Original Article

Utility of Technetium-99m Methoxyisobutyl Isonitrile Uptake Analysis for Prediction of the Response to Chemotherapy in Advanced and Relapsed Breast Cancer

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**Background:** Technetium-99m methoxyisobutyl isonitrile (Tc-SESTAMIBI) is a substrate of P-glycoprotein and multidrug-resistance associated protein in drug-resistant cells. To assess the clinical effectiveness of Tc-SESTAMIBI for predicting the chemotherapy response to treatment with anthracyclines and vinca alkaloids, we retrospectively evaluated the relationship between the accumulation of Tc-SESTAMIBI and the tumor response.

**Methods:** Thirteen patients, including 12 advanced cases and 1 relapsed case, were investigated, all of whom had been treated with anthracyclines or a vinca alkaloid regimen. The accumulation of Tc-SESTAMIBI was compared at 10 min and 2 h after Tc-SESTAMIBI administration. The relationship between the accumulation of Tc-SESTAMIBI and the tumor response following treatment with anthracyclines and vinca alkaloids was assessed.

**Results:** Eight of 13 patients responded to treatment with anthracyclines and vinca alkaloids, whereas 5 patients did not respond to treatment. At 10 min, 6 (75.0%) of the 8 responding patients had a high accumulation of Tc-SESTAMIBI, whereas 4 (80.0%) of the 5 non-responding patients had a low accumulation of Tc-SESTAMIBI. The overall predictive value was 76.9%. The relationship was not statistically significant (Fisher’s test). The difference in the decrease of accumulation of Tc-SESTAMIBI between 10 min and 2 h was not associated with tumor response to treatment in 6 of the responding patients with high accumulation. Two false negative cases and one false positive case were observed, suggesting the presence of another factor contributing to drug sensitivity in tumor response, such as apoptosis-related genes.

**Conclusions:** Assessment of the initial accumulation of Tc-SESTAMIBI can be a predictive marker of tumor response to treatment with anthracyclines and vinca alkaloids in patients with advanced and relapsed breast cancer. Further studies are required to explore other factors involved in the tumor response to treatment with anthracyclines and vinca alkaloids.


Key words: Breast cancer, Tc-SESTAMIBI, Anthracyclines, Vinca alkaloids, MDR
ated decrease in the intracellular concentration of chemotherapeutic drugs is thought to contribute to drug resistance in tumor cells. Recent reports indicate that Tc-SESTAMIBI is recognized as a transport substrate by P-gp and MRP expressed in MDR tumor cells, suggesting that Tc-SESTAMIBI enables quantitative characterization of the transport properties of P-gp and MRP in tumor cells. Based on these findings, we retrospectively investigated whether the accumulation of Tc-SESTAMIBI in tumors assessed using scintigraphy predicts the chemotherapeutic response to anthracycline and vinca alkaloid regimens in patients with advanced and relapsed breast cancer. Our findings indicate that the initial accumulation of Tc-SESTAMIBI predicts in part the chemotherapeutic response to treatment with anthracyclines and vinca alkaloids in patients, even in the presence of other factors involved in drug sensitivity.

**Patients and Methods**

**Patients**

Thirteen female patients (age 30-70 years) with breast cancer, including four cases with stage IIIb disease, and eight cases with stage IV disease according to the general rules for the clinical and pathologic recording of breast cancer by the Japanese Breast Cancer Society, and one relapsed case treated in our department between September, 1997 and August, 2000 were eligible for the analysis. The patients had primary breast cancer histologically confirmed by core needle biopsy or incisional biopsy, and all had bidimensional measurable lesions and were treated with anthracycline-based or vinca alkaloid chemotherapy regimens. In addition to histologic analysis, specimens underwent estrogen receptor (ER), progesterone receptor (PgR), and DNA ploidy analysis. Four stage IIIb patients received neoadjuvant chemotherapy before radical mastectomy, and seven stage IV patients also underwent mastectomy for local tumor control.

Informed consent for Tc-SESTAMIBI imaging was obtained from all patients before the examination. In brief, the procedures were explained to the patients as follows: First, it was explained that examination with Tc-SESTAMIBI is not yet established as a procedure for determining the chemotherapy regimen; Second, the examination using Tc-SESTAMIBI is not part of the chemotherapy protocol; Third, it was explained that the examination with Tc-SESTAMIBI is not mandatory, but based on previous reports, it seemed promising to investigate the clinical usefulness of Tc-SESTAMIBI imaging to determine whether the accumulation of Tc-SESTAMIBI predicts the tumor response to chemotherapy with anthracyclines and vinca alkaloids. Based on these explanations in terms of the current scientific significance and ethical considerations regarding Tc-SESTAMIBI imaging, we can retrospectively compare the accumulation of Tc-SESTAMIBI and the tumor response. Our final goal is to help develop personalized chemotherapy, and to contribute to improved survival in advanced and relapsed breast cancer. After this discussion, informed consent was obtained.

**Chemotherapy Regimen and Response Assessment**

The chemotherapy regimens included in this analysis were CEF (cyclophosphamide + epirubicin + 5-fluorouracil), CAF (cyclophosphamide + Adriamycin + 5-fluorouracil), and KW 2307 (vinorelbine). Treatment was conducted using the following dose and schedule. In the CAF and CEF treatment regimens, cyclophosphamide (200 mg/m²), epirubicin (30 mg/m²) and adriamycin (30 mg/m²) and 5-fluorouracil (500 mg/m²) were administered intravenously on days 1 and 8 of a 4-weeks cycle, while 5-fluorouracil was administered in a drip-infusion for 1 h at the same schedule. Medroxyprogesterone acetate (MPA) was orally administered at a dose of 600 mg/body/day. KW 2307, approved for use in phase II studies by the Institutional Review Board Committee at Hiroshima University on January 24, 1997 (Approval No. 00159), was given at a dose of 20 mg/m² weekly. Tumor response was assessed every 4 weeks after beginning treatment using standard response criteria. Complete response (CR) required total resolution of all measurable disease. Partial response (PR) was defined as a greater than 50% reduction in the sum of the products of the greatest diameters of measurable lesions. No change (NC) was diagnosed for all patients who had less than PR but no evidence of progressive disease (PD). Progressive disease was defined as an unequivocal increase of more than 25% in the sum of the products of measured lesions.

**Tc-SESTAMIBI Imaging**

Tc-SESTAMIBI (DuPont, Boston, MA) imaging was performed just prior to chemotherapy.