Original Article

Effect of trifluoperazine on Tc-99m sestamibi uptake in patients with advanced nonsmall cell lung cancer

Ümmühan Abdülrezzak, Zeynep Erdoğan[1], Güler Silov[1], Ayşegül Özdal[1], Özgül Turhal[1]

Department of Nuclear Medicine, Erciyes University School of Medicine, [1]Department of Nuclear Medicine, Kayseri Training and Research Hospital, 38010-Kayseri, Turkey

ABSTRACT

Objective: The aim of this study was to investigate whether there is an effect of trifluoperazine on Tc-99m methoxyisobutylisonitrile (MIBI) uptake in patients with advanced nonsmall cell lung cancer (NCLC). **Materials and Methods:** A total of 23 patients with biopsy-proven advanced NCLC who had no previous history of chemo-radiotherapy, underwent baseline dual phase planar, single photon emission computed tomography and whole body Tc-99m MIBI scintigraphy performed at 20 and 120 min. After oral administration of trifluoperazine (5 mg, 2 times a day, for 5 days), dual phase Tc-99m MIBI scintigraphy was repeated. For each patient, and for both studies, regions of interest were drawn over the tumor area (T) and over the normal lung area (L) on the contralateral side in transverse slices where tumor was visualized clearly. Then, early and delayed T/L ratios and washout rate (WR) were calculated. **Results:** Tc-99m MIBI was accumulated in the cancer tissue in all of the patients. Delayed ratio after the oral administration of trifluoperazine (DR2) was significantly higher ($P = 0.039$) than delayed ratio before trifluoperazine (DR1). We found no significant differences of early ratio before trifluoperazine (ER1) and early ratio after trifluoperazine (ER2), and washout rate before (WR1) and washout rate after trifluoperazine (WR2). **Conclusion:** In patients with advanced NCLC, trifluoperazine treatment in addition to chemotherapy might be useful. However, our results need to be confirmed in larger series of patients.

Keywords: Nonsmall cell lung cancer, Tc-99m MIBI, trifluoperazine

INTRODUCTION

In the treatment of lung cancer, several chemotherapeutic agents are widely used but they are not always effective. To improve the quality of life and increase in median survival of patients, selection of the most sensitive and most effective ones of these agents is important. The occurrence of multidrug resistance (MDR) is a major cause of resistance to chemotherapeutic agents in patients with lung cancer, in part owing to the overexpression of MDR-related *P* glycoprotein (Pgp). Some of the mechanisms responsible for resistance in these tumors are changes in tumor perfusion and oxygenation and factors associated with MDR.[1] It is difficult to predict the prognosis and early chemotherapy response of nonsmall cell lung cancer (NCLC) by means of morphologic imaging techniques such as computed tomography (CT) and magnetic resonance imaging. Clinically, Tc-99m methoxyisobutylisonitrile (MIBI) scintigraphy is useful in predicting the efficacy of chemotherapy in lung cancer, malignant lymphoma, and breast cancer.[2-4]

Tc-99m MIBI is a lipophilic cation developed primarily as a myocardial imaging agent, passes through the cell membrane due to negative transmembrane potential and accumulates in mitochondria reversibly.[5] Mitochondria are important in the pathophysiology and treatment of cancers and play a key role in cell life and death.[6] Although the exact mechanism of Tc-99m MIBI uptake in tumors disclosed, increased metabolic rate of tumor cells, increased cellular mitochondrial content and increased potential difference between the inner and outer part

Address for correspondence:
Dr. Zeynep Erdoğan, Department of Nuclear Medicine, Kayseri Training and Research Hospital, 38010-Kayseri, Turkey.
E-mail: zeynep_erdogan@yahoo.com

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of the mitochondrial membrane, can play an important role in the tumor uptake of this agent, or the uptake may be caused by indirect phenomena, such as increased tumor blood flow and capillary permeability and Tc-99m MIBI is suggested as a suitable agent for tumor imaging.[7] Furthermore, it has been demonstrated that Tc-99m MIBI is a transport substance and a noninvasive marker for MDR related Pgp and that tumor cell accumulation is enhanced by inhibition of the efflux transport function and inversely related to the level of Pgp.[8]

These results provided the basis for clinical studies that investigated the role of Tc-99m MIBI in predicting the response to chemotherapy in patients with lung carcinoma and Pgp or MDR-related protein expression.[9-11] Increased MIBI uptake in NCLC has been reported to be related to a positive response to chemotherapy.[9] Also, in a group of malignant tumors such as lymphoma, soft tissue sarcoma and breast cancer, decreased or lack of Tc-99m MIBI uptake is known to be related to a negative response to chemotherapy.[4,12,13]

On the other hand, multifactorial drug tolerance has been reported in lung cancers.[14,15] However, there are some studies showing that the presence of Pgp in primary lung cancer may not play an important role on Tc-99m MIBI uptake.[16,17] Yüksel *et al.* reported that higher Tc-99m MIBI uptake in NCLC is associated with a positive response to chemotherapy and Pgp expression plays only a minor role in Tc-99m MIBI uptake. This study also reported that washout rate (WR) of responders was not significantly different from that of nonresponders.[9] Aloj *et al.* reported in their study of breast cancer tissue cultures, reduced or lack of Tc-99m MIBI may be an *in vivo* indicator of high levels of Bcl-2 in tumor tissue.[18] Also in this study, Tc-99m MIBI uptake has been reported to have increased by 10-fold in the cells having high levels of Bcl-2 after treatment with staurosporine. As a nonselective protein kinase C inhibitor staurosporine, trifluoperazine is a calcium/calmodulin-dependent protein kinase inhibitor, and trifluoperazine can induce cell death by inhibiting high expression of Bcl-2 in dopaminergic neuronal cell lines.[19]

Trifluoperazine is widely used as an antipsychotic drug due to its interaction with many types of ion channels. It is also a calmodulin antagonist, inhibitors of protein kinase C, and adenylate cyclase.[20,21] Trifluoperazine is known to reverse MDR of tumor cell lines by blocking Pgp efflux function. Shin *et al.* reported that trifluoperazine induced the downregulation of Pgp and MDR1b mRNA in L1210/Adr cells.[22]

It is widely accepted that phenothiazines are localized predominantly in the mitochondria of normal and cancer eukaryotic cells,[23,24] which is indicative that the mechanism(s) of their cytotoxic activity is/are probably associated predominantly with mitochondrial function. Since phenothiazines affect ATP production by different ways in normal and leukemic cells, it may be speculated that mitochondria mediate this selectivity. Mitochondria have been shown to play a key role in apoptosis.[25] In a study of Takeshita *et al.*, they found that verapamil and trifluoperazine substantially reversed resistance to Adriamycin in the Pgp positive cell lines, whereas cyclosporin A was relatively ineffective.[26]

The aim of the present study was to determine the effect of trifluoperazine on dual phase Tc-99m MIBI uptake in patients with advanced NCLC.

MATERIALS AND METHODS

Twenty-three patients including 18 men and 5 women (mean age, 59.7 ± 11.08 years) with newly diagnosed advanced NCLC (stage IV) were prospectively enrolled in the study. Tumors were classified according to the WHO nomenclature and the tumor-node-metastasis system was used for staging, and tumor size ranged between 2 and 10 cm. No patient had received previous chemotherapy or radiotherapy. The study protocol was approved by the Local Ethics Committee, and all the patients gave an informed consent.

Tc-99m MIBI scintigraphy and CT was performed prior to starting any treatment. After oral administration of trifluoperazine (5 mg, 2 times a day, for 5 days), Tc-99m MIBI scintigraphy was repeated.

Each patient received 20 mCi (740 MBq) Tc-99m MIBI by intravenous injection in the arm contralateral to the thoracic mass. 20 (early image) and 120 min (delayed image) after injection, planar, single photon emission computed tomography (SPECT) and whole body images were obtained with a double head gamma camera equipped with a high resolution parallel hole collimator (Siemens ECam; Siemens Medical Systems, Hoffman Estates, IL USA, 1999). The energy peak was centered at 140 keV with a 20% window. For SPECT of the torax, 64 projections were obtained using a 64 × 64 matrix, in "step and shoot" mode, at 20 s per view. Image reconstruction was performed using filtered back projection with Butterworth filter and transverse, coronal, and sagittal sections were reconstructed.

Reconstructed images were evaluated qualitatively for accumulation of Tc-99m MIBI corresponding to the location of the masses on CT. For each patient, and for both studies, manual regions of interest were drawn over the tumor area (T) and another region of interest of the same size over the symmetrical normal lung (L) area on the contralateral side using a mirroring technique in transverse slices which displayed the clearest lesion on early and delayed images. Then, early (ER) and delayed (DR) T/L ratios and WR were calculated semiquantitatively before (ER1, DR1, WR1) and after (ER2, DR2, WR2) oral administration of trifluoperazine. WR was determined using the following formula:

$$WR\% = ER - DR / ER \times 100$$

The data for early and delayed T/L ratios were expressed as mean ± standard deviation (SD). For intragroup comparison of repeated measurements, paired samples *t*-test was used to evaluate the significance of differences. A *P* value of 0.05 or less was considered to be statistically significant.

RESULTS

Of all patients, prior to trifluoperazine administration, consistent with the tumor region in CT, Tc-99m MIBI uptake was observed and was considered to be positive. In all patients, trifluoperazine was well tolerated and no associated extrapyramidal syndromes occurred.

In the baseline study, ER1, DR1 and WR1 mean ± SD are 1.81 ± 0.38, 1.60 ± 0.33 and 11.08 ± 11.02, respectively. After trifluoperazine administration, ER2, DR2, and WR2 mean ± SD are 1.87 ± 0.40, 1.68 ± 0.34 and 9.17 ± 8.26, respectively.

Delayed ratio following trifluoperazine administration (DR2) was significantly higher ($P < 0.05$) than delayed ratio before the therapy (DR1). ER2 was higher than ER1 and WR2 was lower than WR1 but we found no significant differences ($P > 0.05$) between ER1 and ER2; WR1 and WR2.

The clinical and scintigraphic data of all patients are reported in Table 1. Early and delayed ratios and WRs before and after administration of trifluoperazine are given in Table 2.

DISCUSSION

Visualization, determination, and inhibition of MDR will be the most important process to improve chemotherapeutic regimens. Because clinical studies have shown that overexpression of MDR-related proteins such as Pgp, MDR protein (MRP) are prognostic indicators of a poor response to chemotherapy.[9,27,28] As an energy-dependent drug efflux pump, Pgp reduces the accumulation of chemotherapeutic drugs in MDR cells.

For functional and noninvasively visualization of MDR, previous studies have reported a significant correlation between Tc-99m MIBI accumulation and Pgp expression in immunohistochemistry in several types of cancer.[3,29,30] Also, a reduction in the apoptotic index and marked overexpression of Bcl-2 failed to accumulate Tc-99m MIBI *in vivo*.[31] The cationic charge and lipophilicity of Tc-99m MIBI, mitochondrial and plasma membrane potentials of tumor cells, and cellular mitochondrial content can all play significant roles in the tumor's uptake of this agent, or the uptake may be caused by indirect phenomena such as increased tumor blood flow, tumor necrosis, metabolic demand, and vascular permeability.[32,33] It has recently been reported that Tc-99m MIBI is a substrate for Pgp and MRP, and thus it is extruded from cell like chemotherapy drugs.[8,34] The retention of Tc-99m MIBI in cells depends on the expressions of Pgp and MRP, which function as ATP-dependent efflux pumps for many cytotoxic substances, most of which fare lipophilic cations. Furthermore, in experimental tissue culture studies in tumors suggested that, high levels of anti-apoptotic protein Bcl-2 which are located in the outer mitochondrial membrane impair the mitochondrial membrane potential by reducing the release of cytochrome C and inhibit influx of various chemotherapeutic agents across the cell membrane.[35] High levels of Bcl-2 have been found in a wide variety of human cancers and correlate with relative resistance to current chemotherapeutic regimens and radiotherapy.[36] In our study, Tc-99m MIBI was accumulated in tumor regions of all patients independent of tumor size. Changes in the uptake of MIBI in the early phase of apoptosis obtained by trifluoperazine

Table 1: Clinical and scintigraphic data of 23 patients with advanced NCLC

Patient number	Age	Gender	Tumor size (cm)	Before trifluoperazine			After trifluoperazine		
				ER1	DR1	WR1	ER2	DR2	WR2
1	56	Male	10	1.48	1.23	16.89	1.32	1.30	1.52
2	71	Male	5	1.50	1.26	16.00	1.58	1.42	10.13
3	75	Male	7	2.10	1.88	10.48	2.57	2.10	18.29
4	61	Male	5	2.21	1.71	22.62	2.44	1.65	32.38
5	47	Female	5	2.14	1.89	11.68	1.87	2.02	−8.02
6	47	Male	2.5	1.57	2.01	−28.03	1.76	1.76	0.00
7	73	Male	6.5	2.32	2.05	11.64	2.62	2.54	3.05
8	70	Male	4.5	1.56	1.38	11.54	2.30	1.85	19.57
9	53	Male	7	1.52	1.48	2.63	1.59	1.38	13.21
10	76	Male	6	1.70	1.23	27.65	1.54	1.44	6.49
11	73	Female	2	1.23	1.19	3.25	1.45	1.12	22.76
12	52	Male	5	1.43	1.38	3.50	1.52	1.40	7.89
13	46	Male	7	1.53	1.51	1.31	1.38	1.29	6.52
14	59	Male	8	2.53	2.21	12.65	2.49	2.25	9.64
15	60	Female	3	1.52	1.20	21.05	1.50	1.45	3.33
16	78	Male	6	1.52	1.23	19.08	1.65	1.49	9.70
17	56	Male	6	1.62	1.50	7.41	1.64	1.58	3.66
18	37	Male	2	2.62	2.11	19.47	2.17	1.98	8.76
19	52	Male	5	1.86	1.65	11.29	1.93	1.82	5.70
20	61	Female	6	1.75	1.58	9.71	1.78	1.62	8.99
21	53	Male	4	1.73	1.56	9.83	1.78	1.63	8.43
22	61	Male	6	2.27	2.03	10.57	2.15	1.95	9.30
23	56	Female	7	1.85	1.43	22.70	1.87	1.69	9.63

ER:Early ratio, DR: Delayed ratio, WR: Washout rate, NCLC: Nonsmall cell lung cancer

Table 2: Tc-99m MIBI uptake ratios and WRs before and after administration of trifluoperazine

	Tc-99m MIBI uptake (mean±SD)		
	ER	DR	WR
Before trifluoperazine	1.81±0.38	1.60±0.33*	11.08±11.02
After trifluoperazine	1.87±0.40	1.68±0.34*	9.17±8.26

*P=0.039. SD: Standard deviation, ER: Early ratio, DR: Delayed ratio, WRs: Washout rates, MIBI: Sestamibi

may be indicative of Bcl-2 expression or Pgp expression in tumor cells.

For inhibition of MDR, MDR modulators have been suggested to reverse Pgp-mediated drug resistance. Since no MDR modulators applicable to regular clinical use have been identified so far, the search is still on. Piwnica-Worms *et al.* have demonstrated that after administration of drugs that can inhibit the activity of Pgp, such as verapamil and cyclosporin, the uptake of Tc-99m MIBI is increased about 10 times in cells with low expression of Pgp.[8] Additionally, phenothiazines can strongly influence biophysical properties of one-component lipid bilayers as well as model membranes containing cholesterol-enriched microdomains.[37] Trifluoperazine was one of the first MDR modulators tested in clinical trials, but the outcome was negative since the plasma concentrations of trifluoperazine achieved were so far too low to be effective.[38] Then inhibition of Pgp transport activity by trifluoperazine was confirmed in various cellular models.[39,40] A definite limitation of our study was that numbers of patients were relatively small. We could not perform immunohistochemical screening to all of our patients.

Easy availability and lower cost of Tc-99m MIBI scintigraphy compared with positron emission tomography, coupled with its high specificity and positive predictive value, makes it attractive as a diagnostic modality.

CONCLUSION

Tc-99m MIBI scan may have an important prognostic role by establishing whether individual patients will benefit from the use of Pgp inhibitors or Bcl-2 antagonists. Tc-99m MIBI scintigraphy with administration of trifluoperazine can predict which patients with advanced NCLC will respond chemotherapy + MDR modulators without a significant loss of life quality for patients.

Comparative functional imaging and pathology studies as well as functional imaging studies after administration of MDR modulators and Pgp inhibitors are required to further clarify a potential prognostic and therapy-guiding role of Tc-99m MIBI functional tumor imaging.

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Conflicts of interest
There are no conflicts of interest.

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