References

1. Risdall RJ, Brunning RD, Hernandez JI, Gordon DH. Bacteria-associated hemophagocytic syndrome. Cancer 1984; 54:2968-72.
2. Boruchoff SE, Woda BA, Pihan GA, Durbin WA, Burstein D, Blacklow NR. Parvovirus B19-associated hemophagocytic syndrome. Arch Intern Med 1990; 150:897-9.
3. Su IJ, Hsu YH, Lin MT, Cheng AL, Wang CH, Weiss LM. Epstein-Barr virus-containing T-cell lymphoma presents with hemophagocytic syndrome mimicking malignant histiocytosis. Cancer 1993; 72:2019-27.
4. Chen RL, Lin KH, Lin DT, et al. Immunomodulation treatment for childhood virus-associated haemophagocytic lymphohistiocytosis. Br J Haematol 1995; 89:282-90.
5. Chen JS, Lin KH, Lin DT, Chen RL, Jou ST, Su IJ. Longitudinal observation and outcome of nonfamilial childhood haemophagocytic syndrome receiving etoposide-containing regimens. Br J Haematol 1998; 103:756-62.
6. Okuda T, Yumoto Y. Subacute necrotizing lymphadenitis with a clinical course mimicking virus-associated hemophagocytic syndrome. Rinsho Ketsueki 1994; 35:689-93.
7. Yufu Y, Matsumoto M, Miyamura T, Nishimura J, Nawata H, Ohshima K. Parvovirus B19-associated haemophagocytic syndrome with lymphadenopathy resembling histiocytic necrotizing lymphadenitis (Kikuchi's disease). Br J Haematol 1997; 96:868-71.
8. Ambruso DR, Hays T, Zwartjes WJ, Tubergen DG, Favara BE. Successful treatment of lymphohistiocytic reticulosis with phagocytosis with epipodophyllotoxin VP 16-213. Cancer 1980; 45:2516-20.

Technetium-99m sestamibi scintigraphy in monitoring patients with multiple myeloma

Technetium-99m-Sestamibi (^{99m}Tc-sestamibi) scintigraphy has been shown to be capable of differentiating patients with multiple myeloma (MM) in remission from those with active disease.[1-10] We studied 5 patients with MM (2 females and 3 males, age 53±17 years) before and after treatment. 99mTc-sestamibi scintigraphic results were concordant with clinical status.

^{99m}Tc-sestamibi scintigraphy was performed as previously described.[8,9] The patients were clinically and biochemically evaluated at the time of both ^{99m}Tc-sestamibi scans to determine their clinical status.

Case #1. A 72-year old man with MM. X-ray skeletal survey was negative, while ^{99m}Tc-sestamibi scan showed intense and diffuse bone marrow uptake (spine, pelvis, ribs, proximal part of both humeri and femora) with no focal increased uptake (Figure 1A). ^{99m}Tc-sestamibi scan performed after treatment with melphalan and prednisone was normal (Figure 1B). At this time the patient was considered in complete remission (plasma cell infiltration 2.5%, Hb 13.4 g/dL, monoclonal component undetectable).

Case #2. A 42-year old woman with low secretive MM. The first ^{99m}Tc-sestamibi scintigraphy showed intense and diffuse bone marrow uptake (pelvis, sternum, proximal part of both humeri and femora) and

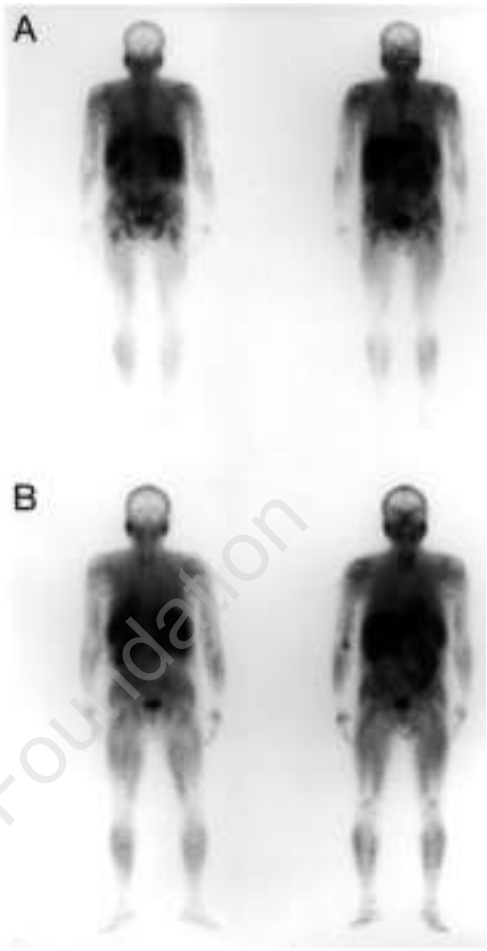

Figure 1. Posterior (left) and anterior (right) whole body scintigraphy acquired 10 minutes after i.v. injection of 99mTc-sestamibi before (A) and after (B) therapy. Before therapy (A) diffuse radiotracer uptake is visible in the spine, pelvis, ribs and proximal parts of both humeri and femura. No abnormalities are observed after therapy (B).

focal increased uptake in thoracic vertebrae (T5, T9). After 2 courses of VAD chemotherapy, increased plasma cell infiltration (72%) was found in the bone marrow, monoclonal component was 0.6 g/dL, and Hb was 10.6 g/dL. A second ^{99m}Tc-sestamibi scintigraphy showed intense and diffuse uptake in the spine and focal abnormalities in T5 and T9 as well as in the skull (fronto-parietal region).

Case #3. A 66-year old woman with micromolecular MM. Baseline ^{99m}Tc-sestamibi scintigraphy showed intense and diffuse uptake in the bone marrow (pelvis, ribs, proximal part of humeri, femora and spine) without focal increased uptake. After receiving 12 courses of melphalan and prednisone, the patient's bone marrow was normal and ^{99m}Tc-sestamibi scintigraphy did not show abnormal bone marrow uptake of the radiotracer.

Case #4. A 30-year old man with juvenile micromolecular MM. ^{99m}Tc-sestamibi scintigraphy showed several focal areas of increased radiotracer uptake.

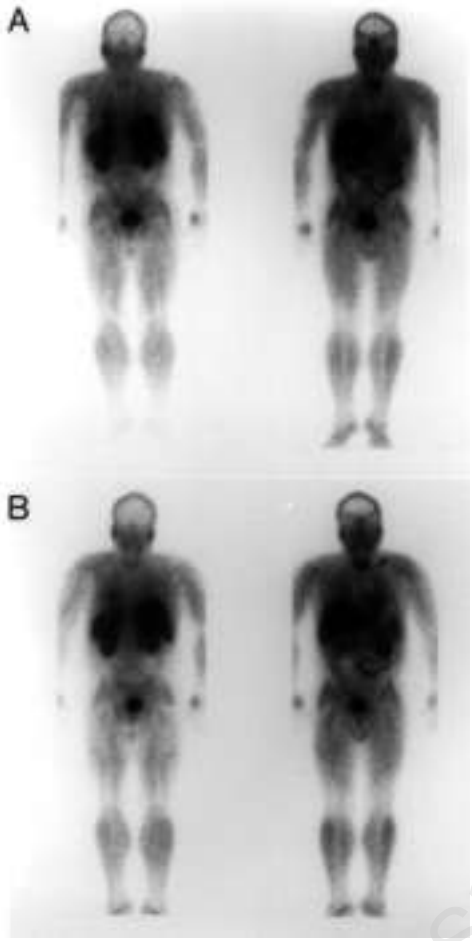

Figure 2: Posterior (left) and anterior (right) whole body scintigraphy acquired 10 minutes after i.v. injection of 99mTc-sestamibi. The scintigraphy performed before therapy (A) shows a normal pattern of uptake of the radiotracer, while after therapy (B) a focal area of increased uptake of 99mTc-sestamibi is evident in the left clavicle.

The patient received chemotherapy (VAD x3, MTX+ CTX+ prednisone x3), and underwent radiotherapy of the cervical tract, clavicles and skull. After 6 months X-ray skeletal survey showed all the pre-existing plus new osteolytic lesions. ^{99m}Tc-sestamibi scintigraphy showed no uptake in the radio-treated lesions, while new areas of focal uptake in the skeleton were observed.

Case#5. A 55-year old man with MM. X-ray skeletal survey showed a few osteolytic cranial lesions, the largest one (2.5 cm diameter) located in the right fronto-parietal region. Osteolytic lesions with pathologic fractures were also seen in the 5th left rib and in the 5th and 6th right ribs. In the same period a ^{99m}Tc-sestamibi scan was normal (Figure 2A). On the basis of hematologic findings (bone marrow plasma cells 6%, monoclonal component 1.6 g/dL, Hb 11.5 g/dL) the patient was considered in continuous clinical remission. After 6 months ^{99m}Tc-sestamibi scan showed focal radiotracer uptake in the left clavicle (Figure 2B). This clavicle fractured one week later and X-ray confirmed the presence of a pathologic fracture through an osteolytic lesion.

Our findings in this small group of patients affected by MM suggest that ^{99m}Tc-sestamibi scintigraphy is a suitable method for evaluation of therapeutic response and for monitoring patients during follow-up. Whole body scanning with this tracer provides a simple and sensitive index of the biological activity of disease.

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References

1. Durie BGM, Waxman A, Jochelson M, Giles FJ, Hamburg G Avedon M. Technetium-99m-MIBI scanning in multiple myeloma (MM) [abstract]. Proc Am Soc Clin Oncol 1994; 13:411.
2. Tirovola EB, Biassoni L, Britton KE, Kaleva N, Kouykin V, Malpas JS. The use of 99m-Tc-MIBI scanning in multiple myeloma. Br J Cancer 1996; 74:1815-20.
3. Adams BK, Fataar A, Nizami MA. Technetium-99m-sestamibi uptake in myeloma. J Nucl Med 1996; 37:1001-2.
4. Unlu M, Haznedar R, Atavi S, Inamr S, Turgut B. Detection of bone lesions in multiple myeloma using Tc99m MIBI scintigraphy. J Nucl Med 1995; 36:190P.
5. Biassoni L, Tirovola E, Kaleva N, Koukyn V, Britton KE. Myeloma imaging with Tc99m MIBI. Eur J Nucl Med 1995; 22:856.
6. Nquyen K, Waxman A, Grupta J, et al. Characteristics of Tc99m-MIBI in the evaluation of multiple myeloma. J Nucl Med 1996; 37:267P.
7. El-Shirbiny AM, Yeung H, Imbriaco M, Michaeli J, Macapinlac H, Larson SM. Technetium-99m-MIBI versus fluorine-18-FDG in diffuse multiple myeloma. J Nucl Med 1997; 38:1208-10.
8. Pace L, Catalano L, Pinto A, et al. Different patterns of technetium-99m sestamibi uptake in multiple myeloma. Eur J Nucl Med 1998; 25:714-20.
9. Catalano L, Pace L, Califano C, et al. Detection of focal myeloma lesions by technetium-99m-sestaMIBI scintigraphy. Haematologica 1999; 84:119-24.
10. Durie BGM, Waxman AD, D'Agnolo A. Whole-body Tc-99m-MIBI scanning in the serial evaluation of MM. J Nucl Med 1998; 39:P138.

Might arsenic trioxide be useful in the treatment of advanced myelodysplastic syndromes?

Failure of conventional therapies is dramatic in patients with advanced myelodysplastic syndromes (MDS), thus therapeutic approaches that increase the apoptotic rate of myelodysplastic syndrome (MDS) cells might be advantageous. We studied the behavior of cells exposed to As_2O_3 *in vitro* from patients with advanced MDS. Our data show that therapeutically useful concentrations of As_2O_3 increase the rate of apoptosis in short-term cultures. Moreover, pre-treatment with GM-CSF increased the sensitivity of the cells to the effect of As_2O_3.

Sir,

The search for therapy of myelodysplastic syndromes has so far been unsuccessful. Single agent chemotherapy as well as acute myeloid leukemia (AML)-type chemotherapy, alone or in combination with human growth factor (HGF), have not shown a clear beneficial effect on survival in MDS or in MDS-related AML.

Morphologic features of apoptosis are easily demonstrable in MDS cell populations.[1] Moreover, data about fas expression in $CD34^+$ MDS cells show that the myeloblast populations that emerge with disease progression are more resistant to *fas*-induced cell death.[2] Thus, it is possible to hypothesize that, in advanced phases of MDS, an increase in the apoptotic rate of MDS cell populations might be advantageous.

Recently, much attention has been drawn to the use of As_2O_3 as a useful agent in the treatment of AML-M3 that has become resistant to standard retinoic acid treatment.[3] In a patient with retinoic-resistant AML-M3 treated with arsenic trioxide we observed a very good correspondence between the levels of drug-induced apoptosis in affected cells *in vivo* and that observed *in vitro* in liquid culture. This correspondence was maintained during progression of the disease (4 and AD, personal communication).

In the present study, we collected blood samples from 14 patients with the diagnoses shown in Table 1. Bone marrow or peripheral mononuclear cells were seeded in 6-well plates (250,000 cells/mL IMDM/10% FCS). After 24 hours, As_2O_3 was added at concentrations of 0.1, 0.5, 1 and 2 μM. After 5 days in culture, culture aliquots were stained with propidium iodide and analyzed by FACS using Lysis II software. The percentage of cells in the hypodiploid peak was used to assess the percentage of apoptotic cells. A minimum of 10,000 events were taken for each sample.

The result obtained show that micromolar concentrations of As_2O_3 were effective at inducing apoptosis in 7/11 advanced MDS cases. No apoptosis was induced in cases of AML-M0 and Ph+ALL.

We also observed that the drug was more effective in inducing apoptosis when the initial spontaneous levels of apoptosis were low, suggesting that the drug might preferentially act on cycling cells. To test this hypothesis we repeated the experiments adding the

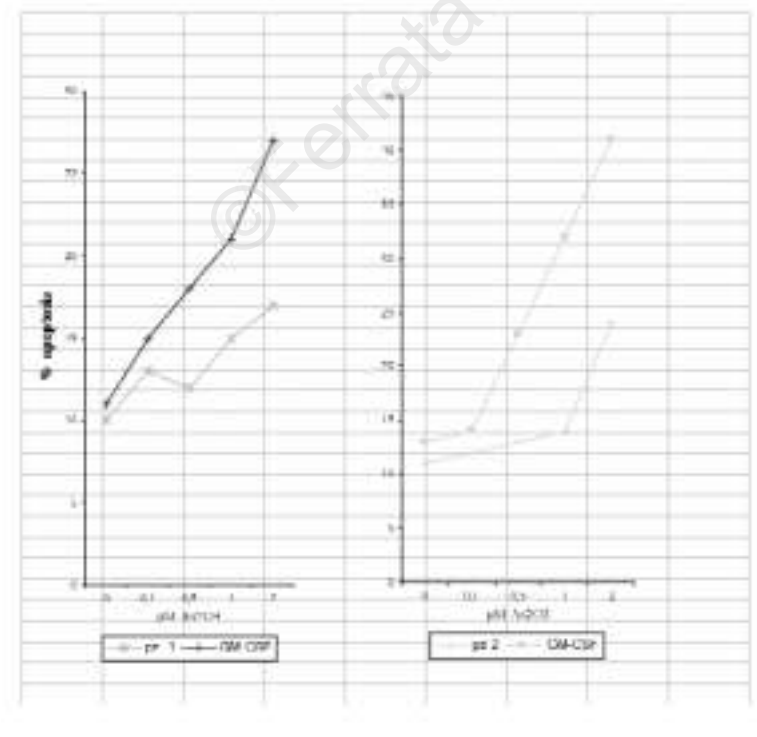

Figure 1.