verified in a larger series with additional investigation at the molecular level.

Key words: Tc-99m sestamibi, lung cancer, multidrug resistance

INTRODUCTION

Tc-99m methoxyisobutyl isonitrile (MIBI), as an oncologic imaging agent, has been used to evaluate tumors of breast, bone, thyroid and lung.[1–4] The initial results demonstrated that a positive Tc-99m MIBI scan might be helpful in clinical diagnosis of lung malignancy. With regard to the detection of primary lung tumor, Chiti et al. reported a sensitivity of 85% and specificity of 100%.[5] Aktolun et al. concluded that Tc-99m MIBI SPECT also could be used for staging of patients with lung cancer, for evaluation of mediastinal involvement and follow-up to distinguish residual or recurrent disease from radiotherapy necrosis.[6] Recently, Piwnica-Worms et al. showed that Tc-99m MIBI was a transport substance recognized by multidrug resistance (MDR) related P-glycoprotein (Pgp) and that the tumor cell accumulation was enhanced by inhibition of efflux transport function.[7] These results provided the basis for clinical studies that investigated the role of Tc-99m MIBI in predicting chemotherapy response in patients with lung cancer. In these studies, the tumor to background ratio (T/B) of Tc-99m MIBI has been found to correlate inversely with chemotherapy response.[8,9] On the other hand, it is also noted that tumor washout of Tc-99m MIBI may be a useful parameter in

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Table 1 Detailed data of the subjects in our study

Patient	Type	Size (cm)	p30 min	p2 hr	%Rp	t30 min	t2 hr	%Rt	Response
1	SCLC	5 × 4	1.08	1.07	−0.93	1.14	0.96	−15.78	PR
2	SCLC	5 × 4	1.5	1.37	−8.67	1.66	1.55	−6.63	PR
3	NSCLC	5 × 4	NV	NV	0	1.28	1.47	14.8	PR
4	NSCLC	5 × 5	1.37	1.43	4.38	2.77	2.61	−5.78	PR
5	NSCLC	5 × 4	1.43	1.44	0.70	1.72	1.65	−4.1	PR
6	NSCLC	8 × 7	1.33	1.4	5.26	1.54	1.61	4.55	PR
7	NSCLC	5 × 5	1.31	1.36	3.82	1.70	1.73	1.76	PR
8	NSCLC	3 × 2	NV	NV	0	NV	NV	0	PR
9	SCLC	6 × 5	NV	NV	0	1.13	1.19	5.31	PR
10	NSCLC	7 × 7	1.23	1.29	4.88	1.66	1.56	−6.02	PR
11	SCLC	10 × 8	1.21	1.24	2.48	1.28	1.34	4.69	PR
12	NSCLC	10 × 8	1.44	1.07	−25.69	1.54	0.94	−38.96	PR
13	NSCLC	3 × 4	1.33	1.33	0	1.39	1.53	10.07	CR
14	SCLC	3 × 4	NV	NV	0	1.14	1.17	2.63	CR
15	SCLC	5 × 4	1.14	1.16	1.75	1.59	1.76	10.69	CR
16	NSCLC	5 × 4	1.29	1.31	1.55	1.67	1.90	13.77	CR
17	NSCLC	7 × 5	1.02	1.13	10.78	1.13	1.28	13.27	NR
18	NSCLC	4 × 3	1.17	1.23	5.12	1.28	1.46	14.06	NR
19	SCLC	6 × 6	1.26	1.33	5.56	1.47	1.51	2.72	NR
20	SCLC	6 × 5	1.28	1.29	0.78	1.54	1.41	−8.44	NR
21	NSCLC	5 × 4	1.13	1.05	−7.08	1.55	1.48	−4.52	NR
22	NSCLC	6 × 4	1.46	1.32	−9.59	2.07	1.62	−21.74	NR
23	SCLC	3 × 2	1.47	1.18	−19.73	1.69	1.24	−26.63	NR

p30 min and p2 hr, planar tumor to contralateral normal lung ratio at 30 min and 2 hr; t30 min and t2 hr, tomographic tumor to contralateral normal lung ratio at 30 min and 2 hr; %Rp and %Rt, percent retention calculated from planar and tomographic images; SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; NV, non-visualize; PR, partial remission; CR, complete remission; NR no remission

predicting multidrug resistance in patients with lung cancer.[10] The aim of this study was to evaluate the role of Tc-99m MIBI in predicting chemotherapy response in patients with lung cancer by comparing tumor uptake ratios and its retention in delayed imaging with the clinical outcome.

MATERIALS AND METHODS

Subjects

A total of 23 patients (1 woman and 22 men, age range 40–67 years) were included in the study. All patients had bronchospic biopsy before Tc-99m MIBI imaging. The lung lesions were staged by the metastasis-node-metastasis classification. According to lung CT, the smallest tumor size was 2 × 2 cm and the largest was 10 × 8 cm. The clinical characteristics of the patients are given in Table 1. Nine patients had small cell lung carcinoma (SCLC) and 14 patients had non-small cell lung carcinoma (NSCLC). None of the patients received chemo-radiotherapy before Tc-99m ME31 imaging.

Tc-99m MIBI imaging

All patients underwent Tc-99m MIBI imaging 2–5 days before chemotherapy. After i.v. administration of 740 MBq, Tc-99m MIBI planar and SPECT imaging at 30 minutes and 2 hours were performed. Planar images (256 × 256 matrix, 10^6 counts) of the chest were acquired in the anterior and posterior projections on a dual headed SPECT system equipped with a low energy parallel-hole collimation and peaked at 140 keV with a symmetric 20% window. After the planar images, SPECT imaging was performed with a 64 × 64 matrix for 64 projections and an imaging time of 40 sec per projection. The tomographic images were reconstructed with a Ramp-Hanning filter with a cut-off frequency of 0.8 cycles cm^{-1}. Neither attenuation correction nor scatter correction was performed.

Chemotherapy regimen

After Tc-99m MIBI imaging, all patients received cisplatin based chemotherapy. Fourteen of them received a combination of PE (cisplatin 80 mg/m^2 day 1 and etoposide 100 mg on days 1, 2 and 3 every 3 weeks), 5 patients PV (cisplatin 80 mg/m^2 on day 1 and vinorelbine 30 mg on days 1 and 8 every 3 weeks, 3 patients PG (cisplatin 80 mg/m^2 on day 1 and gemcitabine 1250 mg on days 1 and 8 every 3 weeks) and one patient MIC (mitomycin 6 mg/m^2 on day 1 and ifosfamide 3 g/m^2 on day 1, cisplatin 50 mg/m^2 on day 1 every 3 weeks). Response to chemotherapy was evaluated according to the WHO criteria and was grouped as complete response, partial response, stable

Table 2 Comparison of Tc-99m MIBI planar images according to response to chemotherapy

	n	p30 min	p2 hr	%Rp
CR	4	1.19 ± 0.15	1.20 ± 0.15	0.82 ± 0.95
PR	12	1.24 ± 0.18	1.22 ± 0.18	–1.14 ± 8.59
NR	7	1.25 ± 0.16	1.21 ± 0.10	–2.02 ± 10.61

p30 min and p2 hr, planar tumor to contralateral normal lung ratio at 30 min and 2 hr; %Rp, percent retention calculated from planar images; PR, partial remission; CR, complete remission; NR, no remission

Table 3 Comparison of Tc-99m MIBI tomographic images according to response to chemotherapy

	n	t30 min	t2 hr	%Rt
CR	4	1.44 ± 0.23	1.59 ± 0.31	9.29 ± 4.72
PR	12	1.53 ± 0.46	1.46 ± 0.45	–3.84 ± 13.52
NR	7	1.53 ± 0.30	1.42 ± 0.13	–4.46 ± 15.88

t30 min and t2 hr, tomographic tumor to contralateral normal lung ratio at 30 min and 2 hr; %Rt, percent retention calculated from planar images; PR, partial remission; CR, complete remission; NR, no remission

disease and progressive disease according to follow-up lung CT examinations obtained three weeks after the last chemotherapy. Definition of complete remission (CR) was the complete disappearance of all tumor lesions for at least three weeks. Partial response (PR) was defined as a reduction of 50% in the product of the longest perpendicular diameters of the lesions. Progressive disease (PD) was defined as a 25% increase in the product of the longest perpendicular diameters of the lesions or development of new lesions irrespective of response elsewhere. Stable disease (SD) was defined as the criteria which fall in between PR and PD. Finally, the patients were classified as complete responders (CR), partial responders (PR) and non-responders (NR), including patients with stable disease and progressive disease.

Image analysis

The data were evaluated visually and quantitatively with guidance of the thorax CT findings. Early (30 min) and delayed (2 hr) Tc-99m MIBI images were examined visually by two nuclear medicine physicians with regard to increased uptake relative to background activity.

In early and delayed planar studies, quantitative analysis of the tumor mass was performed by manually drawing regions of interest over the entire tumor (T) from the projection in which the tumor was visualized best. The same ROI was placed over the contralateral normal lung tissue (N) by the mirroring technique. In 2 patients who had a lung mass located in the right lower lobe we manually drew a smaller contralateral ROI (N) in order to avoid the cardiac activity. In the analysis of SPECT images, one transverse section that demonstrated the

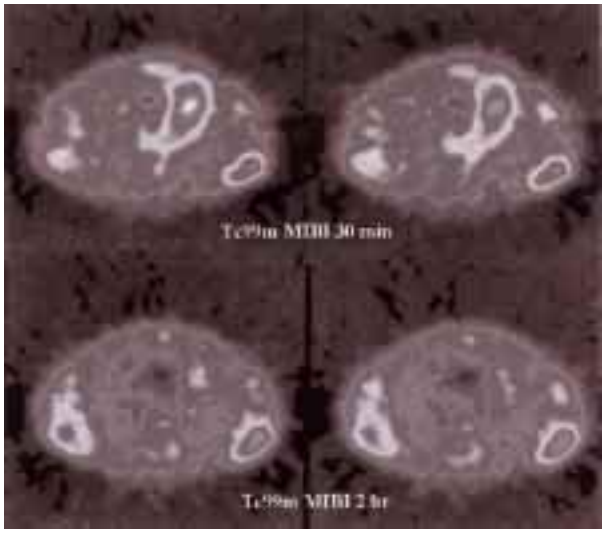

Fig. 1 A representative case who did not respond to chemotherapy regimen (Patient no. 22). At 30 min transverse slices showed increased uptake in the left upper lung corresponding to the tumor. But 2 hr SPECT images of Tc-99m MIBI showed only faint uptake in the tumor area. The tumor demonstrated significant washout.

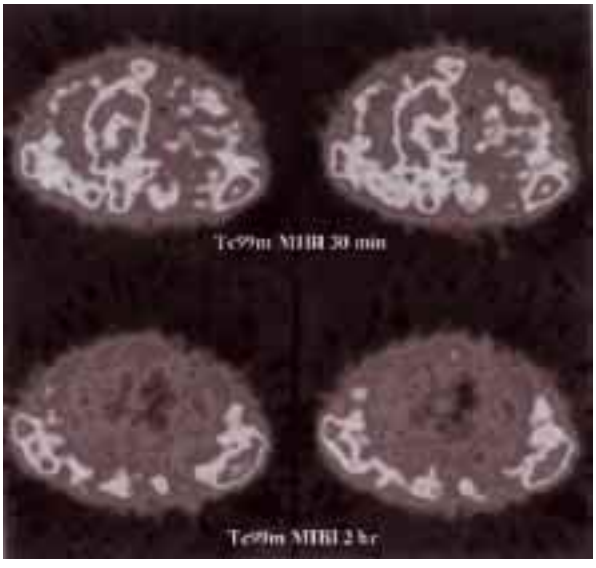

Fig. 2 A representative case with partial response (Patient no. 12). A tumor mass in the right upper lung showed Tc-99m MIBI accumulation at 30 min SPECT images. On the other hand, 2 hr SPECT images Tc-99m MIBI did not demonstrate an abnormal uptake suggesting the rapid washout of Tc-99m MIBI from tumor.

lesion most clearly was selected on both early and delayed images. Identical regions of interests (ROIs) were drawn over the tumor uptake and the contralateral lung tissue. The ratio of average counts of tumor to contralateral normal lung (T/N) was measured for each planar and SPECT study. The percent retention (R%) was calculated as R% = 100 × (T/N at 2 hr – T/N at 30 minutes)/T/N at

30 minutes. The T/N value at 30 min, T/N at 2 hr and percent retention were expressed as the mean ± sd. To test for differences among these parameters, Kruskal-Wallis one-way ANOVA test was used for the three groups. Wilcoxon matched pairs signed-ranks test was used for comparison of T/N and %R uptake ratios obtained by planar and SPECT studies. Results were considered significant when the p value was <0.05.

RESULTS

Four of 23 patients had primary lung tumors (pts 3, 8, 9, 14) that were non-visualized on the Tc-99m MIBI planar images. One of these patients (No. 8) had a left lung upper lobe lesion measuring 3×2 cm, which also was non-visualized on the SPECT image. The patient had a diagnosis of squamous lung cancer and showed partial remission after chemotherapy. Finally visual assessment including SPECT data showed Tc-99m MIBI uptake in 22 patients.

Chemotherapy response was predicted by clinical evaluation and there were 12 patients who had partial remission, 4 patients who had complete remission, 3 patients who had no change and 4 patients who had progressive disease. Tables 2 and 3 show the T/N ratios at 30 min and 2 hr and the retention indexes in planar and tomographic images of all patients. There was a statistically significant difference between planar and tomographic images with respect to the T/N ratios at 30 min and 2 hr. On the other hand, the difference with respect to percent retention was not significant.

In the Kruskal-Wallis one-way ANOVA test, there was no significant correlation between early, delayed T/N ratios and percent retention of Tc-99m MIBI with chemotherapeutic response of the lung cancer among the three groups ($p > 0.05$). There was considerable overlap between the patients.

DISCUSSION

Tc-99m MIBI is a lipophilic cation used for the evaluation of several types of tumors. The tumor uptake mechanism of Tc-99m MIBI is related to many factors and not yet clearly understood. It appears that the tumor uptake of Tc-99m MIBI is not a tissue specific process, but is mainly dependent on cell metabolism and affected by the metabolic processes and mitochondrial and plasma membrane potentials. Increased tumor blood flow and capillary permeability are some of the other mechanisms that effect tumoral uptake of Tc-99m MIBI.[11,12] Recently it was reported that Tc-99m MIBI uptake is inversely proportional to the level of Pgp and MRP expression.[13]

Resistance to chemotherapy is a major problem in the treatment of lung cancer. The causes are not clear but may be due to a combination of tumor characteristics and pharmacological factors. Pharmacological factors include the dose, schedule of the drug and drug metabolism, which may relate to concomitant medication and to genetic variations as well as necrotic components of the tumor. Tumoral factors can be defined as the tumor volume, adequacy of blood supply and specific cellular mechanism. In lung cancer, there are additional resistance mechanisms that remain rather obscure and complex. Four types of multidrug resistance have been defined in lung cancer on the basis of the cellular drug targets involved; classical multidrug resistance (MDR), non-P-glycoprotein MDR (also called MRP), atypical MDR (mediated through altered expression of topoisomerases II) and lung resistance-related protein (LRP).[14,15] Tc-99m MIBI has been reported to be a substrate of both Pgp and MRP and suggested to be a non-invasive marker to diagnose the function of MDR related proteins in cancer. On the other hand, the literature so far contains no cumulative data to support the relationship between Tc-99m MIBI and a non-MDR related mechanism, such as LRP.

In this study, we investigated the role of Tc-99m MIBI scintigraphy in the prediction of chemotherapy response in cases of lung cancer. No significant correlation could be found between Tc-99m MIBI uptake parameters in tumor tissue and the clinical outcome. There was not a significant difference between three groups of patients (CR, PR and NR) with respect to Tc-99m MIBI uptake and washout kinetics. There have been reports that investigate the role of Tc-99m MIBI in predicting the therapy response in lung cancer, but the results are conflicting. Koukourakis et al. studied 25 patients with non-small cell lung cancer and concluded that increased tumor clearance of Tc-99m MIBI was significantly correlated with resistance to chemotherapy.[10] Kostakoğlu et al. supported this finding in lung cancer by showing that the early tumor/background uptake ratio was inversely correlated with Pgp, but tumor washout was not found to correlate with Pgp expression.[8] Ceriani et al. also supported this finding that early tm/bg ratio of Tc-99m MIBI was an effective tool for predicting the clinical response to chemotherapy in lung cancer.[9] In contrast with these reports, Sasaki et al. performed SPECT in 10 patients with lung cancer before surgery. Pgp expression was determined by immunohistochemical staining. Neither early and delay uptake, nor washout rates were significantly different in Pgp positive ($n = 2$) and negative groups ($n = 8$). They observed no significant correlation between cisplatin chemosensitivity and Tc-99m MIBI uptake.[16] The same group also studied 25 lung cancer patients with Tc-99m MIBI before chemotherapy and, in accordance our results, concluded that imaging was not a predictive test for evaluating treatment response.[17]

The absence of a correlation between the clinical outcome and Tc-99m MIBI results in our series may be explained by the effects of chemotherapeutics that act independently of Pgp. The natural lipophilic products involved in MDR include antineoplastic drugs such as

the vinca alkaloids (vincristine and vinblastine), the anthracyclines (doxorubicin and daunorubicin), the epipodophyllotoxins (etoposide), mitoxantrone and taxol. Although those chemotherapeutics are also selected for multiagent protocols, the conventional multidrug therapy used in the treatment of lung cancer mainly constitutes cisplatin based protocols, which are not effected by MDR related proteins. On the other hand, high levels of LRP have also been demonstrated in lung cancer cell lines and this protein was shown to induce cross resistance to a number of cytotoxic drugs including cisplatine.[18] In this respect, the over expression of LRP may confer the main resistance to cisplatin therapy in our series. In a recent study Sasaki et al. demonstrated that Tc-99m MIBI could predict the chemosensitivity of lung cancer to mitomycin C independently of Pgp expression.[16] Our series constituted only one patient who was treated with the multiagent protocol including mitomycin C; therefore our results are not sufficient to elucidate their finding. One of the limitations of this study is the lack of histopathological evaluation of Pgp, MRP and LRP in our histopathological specimens. Nevertheless, the heterogeneous distribution of Pgp has been reported in non-small lung cancers and it should be kept in mind that immunohistochemically negative results determined from a small biopsy specimen might not always reflect the whole tumor expression.[19]

Another factor that influences the absence of a correlation between Tc-99m MIBI results and the clinical outcome may be the heterogeneous distribution of our patient group, as 61% of the patients were NSCLC and 39% of them were SCLC. Our results might be different if a selective population consisting of SCLC patients were studied. According to the conventional protocols, chemotherapy is accepted as the principal treatment for small-cell lung cancer. Response rates to multiagent chemotherapy are high at up to 75–80% in extensive disease and up to 85–95% in limited disease. On the other hand, in non-small cell lung cancer, chemotherapy is only established as a useful therapeutic method for advanced disease in stage III and IV cancers and is also considered to be a chemotherapy refractor malignancy.[20] The remarkably high levels of MRP-MDR expression as well as classical MDR, was mainly observed in SCLC. Since classical MDR is considered to play a minor role in the chemosensitivity of NSCLC,[21] we suggest that further studies of patients with SCLC would be valuable in investigating the role of Tc-99m MIBI in predicting the response to chemotherapy.

In this preliminary prospective study, we did not observe a significant correlation between early, delayed Tc-99m MIBI uptake ratios and wash-out rates with response to chemotherapy. Our findings suggest that Tc-99m MIBI imaging is an ineffective method for predicting chemosensitivity in lung cancer. We believe that the accuracy of Tc-99m MIBI imaging will be verified in a large number of patients in additional studies at the molecular level.

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