The use of $^{99m}$Tc-MIBI scanning in multiple myeloma

EB Tirovola, L Biassoni, KE Britton, N Kaleva, V Kouykin and JS Malpas

ICRF Department of Medical Oncology, St Bartholomew's Hospital, London; Department of Nuclear Medicine, St Bartholomew's Hospital, London, UK.

Summary

$^{99m}$Tc-MIBI, also called Sestamibi, is a safe and effective scanning agent in solid tumours. Its use in imaging lesions in multiple myeloma has been studied in 21 patients with either multiple myeloma (19/21) or monoclonal gammapathy of undetermined significance (MGUS) (2/21). $^{99m}$Tc-MIBI scanning was positive in 14 patients, 13 with active myeloma and one patient with MGUS showing possible transformation to a more accelerated phase. In seven patients $^{99m}$Tc-MIBI scanning was negative. In four of them, the result was unexpected, as they had the features of active myeloma. All four were either primarily or secondarily resistant to chemotherapy, with high total cumulative doses of doxorubicin. Overexpression of P-glycoprotein associated with multidrug resistance could be a factor, as it has been shown that $^{99m}$Tc-MIBI is actively eliminated from the cell by P-glycoprotein. With this assumption, sensitivity of the scanning technique in this series is 100%, and the specificity 88%. No toxicity was experienced by any patient. $^{99m}$Tc-MIBI scanning is a useful adjunct to the investigation of multiple myeloma, and may have potential as an in vivo test for multidrug resistance.

Keywords: $^{99m}$Tc-MIBI; myeloma; multiple drug resistance; bone marrow imaging

Technetium-$^{99m}$ 2 methoxy-isobutyl-isonitrile ($^{99m}$Tc-MIBI) is a tracer with gamma emission characteristics that was introduced in 1984 as an alternative to TI-201 for the study of myocardial perfusion. The agent gave satisfactory results and was well tolerated (Wackers et al., 1989). Clinical observations and laboratory information on the mechanism of uptake of $^{99m}$Tc-MIBI led to new proposals for its use in cancer patients.

In 1987, uptake of $^{99m}$Tc-MIBI by pulmonary metastases of thyroid cancer was described by Muller et al. (1987); since then, it has been studied in bronchial carcinomas (Muller et al., 1989), osteosarcomas (Hassan et al., 1989), brain tumours (Albuquerque et al., 1992), tumours of the nasopharynx (Kao et al., 1993), breast cancer (Khalkhari et al., 1994), parathyroid adenomas (Coakley et al., 1989) and lymphomas (Kostakoglu et al., 1992).

In 1994, Durie et al. first showed the increased uptake of $^{99m}$Tc-MIBI by bone lesions in patients with active multiple myeloma (MM). Those preliminary data were encouraging, and were confirmed by Malpas et al. and Unlu et al. in 1995. A potential advantage of $^{99m}$Tc-MIBI scan in predicting multi-drug resistance (MDR) has been suggested by some authors (Ballinger et al., 1995), since there is both in vivo and in vitro evidence that P-glycoprotein (which has been associated with MDR) is responsible for the elimination of MIBI from several types of malignant cells. There have been no clinical studies in myeloma patients to verify the assumption.

The role of $^{99m}$Tc-MIBI in the detection of MM in bone marrow has been examined with regard to reliability, sensitivity and toxicity, and compared with radiography as the standard reliable imaging technique. The potential use of $^{99m}$Tc-MIBI in the management of the disease, as a predictor of MDR, is discussed.

Patients, materials and methods

Twenty-one (21) patients of a median age of 62 years, with multiple myeloma (MM) (19/21) or monoclonal gammapathy of undetermined significance (MGUS) (2/21) were examined with technetium-$^{99m}$-2-methoxy-isobutyl isonitrile ($^{99m}$Tc-MIBI) scan, and the results were correlated with clinical, biochemical and radiological information on each patient.

A dose of 450 MBq of $^{99m}$Tc-MIBI was administered to each patient. After reviewing 10 min, 1, 4 and 24 h planar images, those done at 1 and 4 h after injection were obtained and evaluated in each patient. A Siemens Orbiter 75 gamma camera equipped with a low-energy, general purpose parallel-hole collimator linked to a Micas V computer (Park Medical) was used. Pulse height analysis was carried out with a 15% window on the peak energy of 140 keV for $^{99m}$Tc-MIBI. A posterior view of the pelvis was done for 600 000 counts; the other spot views, anteriorly and posteriorly of the body, were acquired with the same preset time. Physiological uptake of $^{99m}$Tc-MIBI was seen in the heart, thyroid and salivary glands, spleen, kidneys, bladder, lungs, skeletal muscle, liver, gall bladder, biliary system and both small and large intestines.

Criteria of assessment

All examinations were carried out by two nuclear medicine physicians who were unaware of the radiological findings. Results were considered concordant if the detected area of abnormal uptake of $^{99m}$Tc-MIBI matched the osteolytic lesion detected on skeletal survey.

In 2/21 patients magnetic resonance imaging (MRI) scanning was considered necessary to determine the anatomy of the lesion. The patients were clinically and biochemically examined when the $^{99m}$Tc-MIBI and skeletal survey were performed, in order to determine their clinical status (active disease, remission or plateau phase).

Haematological and biochemical examination included a full blood count, liver and renal function tests, serum immunoglobulin levels, protein electrophoresis, C-reactive protein, and urine light chain excretion.

Information relating to the date of onset of the disease, previous treatment (particularly the cumulative total dose of anthracycline given), response to treatment, possible recurrences and their management was noted, so that active disease which was apparently resistant to chemotherapy could be identified.

Correspondence: KE Britton, Department of Nuclear Medicine, St Bartholomew's Hospital, West Smithfield, London EC1A 7BE, UK. Received 11 March 1996; revised 2 July 1996; accepted 3 July 1996.
Calculation of sensitivity and specificity of $^{99m}$Tc-MIBI scanning results was as follows:

$$\text{Sensitivity} = \frac{\text{True positives}}{\text{True positives} + \text{false negatives}}$$

$$\text{Specificity} = \frac{\text{True negatives}}{\text{True negatives} + \text{false positives}}$$

**Results**

Twenty-one (21) patients with a median age of 62 years (range 33 – 81 years), with either multiple myeloma (MM) (19/21) or monoclonal gammopathy of undetermined significance (MGUS) (2/21) were investigated by $^{99m}$Tc-MIBI scanning. Fourteen patients (67%) showed increased uptake at 1 and 4 h after the injection (Figures 1a, b, 2 and 3), while seven (33%) were negative at 4 h (Figure 4). One of these (1/7) showed slightly increased uptake only 1 h after injection. Figures 1 – 5 are 4 h images.

**Figure 1** Active myeloma (patient MB). (a) $^{99m}$Tc-MIBI study (posterior view of pelvis) showing increased uptake in the sacroiliac regions, ischia and proximal femora. (b) $^{99m}$Tc-MIBI study of the thighs (anterior view). Increased uptake of $^{99m}$Tc-MIBI is seen linearly in the bone marrow with the negative parallel lines of cortical uptake between the muscles of the thighs, which show normal uptake.

**Figure 2** Active myeloma (patient PJ). $^{99m}$Tc-MIBI images of the posterior thoracic spine. Extensive bone marrow uptake in the thoracic vertebrae, all the ribs and scapulae is seen, so that the image almost looks like a bone scan. Normal uptake is seen in the heart, liver, spleen and gut inferiorly.

**Figure 3** Active myeloma (Patient GH). $^{99m}$Tc-MIBI study (anterior view of knees) shows mainly symmetrical uptake in the marrow of the distal femora and tibial condyles.
The 14 patients with positive results were examined to see how effective 99mTc-MIBI scanning was in detecting active
disease in bones, and whether clinical, biochemical and
radiological information corresponded with 99mTc-MIBI
scanning.

Twelve of the 14 patients with increased uptake had active
myeloma confirmed both clinically and biochemically; one
was deemed to have indolent MM with an increased 'M'
band and bone marrow involvement, but no symptomatol-
ogy, and a negative skeletal survey. There was enough
evidence to suggest that the patients studied had bone
marrow involvement, and therefore the results of the 99mTc-
MIBI scan in these 13 cases (93%) were characterised as true
positive (TP) (Table I).

Skeletal survey or MRI scanning indicated bony involve-
ment in 11/14 patients (78%) who had positive 99mTc-MIBI
scans. All these patients were diagnosed as having active
disease; three of them were newly diagnosed and therefore
previously untreated (Tables I and II). The results of 99mTc-
MIBI scanning relating to the localisation of bone lesions
were almost or completely concordant with those of skeletal
survey in 6/11 (54%) patients. There was, however, partial
concordance in the results of the remaining five (Table II,
Figure 5a and b).

The 99mTc-MIBI scan was positive in one patient with
MGUS (1/14; 7%). This has to be considered as a false-
positive result (Table I).

The results of the 7/21 (33%) patients in whom 99mTc-
MIBI scanning was negative (6/7) or showed transient uptake
at 1 h (1/7) included four (60%) false negatives (FN) (Table
I). One of these patients (IF) had a history of primary
resistance to therapy, and the other three had received large
cumulative doses of anthracycline, which could have
contributed to their multidrug resistance (MDR) (Table III)
and would be likely, therefore, to cause a negative 99mTc-
MIBI scan.

In the 3/7 (43%) cases with negative 99mTc-MIBI scans, the
results were as expected (true negatives), since one patient
was diagnosed as having MGUS and the remaining two
patients were in remission (Table I).

The sensitivity and specificity of 99mTc-MIBI scanning in
MM patients, estimated according to the above results, were
found to be 82% and 75% respectively. These figures would
significantly increase (the sensitivity to 100% and the
specificity to 88%) if the negative results from the MDR
cases were considered as true.

Discussion

Various bone-seeking radiopharmaceutical agents have been
used in multiple myeloma, the commonest being technetium-
99m methylene diphosphonate (Wahner et al., 1980). It has
been shown that conventional radionuclide bone imaging is
less sensitive at detecting skeletal lesions than conventional
radiography. Conventional radiography will detect individual
lesions in 75–95% of cases, while the equivalent sensitivities
for radionuclide bone imaging range from 40% to 60%
(Feggi et al., 1988). Myeloma generally produces a poor
osteoblastic response and, therefore, radiopharmaceutical
agents, such as technetium-99m-labelled diphosphonate, are
poorly taken up.

At present, the most reliable method of detecting bone
disease in MM is radiography, with about 80% sensitivity
(Waxman et al., 1981). However, the lesions shown on the
radiographic films do not always signify active disease, but
may represent lesions already healed. In addition, radi-
ography is not able to detect areas of disease in the bone
marrow.

In this pilot study, 99mTc-MIBI has produced results
comparable with radiography. Images at 10 min showed
high blood pool activity. Uptake of MIBI was clearly seen at
1 h and contrast increased at 4 h. Fading of uptake at 24 h
was noted in some patients. 99mTc-MIBI is well tolerated and
does not have any toxic effects. There is good concordance
between the findings of the 99mTc-MIBI scan and the skeletal
survey in those patients with active disease. There are some
patients with partially concordant results (Table II), Where
lesions shown on skeletal survey do not always correspond to
the positive areas of the 99mTc-MIBI scan, and vice versa. The
mechanism of uptake of 99mTc-MIBI could help to explain
these results.

The main mechanism of cellular uptake of 99mTc-MIBI has
been shown to involve passive distribution across the plasma
cell and mitochondrial membranes in tissues that maintain
negative plasma membrane potentials or are rich in
mitochondrial content, i.e. myocardial, renal or hepatic cells.
(Piwnica-Worms et al., 1990). However, alterations in cell metabolism, which occur in malignant cells, can affect the membrane potential, which can then influence the accumulation of $^{99m}$Tc-MIBI within the cell (Chen, 1988). Thus, $^{99m}$Tc-MIBI could sequester in abnormal plasma cells and, as a result, disease can be detected in the bone marrow, while

---

**Table II** Sites of disease revealed in the skeletal survey and on $^{99m}$Tc-MIBI scanning in 11 patients with active multiple myeloma and evidence of disease on both imaging tests

| Patient | Symptoms | Skeletal survey (SS) | $^{99m}$Tc-MIBI scan | Previously treated (Y/N) |
|---------|----------|----------------------|----------------------|-------------------------|
| **Completely concordant $^{99m}$Tc-MIBI-SS** |
| JP      | Mid-thoracic back pain | Thoracic, lumbar spine, sacrum, pelvis | Thoracic, lumbar spine, sacrum, pelvis | Y |
| JD      | Back pain | T7 – T10, L ilium, skull | T7, T10, sternum | Y |
| PW      | Back pain | Multiple lesions in spine, pelvis | Multiple lesions in spine and sternum | Y |
| **Almost concordant** |
| RJ      | Back pain | Thoracic spine (T11) lumbar spine | Thoracic spine, pelvis, sternum, R anterior chest | Y |
| GH      | Weight loss, back pain | Thoracic spine (T8 – 10) R femur sacrum | Several sites in spine (TS, sacrum included), femora, tibia, sternum, skull | Y |
| JW      | Weight loss, back pain | Thoracic spine | Thoracic spine, scapula | N |
| SG      | Widespread bone pain | Femora, thoracic and lumbar spine, scapula, clavicle | Femora, mandible, tibia, shafts, knees, sternum, ribs (spine negative) | Y |
| MB      | Right-sided chest pain, weight loss, anaemia | Pelvis, left femur, humeri, skull, ribs | Pelvis, femora, humeri, ribs, widespread spinal lesions, scapula | N |
| **Partially concordant** |
| GT      | Back, left shoulder pain | Thoracic spine, pelvis, humeri | Thoracic spine, left scapula, rib 3 right | Y |
| PJ      | Back and right shoulder pain, leg weakness | L2, L4, right humerus | Widespread lesions in spine, humeri, ribs, pelvis, sternum, scapula, femora | Y |
| DL      | Renal impairment, confusion, anaemia | Left scapula, right humerus, lumbar spine, skull | Scapula, femur, pelvis | N |

---

*Figure 5* Active myeloma (patient RJ). (a) $^{99m}$Tc-MIBI study (posterior view of upper abdomen). There is abnormal accumulation of $^{99m}$Tc-MIBI in the marrow of the lower thoracic spine. No uptake seen in the lumbar spine as this had recently been treated with radiotherapy. (b) MRI of the spine. Multiple areas of involvement of the marrow owing to myeloma are seen in the sagittal sections of the thoracolumbar spine.
radiography is unable to reveal abnormalities of constituents of the marrow. Furthermore, healed lesions which might appear on the radiographic films or MRI scans of previously treated patients do not show increased uptake on 99mTc-MIBI scanning (Figure 5a and b). It is, however, interesting that there are abnormal areas on skeletal survey that do not appear positive on 99mTc-MIBI scanning in previously untreated patients. These may represent areas of drug resistance, since there is both in vitro and in vivo evidence that P-glycoprotein (which is associated with drug resistance in MM) is responsible for the elimination of 99mTc-MIBI from malignant cells (Ballinger et al., 1995).

The potential application of 99mTc-MIBI scanning in the functional detection of drug resistance, either before chemotherapy in various tumours known to be primarily resistant, or during chemotherapy to monitor acquired drug resistance has been explored (Moretti et al., 1995a, b). It has been shown that 99mTc-MIBI is a transport substrate recognised by the human MDR1 P-glycoprotein (P-gp), which recognises and transports out of the cell a large group of cytotoxic compounds having little or no structural or functional similarities other than being relatively small, hydrophobic and cationic (i.e. anthracyclines) (Pearce et al., 1989). 99mTc-MIBI also fulfills these requirements. In vitro studies have confirmed that it can be transported by P-gp (Piwnica-Worms et al., 1993). It has also been immunohistochemically confirmed that P-gp expression is associated with MDR in myeloma cells (Dalton et al., 1989). The four cases in our study in which 99mTc-MIBI scanning was negative or showed slightly increased uptake only at 1 h after injection, despite the activity of the disease, could be explained by 99mTc-MIBI elimination of myeloma cells as a result of MDR P-gp overexpression, since the clinical histories indicated either primary or acquired drug resistance. Immunohistochemical detection and quantitation of P-gp in suspicious areas showing no uptake of 99mTc-MIBI would help to confirm the overexpression of P-gp and its relation to 99mTc-MIBI negativity, and these studies are in progress.

If the drug-resistant cases are accepted as true-negative results, then the sensitivity and specificity of 99mTc-MIBI scanning increase considerably, from 82% to 100%, and from 75% to 88% respectively.

The unexpected positive scan in one patient with MGUS raises the question whether 99mTc-MIBI scanning could detect progression of MGUS to MM earlier than any other imaging procedure; this is a matter for further research.

In conclusion, this pilot study shows that 99mTc-MIBI scanning is a useful addition to the investigation process for MM, and in the management of patients with plasma cell disorders.

---

**References**

ALBUQUERQUE L, BAILLET G, DELATTRE J, CHEN Q AND POISSON M. (1992). Tomoscanographie cerebrale au MIBI dans la surveillance des tumeurs gliales de l’adulte. J. Med. Nucl. Biophys., 16, 181.

BALLINGER JR, HUA HA, BERRY BW, FIRBY P AND BOXEN I. (1995). 99mTc-sestamibi as an agent for imaging P-glycoprotein-mediated multi-drug resistance: in vitro and in vivo studies in a rat breast tumour cell line and its doxorubicin-resistant variant. Nucl. Med. Commun., 16, 253 – 257.

CHEN L. (1988). Mitochondrial membrane potential in living cells. Annu. Rev. Cell Biol., 4, 155 – 181.

COAKLEY AJ, KETTLE A, WELLS CP, O’DOHERTY MJ AND COLLINS R. (1989). Technetium-99m sestamibi: a new agent for parathyroid imaging. Nucl. Med. Commun., 10, 791 – 794.

DALTON WS, GROGAN TM, RYBSKI JA, SCHEPER RJ, RICHTER L, KAILI J, BROXTERMAN HJ, PINEDO HM AND SALMON SE. (1989). Immunohistochemical detection and quantitation of P-glycoprotein in multidrug resistant human myeloma cells: association with level of drug resistance and drug accumulation. Blood, 73, 747 – 752.

DURIE BGM, WAXMAN A, JOCHELSON M, GILES FJ, HAMBURG S AND AVEDON M. (1994). Technetium-99m-MIBI scanning in multiple myeloma (MM) (abstract). Proc. Am. Soc. Clin. Oncol., 13, 411.

---

**Table III** Clinical, biochemical and radiological characteristics of patients with primary or multidrug resistance (MDR)

| Patient | Symptoms | Urine light chain excretion (g 24 h<sup>−1</sup>) | Skeletal survey (SS) | 99mTC-MIBI Onset/treatment |
|---------|----------|-------------------------------------------------|---------------------|---------------------------|
| AW      | Back pain| 1.9                                             | C5, T5, L5, pelvis humeri, femora | Increased uptake in T/L spine, but transient | 1991/1994 | VAMP/Interferon prednisolone +PD |
| IF      | Back pain| 2                                               | Right femur, skull T7, L2, right humerus | Negative | 1994/Melphalan and prednisolone. No response |
| AH      | Back pain| 3.6                                             | Vertebral column medulla (plasma cytomia), pelvis | Negative | 1994/1994 on C-VAMP when 99mTc-MIBI performed |
| AP      | Pain in left humerus and lower ribs | 2.4                                             | Ribs, shoulders, C5–7, T9–10, skull | Negative | 1994/1994/C-VAMP. No response |

C-VAMP, cyclophosphamide (C), vincristine (V), doxorubicin (A), methyl-prednisolone (MP); PD, progressive disease.
MORETTI JL, CAGLAR M, BOAZIZ C, CAILLAT-VIGNERON N AND MORERE JF. (1995a). Sequential functional imaging with technetium-99m hexakis-2-methoxy-isobutylisonitrile and indium-111 octreotide: can we predict the response to chemotherapy in small cell lung cancer? Eur. J. Nucl. Med., 22, 177 – 180.
MORETTI JL, CAGLAR M, DURAN-CORDOBES M AND MORERE JF. (1995b). Can nuclear medicine predict response to chemotherapy in small cell lung cancer? Eur. J. Nucl. Med., 22, 97 – 100.
MULLER S, GUTH-TOUGELIDES B AND CREUTZIG H. (1987). Imaging of malignant tumours with Tc-99m MIBI (abstract). Eur. J. Nucl. Med., 28, 562.
MULLER S, REINERS C, PAAS M, GUTH-TOUGELIDES B, BUDACH V, KONIETZKO N AND ALBERTI W. (1989). Tc-99m MIBI and TI-201 uptake in bronchial carcinoma (abstract). Eur. J. Nucl. Med., 30, 545.
PEARCE HL, SAFA AR, BACH NJ, WINTER MA, CITRANT MC AND BECK WT. (1989). Essential features of the P-glycoprotein pharmacophore as defined by a series of reserpine analogs that modulate multidrug resistance. Proc. Natl Acad. Sci. USA, 86, 5128 – 5132.
PIWNICA-WORMS D, CHIU ML, BUDDING M, KRONAUGE JF, KRAMER RA AND CROOP JM. (1993). Functional imaging of multidrug resistant P-glycoprotein with an organotechnetium complex. Cancer Res., 53, 1 – 8.
PIWNICA-WORMS D, KRONAUGE JF AND CHIU ML. (1990). Uptake and retention of Hexakis (2-methoxyisobutyl isonitrile) Technetium (I) in cultured chick myocardial cells: mitochondrial and plasma potential dependence. Circulation, 82, 1826 – 1838.
UNLU M, HAZNEDAR R, ATAVCI S, INANIR S AND TARGUT B. (1995). Detection of bone lesions in multiple myeloma using Tc-99m MIBI scintigraphy (abstract). Proceedings of the 28th Congress of the European Association of Nuclear Medicine (Brussels, 27 August, 1995). Eur. J. Nucl. Med., 22 (suppl.), 739.
WACKERS FJ Th, BERMAN DS, MADDAAHI J, WATSON DD, BELLER GA, STRAUSS HW, BOUCHER CA, PICARD M, HOLMAN BL, FRIDRICH R, INGLESE E, DELALOYE B, BISCOF-DELALOYE A, CAMIN L AND MCKUSICK K. (1989). Technetium-99m hexakis 2-methoxyisobutyl isonitrile: human biodistribution, dosimetry, safety and preliminary comparison to thallium-201 for myocardial perfusion imaging. J. Nucl. Med., 30, 301 – 311.
WAHNEM H, RYLE R AND POEABONE J. (1980). Scintigraphic evaluation of the skeleton in multiple myeloma. Mayo clinic Proc., 55, 739 – 746.
WAXMAN A, SIEMSEN J AND LEVIN AM. (1981). Radiographic and radionuclide imaging in multiple myeloma: the role of Gallium scintigraphy (concise communication). J. Nucl. Med., 22, 232 – 236.