INVITED COMMENTARY

What Can We Expect from MDR Breast Cancer Imaging with Sestamibi?

The outcome of cancer patients after cytotoxic chemotherapy is strongly influenced by a multifunctional cellular system termed multidrug resistance (MDR) (*1*). In spite of recent advances in cancer therapy, MDR remains a major cause of treatment failure. MDR describes the ability of the cell to pump out a variety of structurally unrelated anticancer agents such as anthracylines (doxorubicin, daunorubicin), vinca alkaloids (vincristine, vinblastine), epipodophyllotoxins (etoposide), and taxanes (paclitaxel) (*2*). Some tumors have natural intrinsic resistance and are resistant to many of the most active cytotoxic drugs. This group includes cancers of the kidney, adrenal, pancreas, liver, and colon (*3,4*). During treatment of recurrence, other tumors that are initially sensitive to chemotherapeutic agents often develop acquired resistance to a broad spectrum of cytotoxic drugs, even though these drugs were not administered during the initial cycles of chemotherapy (*5*). Acquired resistance and intrinsic resistance are associated with a poor prognosis, and it is estimated that MDR plays a major role in up to 50% of all cancer cases (*4*). In clinical practice, the presence of MDR is suspected if a patient does not respond to the actual chemotherapeutic regimen. This concept is disadvantageous for the patient and the course of disease and can be accepted only if the appropriate alternatives of in vivo testing of cytotoxic agents are lacking.

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The nuclear medicine community has suggested the use of ^{99m}Tc-sestamibi (hexakis-2-methoxyisobutylisonitrile) scintigraphy as a noninvasive method of in vivo imaging of MDR because it has been shown that sestamibi is a substrate of the membrane-associated permeability glycoprotein (P-glycoprotein [Pgp]), which is considered to be the main actor in MDR (*6,7*). Pgp is encoded by the *mdr1* gene, which is located on chromosome 7q21-1, and has a molecular weight of 170 kDa. Pgp is a transmembrane protein transporter and has a cylindric form with a diameter of approximately 5 nm (*7*). It regulates the efflux of >100 agents, some of which are cytotoxic substrates. MDR in mammalian cells and tumors is associated with overexpression of Pgp, enabling the cell to pump out chemotherapeutic agents. In vitro studies have shown that the transport of sestamibi out of the cell is correlated with the expression of Pgp, and the Pgp-mediated efflux of sestamibi is inhibited by several agents known to be modulators of MDR (*8–12*). Duran Cordobes et al. (*9*) observed that in breast cancer cells, in the presence of verapamil (known to reverse the effect of Pgp), ^{99m}Tc-sestamibi uptake increased by a factor of 2 in Pgp-negative cells but increased by a factor of 12 in cells expressing high Pgp levels. Piwnica-Worms et al. (*10*) showed a sestamibi-enhancing effect also for the Pgp modulators cyclosporin A, quinidine, prazosin, and SDZ PSC 833. The authors concluded that transport analysis with ^{99m}Tc-sestamibi is a sensitive assay for the detection of functional expression of Pgp levels and for the quantitative characterization of transporter regulation in the presence of Pgp modulators.

Several in vivo studies confirmed these in vitro results (*13–16*). In a series of 15 patients with suspicion of primary breast cancer, Moretti et al. (*14*) correlated the results of scintimammography with ^{99m}Tc-sestamibi with the presence of Pgp in the tumor. In a group of 13 malignant lesions, all true-positive scintigrams corresponded to a Pgp-negative tumor. One of 3 sestamibi-negative breast cancers revealed high Pgp expression, indicating that decreased sestamibi accumulation may correlate with resistance to chemotherapy. Del Vecchio et al. (*13*) studied 30 patients with untreated breast carcinomas and correlated the sestamibi efflux rates calculated from decay-corrected time–activity curves over the tumor with Pgp levels measured in the tumors. Although all 30 carcinomas showed high scintigraphic uptake of sestamibi, 10 of these cancers revealed a high Pgp concentration (defined as 5 times more than that of benign breast lesions) and only 20 carcinomas showed a low mean Pgp concentration comparable with that of benign lesions. However, in the group with strong Pgp expression, the sestamibi efflux from tumors was almost 3 times as high as that in the group with low Pgp expression. The authors concluded that the efflux rate of sestamibi may be used for in vivo identification of MDR in untreated breast cancer patients. The same group performed a further analysis of untreated breast cancer patients and correlated the fractional retention of sestamibi with the Pgp expression (*15*). This fractional retention was calculated as the ratios of early (10 min) and delayed (60 and 240 min) region-of-interest imaging of the tumor in decay-corrected counts per pixel. The fractional sestamibi retention was significantly higher in tumors

with low Pgp levels compared with that measured in tumors with high Pgp levels, and the authors proposed sestamibi scintigraphy as a potential method to identify patients with a high probability of developing MDR.

In this issue of *The Journal of Nuclear Medicine*, Mubashar et al. (*17*) present data on 20 patients with untreated breast cancer undergoing early (20 min) and late (120 min) scintimammography with sestamibi. In addition to this first imaging series, the same imaging procedure was repeated in each patient after a 3-d treatment with the MDR modulator toremifene. This study also confirmed a positive correlation between staining intensity of Pgp and the tumor-to-background ratio (T/B) of early and late tumor imaging without toremifene. Because no clear cutoff point between the T/B of Pgp-positive and Pgp-negative tumors could be detected, the authors found the change in T/B of early and late imaging to be a better predictor of Pgp status. Sensitivity of this parameter was 100% (11/11 highly positive tumors) and specificity was 67% (6/9 negative or nearly Pgp-negative tumors).

These data provide further evidence that sestamibi imaging of breast cancer patients can give in vivo information about the functional expression of Pgp and may serve as a valuable tool in deciding whether a high probability of MDR exists and whether alternative chemotherapy regimens should be chosen. The following advantages of this form of in vivo testing can be expected:

- The patient does not have to undergo potentially useless chemotherapy, which can be accompanied by severe side effects and lead to progression of disease. Chemotherapy induces severe side effects such as thrombopenia and leukopenia, diarrhea, and nausea (*18,19*). The lethality of chemotherapy in breast cancer patients depends on the stage of disease and the therapeutic regimen.
- Core biopsy, which is an invasive procedure, is unnecessary.
- In vivo testing should reflect the functional status of Pgp in a better way than that of in vitro testing. This can be proposed because of methodologic problems of Pgp detection (protein or messenger RNA related) by polymerase chain reaction and because of heterogeneous expression of Pgp within a tumor giving false-positive and false-negative results. Heterogeneity of Pgp expression determined by immunohistochemical studies may yield confounding results (*20*). However, cellular in vitro chemosensitivity assays such as adenosine triphosphate (ATP) tumor chemosensitivity assays are being investigated in phase II and phase III trials and may be introduced in clinical routine within the next several years.
- Fujii et al. (*21*) observed a high correlation between the retention index of sestamibi in breast carcinomas and the chemosensitivity of surgical specimens to anthracyclines such as doxorubicin and epirubicin. However, the in vitro testing of histopathologic specimens by different cytotoxic agents to exclude ineffective drugs may alter the properties of the tested cells and, therefore, not represent the original functional status of the tumor.

Several points must be further considered and studied:

- The method of in vivo testing of MDR by scintigraphy must be standardized before its application in clinical settings. The question of which parameter of sestamibi scintigraphy correlates best with functional Pgp expression and MDR must be answered first. There is evidence that the measurement of sestamibi uptake in the tumor alone is not as reliable as parameters such as the efflux rate or the fractional retention obtained by dynamic imaging. Del Vecchio et al. (*13,15*) and Mubashar et al. (*17*) report that these parameters are reliable and can be generated by comparing early (10–20 min) and late (60–240 min) imaging. Although the acquisition parameters of scintimammography and scintigraphy with ^{99m}Tc-sestamibi can be considered as standardized (*22,23*), the optimal time point for late imaging has yet to be determined.
- Kostakoglu et al. (*20*) prospectively studied 30 breast cancer patients and compared 3 different subgroups scored in relation to the intensity of Pgp expression. The authors found that the correlation between sestamibi T/B and Pgp expression in the intermediate group (strong to weak Pgp expression) was less marked than that in the group with strong or weak to no expression. This is in accordance with the findings of Mubashar et al. (*17*), who showed that a single measurement of the T/B is of limited reliability because an overlapping between the uptake values of Pgp-positive and Pgp-negative tumors exists. This is the result of heterogeneity of Pgp expression. In these patients, the functional relevance of Pgp expression is difficult to estimate by immunohistochemistry and a single sestamibi uptake measurement. Again, sestamibi scintigraphy based on serial image acquisition (efflux rate, fractional retention) offers the unique possibility to deliver in vivo data about the functional impact even of heterogeneous Pgp distribution within a tumor.
- Although Pgp can be considered to be predominantly responsible for MDR, additional factors can contribute to this phenomenon. It is known that the MDR-associated protein (MRP) and the breast cancer resistance protein that are members of the ATP-binding-cassette superfamily of membrane transporters also function as en-

ergy-dependent efflux pumps of several structurally diverse chemotherapeutic agents (*24*). In vitro studies showed that sestamibi is a substrate not only of Pgp but also of MRP (*25–27*). Kao et al. (*28*) studied 48 patients with infiltrating breast cancer to evaluate the relationship between sestamibi uptake (T/B) during early imaging and immunohistochemical analysis of Pgp and MRP expression. Their data show that both transport systems (Pgp and MRP) function as efflux pumps for sestamibi, even if Pgp plays the major role.

- So far, no studies have investigated the prognostic impact of scintimammography or scintigraphy with sestamibi on the clinical development of breast cancer patients after chemotherapy. Ideally, a 2-arm study would look at a first group receiving standard chemotherapeutic regimen and compare these results with those of a second group receiving chemotherapy after stratification for MDR by sestamibi scintigraphy. This would mean that, in the case of a sestamibi-related high probability of MDR, an alternative chemotherapeutic regimen would be chosen. The clinical outcome of both groups would then be compared to determine the prognostic value of in vivo sestamibi testing before a single treatment.

Two research groups following a different, MDR-unrelated, concept have performed serial scintigraphies with ^{99m}Tc-sestamibi before chemotherapy and after each cycle of treatment (*29,30*). Both groups have monitored patients with locally advanced breast carcinoma after neoadjuvant chemotherapy by radionuclide imaging and concluded that ^{99m}Tc-sestamibi scintigraphy is an effective tool for therapy monitoring, being superior to mammographic and clinical evaluation. The disadvantage of this concept still is that chemotherapy itself, with all of its side effects, is used as a method of in vivo testing (*31*). Imaging of patients with radiolabeled, chemotherapeutic agents would be another alternative of MDR in vivo testing and allow a direct estimation of the cellular drug concentration.

Several agents, such as calcium-channel blockers (e.g., verapamil), calmodulin antagonists (e.g., phenothiazine antipsychotics), cyclosporins (e.g., cyclosporin A), and steroids, have an antagonizing effect on the MDR mechanisms (*2*). Many in vitro studies have shown that these so-called chemosensitizers are able to inhibit the MDR efflux pumps and lead to a higher intracellular accumulation of cytotoxic agents and Pgp substrates such as sestamibi and tetrofosmin (*9–11,32*). These promising data stimulated interest in the research community that administration of MDR modulators would be capable of enhancing the cytotoxic effect of chemotherapy in drug-resistant patients. However, the therapeutic effectiveness of pharmacologic reversal of MDR was low for solid tumors in animal studies. Tunggal et al. (*33*) observed that a high cellular concentration of a solid tumor decreased markedly the effect of reversal agents. Another limiting factor preventing successful treatment with chemosensitizers was the presence of strong side effects of modulator agents such as verapamil or cyclosporin A. These agents have to be administered in high concentrations to expect an antagonizing effect. Therefore, the aim of current studies is to identify agents that have acceptable characteristics to be used for patient treatment.

Toremifene is an antiestrogen related to tamoxifen, and both are used in the antihormonal treatment of breast cancer patients. Independent of its effect on estrogen receptors, toremifene has MDR-modulating properties (*34*). In vitro studies gave evidence that toremifene increases the intracellular accumulation of vinblastine and doxorubicin in breast cancer cells by inhibiting the Pgp-mediated MDR (*34–38*). Because of a significant binding of toremifene to serum proteins (α-1-acid glycoprotein), relatively high doses of the agent are necessary to reach therapeutically efficient concentrations in patients (*39*). Recently, phase I and phase II trials assessed the tolerability of a short course of treatment with high doses of toremifene (*40*) and showed that high-dose toremifene treatment in combination with vinblastine was well tolerated. Furthermore, it seems possible to achieve in vivo the toremifene concentrations required for MDR reversal. Other combinations of MDR modulators and chemotherapy agents are also being investigated to obtain toxicity data (*41,42*).

Mubashar et al. (*17*) present data on 20 breast cancer patients who were treated with toremifene using the 3-d protocol with doses of 780 mg/d. Early and late sestamibi imaging was performed before and after toremifene treatment to evaluate the MDR-modulating effect of the agent. The authors observed no serious grade III or grade IV toxicity. One patient was withdrawn from the study because of diarrhea and 3 patients reported mild nausea and dizziness. When calculating the mean values of the T/B of scintimammography and comparing the values before toremifene with those after toremifene, unexpectedly, the authors did not find a significant increase of sestamibi accumulation. However, a strong relationship was found between Pgp positivity and the change in the T/B before and after toremifene treatment of late imaging in the same patient, indicating the MDR-inhibitory effect. Once again, these data provide evidence that evaluation of the intraindividual sestamibi dynamic is essential for valuable in vivo testing of MDR.

Furthermore, Mubashar et al. (*17*) also investigated the change of the T/B before and after toremifene in 2 different groups: patients with breast cancers showing no Pgp expression or weak Pgp expression and patients with breast cancers showing high Pgp expression. Although increasing sestamibi uptake was confirmed in the last group after toremifene, the other group had a totally unexpected decrease in T/B at 120 min, indicating that

toremifene itself has an inhibitory effect on sestamibi uptake if Pgp expression is low. This finding is in agreement with earlier observations showing that MDR modulators can also have competitive effects with chemotherapeutic agents (*2*). The data of Mubashar et al. stress the feasibility of sestamibi imaging as a method of in vivo testing not only for MDR but also for the effect of MDR-modulating agents. The authors conclude that the intracellular concentration of certain cytotoxic agents may be, similar to sestamibi, inhibited by the MDR modulator, which could then result in a reduced therapeutic efficacy. These propositions must be proven in clinical studies and would mean that in vivo testing by sestamibi scintigraphy during therapy with MDR modulators has to be correlated with response to chemotherapy and clinical outcome. Nuclear medicine research must address this promising issue in future projects to be able to introduce in vivo testing with sestamibi in clinical practice.

In summarizing the latest development of MDR imaging with sestamibi in breast cancer patients, 2 points seem to be essential: First, sestamibi in vivo testing for MDR in breast cancer patients delivers valuable results if dynamic acquisition protocols (e.g., early and late imaging) are used. Second, clinical studies that confirm the prognostic value of in vivo MDR testing before chemotherapy are necessary before this procedure is introduced into clinical routine.

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