Fluorodeoxyglucose positron emission tomography in multiple myeloma, solitary plasmocytoma and monoclonal gammapathy of unknown significance

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The aim of our study was to evaluate the role of fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) in 49 patients with plasma cell malignancies. FDG-PET results were verified by conventional imaging methods, including plain radiographs, magnetic resonance imaging (MRI) and computer tomography (CT). Focally increased FDG uptake was observed in three (23 %) of 11 newly diagnosed myeloma patients with negative bone radiographs. Focally increased tracer uptake was found in five of 26 patients with MM in remission but with suspected relapse. Of the 20 patients who had negative FDG-PET scans, only one relapsed 12 months after FDG-PET examination.. FDG-PET was positive in two of six patients with MGUS and with suspected progression to MM or with suspected other malignancy. In one case a thyroid carcinoma was later detected, in the other an intestinal tumor was found.

We conclude that FDG PET might contribute to initial staging of MM patients with negative bone radiographs and is useful for the follow-up of patients in remission especially in non-secretory MM and in patients with large plasmocytoma (>5 cm) after radiochemotherapy.

Keywords: multiple myeloma; monoclonal gammapathy of unknown significance; plasmocytoma; PDG-PET

The diagnosis of multiple myeloma (MM) is based on well-established criteria for bone marrow infiltration, quality and quantity of monoclonal immunoglobulin (M-Ig), quantity of polyclonal immunoglobulins, and bone lesions [1, 2, 3]. In asymptomatic patients with Durie-Salmon stage I MM watchful waiting is recommended and the treatment is started when the disease progresses to a higher clinical stage [4, 5, 6].

Skeletal imaging techniques play a vital role in the decision-making about the initiation of treatment because in patients with normal blood count and normocalcemia the decision to treat depends on the presence or absence of osteolytic lesions.

Bone radiograph imaging of the whole skeleton excluding distal parts of the extremities is a standard procedure for diagnostic evaluation of patients with plasma cell dyscrasias. However, its value is limited by the fact that at least 50 to 60% of the bone hydroxyapatite must disappear to receive a clear radiograph image of an osteolytic lesion in a vertebra [7].

Magnetic resonance imaging (MRI) is more sensitive than conventional radiographs for skeletal imaging [9, 10, 11]. MRI is the most sensitive and therefore the most useful method for the detection of soft tissue masses, bone-infiltrating lesions, or lesions outgrowing from bone and affecting adjacent soft tissues [12].

Skeletal scintigraphy using technetium diphosphate in not adequate for imaging of MM bone disease because the very low osteoblast activity and hypovascularization of MM lesions lead to frequent false negative results even when very large lesions are present [13, 14]. The recently discovered dickkopf 1 (dkk1) gene blocks the activity of osteoclasts required for the reparation of osteolytic lesions and also for the capture of technetium diphosphate [15].

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Technetium sestamibi (MIBI) scintigraphy has been successfully used for imaging skeletal as well as extraosseal MM lesions. MIBI is captured by mitochondria which are abundant in malignant plasmocytes.

Fluorodeoxyglucose (FDG) is a glucose analogue which contains radioactive fluorine-18. Metabolically active cells accumulate and phosphorylate FDG. This active cellular accumulation permits the visualization of tumors which have more active glucose metabolism than do surrounding normal tissues [16]. At present, fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) is widely used for the detection of metastases and of lymphoma sites [16, 17, 18].

The aim of our study was to evaluate the value of FDG-PET in the management of plasma cell malignancies. Specifically, we studied those subgroups of patients, where other imaging methods often fail to provide data sufficient for the decision whether or not to start treatment. These included untreated patients with newly diagnosed MM and with negative skeletal survey, patients with newly diagnosed solitary plasmocytoma, patients in remission after treatment, and patients with monoclonal gammapathy of unknown significance (MGUS). The contribution of FDG-PET for staging and treatment decisions was compared to that of other imaging methods, such as bone radiographs, CT, MRI, and MIBI.

Patients and Methods

Patients and indications for FDG-PET. Retrospective analysis was performed in 49 patients (21 females and 28 males) with MM or MGUS who underwent FDG-PET from November 2003 to July 2005. The mean age for this group was 58 years (range 32 to 70 years). Diagnosis of MM and MGUS and MM staging was done according to Durie and Salmon criteria [1].

FDG-PET imaging was done in the following clinical situations.

1) As a part of the initial evaluation of new patients referred to us with probable MM but without unequivocal pathologic findings on skeletal survey (13 patients). The aim was to differentiate symptomatic MM requiring therapy from asymptomatic stage IA MM where observation only is appropriate approach.

2) In patients with previously diagnosed MM in remission after treatment (26 patients). FDG-PET was performed to confirm or exclude a relapse in case of clinical suspicion (new bone pain and others).

3) In patients with solitary plasmocytoma where the diagnosis was established using standard diagnostic methods (2 patients). The aim was to find other as yet unidentified lesions.

4) In patients with MGUS where other findings led to a suspicion of a transition to MM or of other malignancy (6 patients).

FDG-PET imaging. Fluorine-18 fluorodeoxyglucose in a dose of 370 MBq for a 70-kg patient was administered intravenously. The accumulation phase was 60 minutes. Imaging was done using the Siemens E.CAT Accel PET scanner in the 3D acquisition mode. Imaging was done from the middle third of the thighs to skull base, but if clinically indicated, whole skull and/or whole legs and feet were acquired, too. Emission scan was 4 minutes per 1 bed, the width of scanning field was 16.5 cm and the transmission was 30%. Image reconstruction was performed using the Ordered Subset Maximization Expectation (OSEM) method corrected for absorption. Scan evaluation was done in three planes (transversal, coronal, and sagittal) and using the pseudo-3D Maximum Intensity Projections (MIP) image. For each pathologic focus, the standardized uptake value (SUV) was evaluated as related to the administered dose and to the weight or surface area of the patient, thus enabling the assessment of metabolic turnover in the focus. If CT or MRI images were available, software fusion of the images was performed in order to identify anatomic correlation for the pathologic focus. Each study was evaluated independently by two nuclear medicine specialists.

Results

FDG-PET as a part of initial evaluation of new patients with negative skeletal survey. The 13 patients in this subgroup fulfilled the criteria for MM because of their bone marrow infiltration and monoclonal immunoglobulin levels but had no detectable skeletal lesions on bone radiographs. FDG-PET was negative in 10 (76 %) patients and in eight (61.5%) patients diagnosis of MM stage IA (asymptomatic MM) was made. With the median follow-up of 14 months (range 7-20 months) none of these eight patients progressed to a symptomatic stage that would require treatment. Another two patients (15%) had both negative FDG-PET and skeletal survey. One of them also had MRI of thoracic and lumbar spine with negative results and the other one had skeletal scintigraphy with a negative result. However, in both these cases therapy had to be initiated due to significant anemia associated with bone marrow infiltration and high monoclonal immunoglobulin concentration (Durie-Salmon stage IIA).

Three patients (23%) of this group of 13 had positive FDG-PET findings.

FDG-PET in patients with MM in remission after chemotherapy. Twenty-six patients had FDG-PET while in remission after chemotherapy, but with clinical suspicion on progression (new bone pain and negative radiographs) . Of the 20 patients who had negative FDG-PET findings one relapsed 12 months after the scan while the remaining 19 patients show no signs of progression with the medium follow-up of 5 months (8-20 months). In five patients (19%) the FDG-PET result was positive and in one patient FDG-PET gave a false negative result.

The false negative finding was in a patient with aggressive MM who at the time of FDG-PET scan had a palpable tumor on his head but FDG-PET was negative.

In three patients FDG-PET was performed after radiotherapy on large myeloma lesions. One of these patients had a large plasmocytoma involving iliac bone and protruding into pelvis, the second patient had involvement of vertebrae, ribs and thorax, and the third patient had massive lesion of vertebra L5. FDG-PET was performed at least 3 months after the conclusion of radiotherapy. In all three cases FDG-PET result was positive. Further radiotherapy was initiated in the first two patients with subsequent FDG-PET scan three months later which was negative. Eighteen months after the conclusion of therapy another control FDG-PET scan was done and revealed a relapse of the pelvic lesion and a new costal lesion in the first patient.

FDG-PET in solitary plasmocytoma. FDG-PET was performed in two patients with newly diagnosed solitary plasmocytoma without other lesions on skeletal survey. No other disease sites were found. In another two patients with previously diagnosed solitary plasmocytoma, FDG-PET was used when clinical parameters suggested the development of MM but bone radiographs were negative. Positive FDG-PET scans were confirmed by CT or by MRI and led to the initiation of treatment.

FDG-PET in patients with monoclonal gammapathy. FDG-PET was done selectively in six patients, where there was a clinical suspicion of the development of MM or other malignant tumor. In four cases the results were negative and the patients remain stable with the median follow-up of 14 months (range 9–16 months). Surprisingly, in the two remaining patients solid malignancies were found – thyroid carcinoma and a small bowel tumor, respectively.

Discussion

Durie published report with the largest number of patients with MM examined by FDG-PET. A total of 66 patients underwent 98 FDG-PET scans for indications including MGUS, previously untreated MM, MM in remission, and relapsed MM. Negative FDG-PET result in MGUS was predictive of stable disease [19].

Another major cohort of 43 patients was described by authors from Köln, Germany [20, 21]. In a way similar to MRI classification, they describe FDG-PET findings as focal, diffuse, or combined. They report that positive focal findings or a combination of focal and diffuse lesions had a predictive value of 100% for active disease. Diffuse FDG-PET activity predicted active MM in only 75% of cases. Again, however, in one of the 10 cases of focal bone plasmocytoma, FDG-PET was negative. There are similar reports with smaller groups of patients [23, 24].

Solitary plasmocytoma is another promising indication for FDG-PET. Schirrmeister [21] used FDG-PET to evaluate 15 patients with verified plasmocytoma. Of these 15 scans, in one case (3 cm lesion in a rib) FDG-PET finding was clearly false negative and in another case the values were borderline. New lesions were detected in four of 11 patients with bone plasmocytoma and in one of four patients with soft tissue plasmocytoma. These findings were all subsequently confirmed by other methods.

In our patients who had FDG-PET as a part of initial evaluation for staging purposes, the proportion of positive FDG-PET results was lower than that in previously published reports. In our hands, FDG-PET detected lesions only in three of 13 patients (23%) while in reports of Bradella and Schirrmeister it was positive in 100% of cases [21, 22]. This disparity is due to the selection of patients. We have only indicated FDG-PET in those patients where previously performed tests and imaging did not confirm MM of a stage higher than IA. In both reports mentioned above, FDG-PET was done in patients with radiographic evidence of MM lesions. In our series, negative FDG-PET in patients with stage IA MM without cytopenias or renal insufficiency was associated with favorable prognosis – none of the patients progressed during the follow-up of 14 months.

FDG-PET was negative in two of our patients with MM of a higher stage. However, in neither of these two cases there were osteolytic lesions. High levels of M-Ig and cytopenias were present due to significant bone marrow infiltration (in one patient 46 g/l monoclonal IgG kappa and 30 % MM cells in the bone marrow, in the other patient 57 g/l monoclonal IgA kappa and packed marrow-type infiltration). Clinical course in both cases was very slowly progressive, with poor response to treatment and without bone disease. We hypothesize that the very slow progression may have been associated with plasmocytes having very low metabolic activity and therefore undetectable by FDG-PET.

We performed FDG-PET in 26 patients in remission at a time when they were receiving no specific anti-myeloma treatment, and the clinician had any doubt about the remission of the disease. Twenty patients had correctly negative FDG-PET results which were associated with good overall prognosis. Only one of these patients relapsed 12 months after FDG-PET. All the remaining patients were progression-free with the medium follow-up of 15 months. However, a false negative finding was obtained in one patient in progression with a cranial lesion expanding to soft tissues. The explanation here could be the high uptake of glucose in the brain and consequent difficulties in detecting lesions in this region.

In all three patients who had solitary plasmocytoma more than 5 cm in diameter FDG-PET performed 3 months after the conclusion of treatment showed persistent pathologic activity. Myeloma lesions and plasmocytomas larger than 5 cm are difficult to treat and require higher dose of radiotherapy than lesions smaller than 5 cm [6]. In one of these cases, FDG-PET revealed progression which had not been detected by standard radiographs or laboratory tests. This progression was subsequently verified using MRI targeted to the lesion.

Six of our patients had FDG-PET and MIBI scans less than 5 months apart. In three patients, FDG-PET was negative while MIBI was positive. All these patients remain progression-free more than 12 months after the FDG-PET scan, although they

have increased percentage of plasmocytes in the bone marrow and M-Ig levels of 20-25 g/l. MIBI positivity in these cases reflected the presence of malignant plasmocytes in the bone marrow, FDG-PET negativity corresponded probably to the stability of disease as evidenced by stable M-Ig levels. FDG-PET and MIBI were concordantly positive in three patients with clearly active disease. However, the number of patients with concomitant FDG-PET and MIBI in our series is too low for any definitive conclusions, but similar results were described by other authors [25, 26]. These disparities could be attributed to differences in the mechanisms of capture of the two radiopharmaceuticals in tissues. Technetium sestamibi is captured when there is an increased number of plasmocytes with their mitochondria in the tissues while FDG accumulation increases with proliferation and metabolic rate of cells. It is likely that in cases of lesions which are highly infiltrated with plasmocytes that do not proliferate rapidly, MIBI but not FDG-PET would be positive.

Important collateral findings from FDG-PET scan in MM patients include infectious foci and non-myeloma malignancies. In our study, a thyroid tumor and an intestinal tumor were found in two MGUS patients. Prevalence of non-myeloma malignancies is higher than in the general population. However the detection of solid tumors in two of six patients with MGUS (33 %) can be attributed to our selection of patients with higher probability of malignancy based on clinical, biochemical and other findings. FDG-PET scan has furthermore detected an ovarian carcinoma in a patient in remission of MM. However, there was also a patient with negative FDG-PET scan who one month later developed ileus and a carcinoid tumor in the colon was found during laparotomy. Carcinoid is a slowly proliferating tumor that may not be always detectable by FDG-PET.

Based on published data and on our experience we regard FDG-PET as a suitable diagnostic approach for selected patients with MGUS, MM and solitary plasmocytoma but not as a standard part of the initial evaluation of these patients. It is important to remember that in some cases of proven myeloma infiltration FDG-PET can be falsely negative.

However, if there is a strong clinical suspicion of active disease which was not revealed by standard imaging techniques, it would be reasonable to perform FDG-PET within the initial evaluation of a patient, especially if MRI is contraindicated or if there are not enough data for a targeted MRI. A focus of activity detected by FDG-PET needs to be confirmed by MRI, CT, or biopsy. FDG-PET is also very useful for monitoring the effect of chemoradiotherapy in patients with large tumors (>5 cm) who require complex treatment and higher doses of radiotherapy than patients with smaller lesions. In remission, FDG-PET permits early detection of relapse if other methods are likely to fail (e.g. non-secretory myeloma, contraindications for MRI, unclear site of relapse). In some patients with solitary plasmocytoma FDG-PET can show disseminated disease – a finding that leads to a change in treatment. It is worthwhile to remember that ongoing chemotherapy or radiotherapy may decrease the metabolic activity of malignant cells and therefore in such cases, FDG-PET must be delayed.

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