

Modulation of the Multidrug Resistance P-Glycoprotein: Detection with Technetium-99m-Sestamibi In Vivo

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Overexpression of the multidrug resistance (MDR1) P-glycoprotein (Pgp) has been documented in nearly all forms of human cancers and increased levels of Pgp in some tumors correlate with poor response to treatment. Technetium-99m-sestamibi has recently been validated as a Pgp transport substrate. Pgp is also normally expressed along the biliary canalicular surface of hepatocytes and the luminal side of proximal tubule cells in the kidney, while not expressed in heart. **Methods:** Focused on these organs with known Pgp status, we present the findings on ^{99m}Tc-sestamibi scintigraphy of three patients with refractory cancer who were imaged before and after administration of SDZ PSC 833, a second-generation, high-potency modulator of Pgp. **Results:** Before treatment with SDZ PSC 833, scintigraphy using ^{99m}Tc-sestamibi showed normal, prompt clearance of the radiotracer from the liver and kidneys relative to the heart. After administration of the Pgp modulator, ^{99m}Tc-sestamibi was selectively retained in the liver and kidneys. **Conclusion:** Hepatobiliary and renal clearance of ^{99m}Tc-sestamibi are Pgp-mediated, and inhibition of Pgp transport in these organs can be successfully imaged using ^{99m}Tc-sestamibi in patients. Similar results might be expected with this and related radiopharmaceuticals for functional imaging of Pgp transport and modulation in tumors.

Key Words: multidrug resistance; P-glycoprotein, technetium-99m-sestamibi

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Resistance of malignant tumors to chemotherapy is a major cause of treatment failure (1-3). One mechanism of multidrug resistance (MDR) in tumors is increased expression of a transmembrane glycoprotein, P-glycoprotein (Pgp), the product of the MDR1 gene (4,5). Pgp functions as an energy-dependent efflux pump for reducing intracellular concentrations of chemotherapeutic agents that are structurally and functionally diverse. Doxorubicin, etoposide, paclitaxel and the *Vinca* alkaloids are among the compounds in the MDR phenotype (3,6). By transporting cytotoxic agents out of cells, Pgp is thought to render tumors resistant to chemotherapy. Reversal of MDR by nontoxic agents that block the transport activity of Pgp has been an important target of pharmaceutical development (7). When co-administered with a cytotoxic agent, these agents, known as MDR modulators, enhance net accumulation of cytotoxic compounds within tumor cells. Additionally, in many different tumors, expression of Pgp and related transporters [e.g., multidrug-resistance-associated protein (MRP), (8)] are important prognostic indicators, and increased levels of Pgp and MRP are found in tumor biopsies from relapsing cancer patients (9-11). The MDR1 gene product is also expressed in normal human cells in a tissue-specific manner, including on the biliary canalicular surface of hepatocytes and the brush border of renal

proximal tubules (12-14). Although the physiological function(s) of MDR1 Pgp is unclear, it appears to be involved in secretion of xenobiotics into the intestine and urine.

Technetium-99m-sestamibi, a lipophilic cationic radiotracer, was originally designed for imaging of myocardial perfusion (15). Recently, this radiopharmaceutical has been validated as a transport substrate for Pgp in cultured multidrug-resistant rodent (16-18) and human tumor cells (16,19), as well as in cells overexpressing the recombinant human MDR1 gene (20). Accumulation of ^{99m}Tc-sestamibi in these cells is inversely proportional to the level of Pgp expression. In rodent models, faster clearance of this radiopharmaceutical is observed in tumors that express Pgp compared with malignancies that do not express the MDR1 gene product (16,17). Preliminary scintigraphic data in patients with breast cancer demonstrate that ^{99m}Tc-sestamibi washout rates from breast cancers overexpressing MDR1 Pgp are threefold faster than those from cancers not expressing elevated levels of the transporter (21). An important extension of these studies would be use of ^{99m}Tc-sestamibi to directly identify modulation of Pgp transport function in humans.

In this report, we present three patients in whom Pgp function in normal organs was assessed with ^{99m}Tc-sestamibi in the absence or presence of SDZ PSC 833 (Novartis (Sandoz) Pharmaceuticals Corp., E. Hanover, NJ), a high-potency, second-generation modulator of MDR Pgp. The cases presented here demonstrate the potential of functional imaging to monitor therapy with MDR modulators in human tissues.

CASE REPORTS

Scintigraphic studies were obtained in three patients (one each with invasive ductal breast carcinoma, serous cystadenocarcinoma of the ovary and adenocarcinoma of the lung, respectively) who were enrolled in an institutionally-approved Phase I clinical trial with paclitaxel and SDZ PSC 833 for recurrent, refractory malignancy.

Whole-body dual-camera scintigraphy was performed on two consecutive days. The first study was performed without the MDR modulator, while the second examination was done after administration of SDZ PSC 833. On each day, ^{99m}Tc-sestamibi was prepared according to the manufacturer's recommendations, and approximately 20 mCi of the tracer were administered intravenously by slow bolus injection. Images were obtained at 15-30 and 60-90 min postinjection. Scintigraphy was performed with a low-energy, all-purpose collimator, an energy window of 140 keV \pm 20% and a scan speed of 15 cm/min. Approximately 2.5 M

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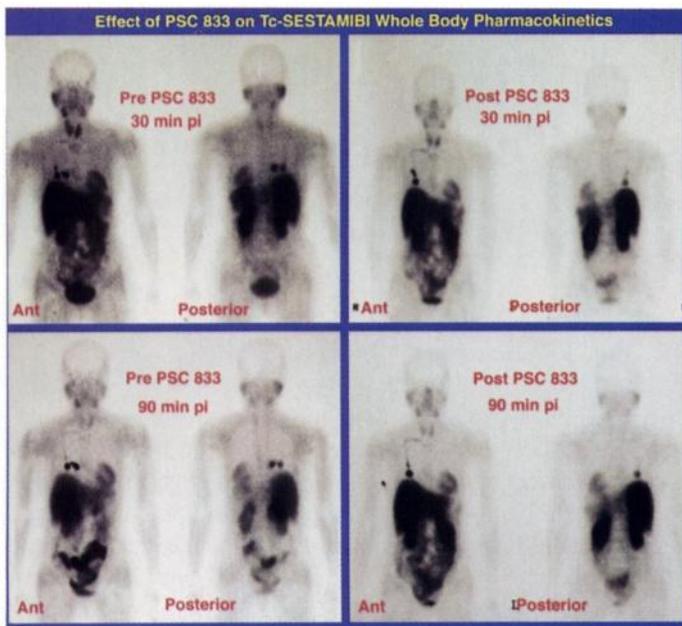


FIGURE 1. Inhibition of normal Pgp function in the liver and kidneys in a 57-yr-old woman. Without SDZ PSC 833, anterior and posterior planar images 30 min (left, top) and 90 min (left, bottom) after administration of ^{99m}Tc -sestamibi show clearance of radiotracer from liver and kidneys. On the 90-min image, activity in these organs is comparable to that in the heart. Only a small amount of radiopharmaceutical is seen in the bladder on the 90-min image because the patient voided. Following administration of SDZ PSC 833 (right, top/bottom), retention of ^{99m}Tc -sestamibi is seen in the liver and kidneys on both images. Activity in the liver and kidneys remains greater than the heart on the 90-min image. The patient did not void between the 30- and 90-min images, so the trace amount of activity in the bladder further reflects decreased excretion of ^{99m}Tc -sestamibi by the kidneys due to modulation of Pgp. Activity over the right hemithorax is in a central venous catheter.

counts were collected for anterior and posterior images with a digital matrix size of 1024×382 . Uptake and clearance of ^{99m}Tc -sestamibi in liver and kidneys were assessed qualitatively by visual inspection relative to the heart, a non-Pgp expressing organ.

All patients received 5 mg/kg of SDZ PSC 833 orally every 6 hr \times 4 doses (two patients) or \times 5 doses (one patient) before the second imaging session with ^{99m}Tc -sestamibi. Whole blood levels of SDZ PSC 833 were determined by the Abbott TDx CsA monoclonal whole blood assay (22). In two of three patients, blood samples were obtained 2–3 hr after the fourth or fifth dose of SDZ PSC 833, contemporaneous with scintigraphy. In the third patient, samples were drawn at a concordant time as scintigraphy but during the previous cycle on protocol. Technetium-99m-sestamibi imaging was performed within 1–2 hr of the fourth or fifth dose of SDZ PSC 833, at which time blood concentrations of SDZ PSC 833 were between 2705 and 3814 ng/ml (2.3–3.2 μM). After pretreatment with SDZ PSC 833 and following injection of ^{99m}Tc -sestamibi, patients also received 40% or 50% of a 175 mg/m² dose of paclitaxel per protocol administered intravenously over 3 hr.

In all patients, laboratory tests of renal (BUN and serum creatinine) and hepatic function [total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT)] performed within 1 wk of the ^{99m}Tc -sestamibi examination were normal: BUN (8–25 mg/dl), creatinine (0.7–1.7 mg/dl), total bilirubin (0.3–1.1 mg/dl), AST (11–47 IU/liter) and ALT (7–53 IU/liter). No patient had liver or renal metastases by computed tomography. Between the first and second days of ^{99m}Tc -sestamibi imaging, the only new drug received by any patient was SDZ PSC 833.

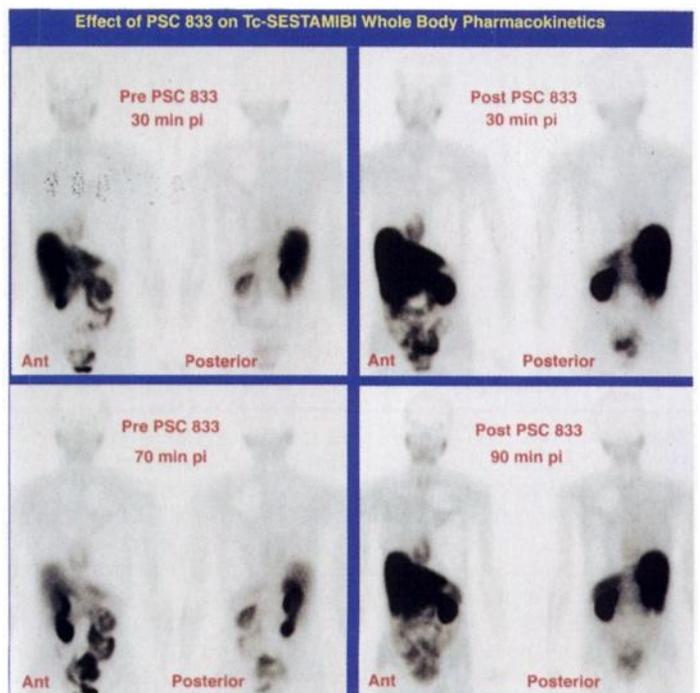


FIGURE 2. Effect of SDZ PSC 833 on pharmacokinetics of ^{99m}Tc -sestamibi in a 61-yr-old woman. Anterior and posterior planar images obtained without SDZ PSC 833 at 30 min (left, top) and 70 min (left, bottom) after injection of ^{99m}Tc -sestamibi show prompt clearance of radiotracer from liver and kidneys. The patient voided before the 70-min image, accounting for the minimal activity in the bladder. After administration of SDZ PSC 833, images at 30 (right, top) and 90 min (right, bottom) depict retention of radiotracer in liver and kidneys.

Patient 1

ES is a 57-yr-old woman with Stage IIIC poorly differentiated serous cystadenocarcinoma of the ovary. She was initially treated with surgery and carboplatin and cyclophosphamide chemotherapy. Upon recurrence of disease, she received combination chemotherapy which included paclitaxel and doxorubicin. Computed tomography of the abdomen and pelvis obtained on the same day as initial imaging with ^{99m}Tc -sestamibi showed multiple sites of disease within the abdomen and pelvis, including masses adjacent to the descending colon and cecum, a presacral mass and a retroperitoneal lymph node. The largest lesion was a 2 \times 2-cm mass adjacent to the descending colon.

Scintigraphy performed prior to administration of SDZ PSC 833 showed prompt clearance of ^{99m}Tc -sestamibi from the liver and kidneys between the 30- and 90-min postinjection images (Fig. 1; left, top and bottom). Following SDZ PSC 833 treatment, images obtained the following day demonstrated retention of the radiopharmaceutical in the liver and kidneys (Fig. 1; right, top and bottom). The images were evaluated qualitatively by comparison to the previous study and the heart, a non-Pgp expressing organ. The known metastases in the abdomen and pelvis were not detected on these ^{99m}Tc -sestamibi studies using planar techniques.

Patient 2

PH is a 47-yr-old woman with Stage IIB invasive ductal carcinoma of the left breast treated with mastectomy and cyclophosphamide, doxorubicin and 5-fluorouracil chemotherapy. Subsequently, she developed bone metastases and was treated with radiation and chemotherapy including etoposide.

The initial examination with ^{99m}Tc -sestamibi showed prompt clearance of the radiotracer from the liver and kidneys. On the second study with ^{99m}Tc -sestamibi, decreased clearance of the radiopharmaceutical from these organs was seen after administration of SDZ PSC 833.

Patient 3

TK is a 61-yr-old woman with Stage IIIB adenocarcinoma of the left lung who had progression of her disease during treatment with cisplatin and etoposide chemotherapy. Computed tomography of the chest performed 3 days before the ^{99m}Tc -sestamibi examination showed a 2×2 -cm tumor near the left pulmonary hilum, collapse of the left lung (except for the superior segment of the lower lobe and part of the lingula) and a large left pleural effusion.

Prompt clearance of ^{99m}Tc -sestamibi from the liver and to a slightly lesser degree from the kidneys was observed on images without SDZ PSC 833, while these organs retained the radiopharmaceutical following administration of the MDR modulator (Fig. 2). The left lung tumor was visualized by ^{99m}Tc -sestamibi scintigraphy but not further addressed in this study.

DISCUSSION

Reversal of MDR-mediated by Pgp has been achieved in experimental systems using a diverse group of drugs, including cyclosporin A and verapamil (7). These first-generation modulators had limited clinical efficacy because toxic side effects occurred before reversal of multidrug resistance could be achieved (23,24). However, Phase I/II clinical trials have begun with second-generation, high-potency modulators of Pgp. Reversal of MDR in patients with refractory lymphomas was recently reported in a clinical trial using dexverapamil, perhaps the least potent of the second-generation modulators (25). Another of the second-generation modulators is SDZ PSC 833, a nonimmunosuppressive analog of cyclosporins A and D (26). In studies of tumor cell lines, SDZ PSC 833 is 10- to 20-fold more potent than cyclosporin A as a modulator of MDR (27). The patients described in this report were imaged with ^{99m}Tc -sestamibi during a Phase I clinical trial with this modulator.

At the time of imaging, SDZ PSC 833 blood concentrations of 2.3–3.2 μM were found in our patients. In various cells that express clinically relevant (low to modest) levels of Pgp, this modulator inhibits Pgp-mediated transport of ^{99m}Tc -sestamibi with a half-maximal effective concentration (EC_{50}) in the submicromolar range for MatB Adr^R cells (17) and 80 nM for V79 cells (18). Drug levels in our patients exceeded by greater than 10-fold these EC_{50} values for SDZ PSC 833-mediated inhibition of ^{99m}Tc -sestamibi transport determined *in vitro* (18). Thus, protocol concentrations of SDZ PSC 833 would be expected to produce maximal inhibitory effects on transport mediated by Pgp.

With focus on the liver and kidneys for these patients, images obtained without SDZ PSC 833 showed prompt clearance of ^{99m}Tc -sestamibi from these organs between 30 min and 60–90 min. In all patients, after administration of the Pgp modulator, retention of the radiopharmaceutical in the liver and kidneys was readily observed on the later images. No new drugs other than SDZ PSC 833 were administered between the first and second imaging study, and none of the patients had abnormal hepatic or renal function. Retention of ^{99m}Tc -sestamibi in these organs is consistent with inhibition of Pgp normally found along the biliary surface of hepatocytes and in the proximal tubules of the kidneys. Decreased clearance of other compounds that are transport substrates for Pgp has been documented in Phase I clinical trials with cyclosporin A. For example, renal clearance of doxorubicin was reduced by 32% in the presence of cyclosporin A and nonrenal clearance decreased by 35% (28). Similar decreases in clearance of etoposide (38% and 52% reductions in renal and nonrenal clearance, respectively) were seen when this drug was used in combination with cyclosporin A as a modulator of Pgp (29). In these clinical trials, reversible hyperbilirubinemia commonly occurred in patients during mod-

ulation of Pgp by cyclosporin A (30). These data support the hypothesis that modulation of normal Pgp function accounts for the retention of ^{99m}Tc -sestamibi in the liver and kidneys after administration of SDZ PSC 833.

By extension of these findings, we envision that ^{99m}Tc -sestamibi or other ^{99m}Tc based lipophilic cationic radiopharmaceuticals (31,32), including novel Q-complexes (33), also could be used to monitor the therapeutic efficacy of MDR modulators in tumors that have functional Pgp. Increased expression of Pgp and related transporters (MRP) has been correlated with a poor prognosis in some tumor types (9–11). Technetium-99m-sestamibi provides an *in vivo* functional assay for the presence of Pgp activity in tumors. These data may not be reliably obtained through amplification of MDR1 transcripts by polymerase chain reaction or detection of the presence or absence of the protein by immunohistochemistry of tumor specimens, respectively. Expression and function of Pgp are not always directly correlated in malignancies. For example, in a panel of acute myeloblastic leukemia cell lines, mature cells expressing high levels of Pgp as detected by specific monoclonal antibodies did not transport known Pgp substrates, while immature cell lines with lower levels of Pgp expression showed transport activity (34). By detecting functional Pgp, imaging with ^{99m}Tc -sestamibi may identify those tumors in which the MDR1 gene product is physiologically active as an efflux pump for chemotherapeutic agents. These patients could potentially benefit from treatment with modulators if cytotoxic agents in the MDR phenotype are inherent to their treatment regimen. Imaging also could be used to tailor pharmacokinetics and monitor inhibition of Pgp function during modulator therapy before administration of cytotoxic drugs.

Patient 1 illustrates a potential limitation of ^{99m}Tc -sestamibi for functional imaging of MDR. Because ^{99m}Tc -sestamibi is significantly cleared by the liver with excretion into the gallbladder and intestinal tract, high background activity is present in the abdomen. This activity potentially could obscure tumor deposits in the abdomen and pelvis. Routine use of SPECT imaging to localize known tumor deposits may decrease this problem. Because successful modulation of Pgp causes retention of radiopharmaceutical in the liver and kidneys, the enhanced background activity of ^{99m}Tc -sestamibi in these organs after modulator therapy also could limit detection of Pgp in known hepatic or renal tumors. However, tumors outside the abdomen and pelvis should not be obscured by this effect. Furthermore, the 30- and 60–90-min imaging times were chosen for the current pilot studies on the basis of known organ pharmacokinetics of ^{99m}Tc -sestamibi (15) and estimates of how *in vitro* cell washout kinetics may translate into humans. Other pilot studies with breast cancer patients have been performed with dynamic sequential imaging for 45 min postinjection followed by several spot images at 2 and 4 hr (21) which may improve detection of rapid as well as prolonged washout compartments and determination of efflux rate constants. The optimum imaging sequence for MDR applications remains to be validated.

CONCLUSION

These cases provide direct evidence that the hepatic and renal excretion pathways of ^{99m}Tc -sestamibi are mediated by MDR1 Pgp and further indicate that modulation of Pgp transport function can be detected in humans using this radiopharmaceutical. Functional imaging with ^{99m}Tc -sestamibi or related radiopharmaceuticals may potentially provide clinically important information about the Pgp status of tumors and successful reversal of transporter activity following modulator therapy.

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Iodine-131 Therapy in Sporadic Nontoxic Goiter

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The effect of radioiodine in the treatment of nontoxic goiter is seldom evaluated quantitatively. The aim of this study was threefold: (a) to assess the effect of ^{131}I on goiter volume, (b) to establish a relationship between CT volume reduction and the amount of radioactivity taken up by the thyroid and (b) to assess the precision of scintigraphic thyroid volume measurements. **Methods:** In 27 patients with sporadic nontoxic goiter, the thyroid volume was estimated from a [^{99m}Tc]pertechnetate scintigram. Two different models (cylinder model and surface model) were applied. The ^{131}I dosage varied between 507 and 3700 MBq. In all patients, noncon-

trast CT scanning of the neck was performed before therapy and 1 yr after therapy. **Results:** The mean CT thyroid volume before therapy was 194 ± 138 ml. A reduction was obtained in all patients and averaged $34\% \pm 17\%$. The volume reduction measured by CT correlated well with the amount of ^{131}I in the thyroid ($r = 0.70$). In thyroids larger than 200 ml, both scintigraphic volume estimation methods were imprecise. For smaller volumes, the surface model was superior. Hypothyroidism developed in 14% of the patients. No other side effects occurred. **Conclusion:** Iodine-131 therapy for volume reduction in nontoxic goiter is a safe and effective treatment. For scintigraphic estimation of thyroid gland volumes smaller than 200 ml, the surface model is preferred.

Key Words: nontoxic goiter; radioiodine therapy; volume reduction

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