Scintigraphy with technetium-99m methoxyisobutylisonitrile in multiple myeloma patients; correlation with the International Staging System

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Abstract

^{99m}Tc-2-methoxyisobutylisonitrile (^{99m}Tc-MIBI) scintigraphy has been suggested in multiple myeloma (MM) patients. According to the International Staging System (ISS), serum b2-microglobulin ($S\beta_2M$) and serum albumin (SA) are dominant predictive factors and different cut-off values of these factors can separate patients into various stages of the disease. The purpose of this study was to assess the relationship between ISS staging, by $S\beta_2M$ and SA, and the ^{99m}Tc-MIBI scan findings. Twenty-five MM patients have been studied. Eighteen patients were at stage I, three at stage II and four at stage III of MM. ^{99m}Tc-MIBI scans were obtained and scored according to intensity (I) and extent (E) of the radiotracer uptake. A summed score (S) for the ^{99m}Tc-MIBI scan was calculated for each patient. A statistically significant negative correlation between E, I and S uptake scores versus the SA levels (P=0.004, 0.049 and 0.018 respectively), as well as a statistically significant positive correlation between E and S scores and the $S\beta_2M$ levels (P=0.012 and 0.032) were detected. A statistically significant difference between the E and S uptake scores among the MM patients examined for every stage separately was also found (P=0.007 and 0.024 respectively). The gradual increase of the E and S scores across the three stages of MM was also significant (P=0.003 and 0.021 respectively), despite the relatively small number of patients in stages II and III. In seven patients who died at the end of the follow-up period all three scores were significantly increased as compared to the scores of the patients who remained alive at that time. *In conclusion*, this study provides additional evidence that ^{99m}Tc-MIBI scan not only reflects myeloma disease activity in bone marrow but it is also well correlated with the $S\beta_2M$ and SA levels according to ISS.

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Introduction

Technetium-99m-2-methoxyisobutylisonitrile (^{99m}Tc-MIBI), which was originally developed as a myocardial perfusion and viability detection agent [1,2], is now an established radiopharmaceutical for tumor imaging [3,4], including multiple myeloma (MM) [5,6]. Previous studies on patients with various bone marrow malignancies showed that ^{99m}Tc-MIBI localization in the femoral marrow correlated with the clinical findings [7] and that ^{99m}Tc-MIBI femoral marrow imaging was potentially useful for detecting minimal residual disease in acute leukemia [8].

The outcome for patients with MM is highly variable. Although the median survival time is three to four years, overall survival ranges from less than six months to more than ten years. This variability derives from the heterogeneity in both myeloma cell biology and multiple host factors. Knowledge of tumor and host factors associated with prognosis of the disease is critical for understanding disease outcome, identifying risk groups, and optimizing patients' treatment. Various prognostic factors have been suggested for classification and staging of patients with MM [9–11]. The recently described International Staging System (ISS) is using univariate and multivariate analyses and three types of modeling approaches [12]. Serum beta2-microglobulin ($S\beta_2M$) and serum albumin (SA) were selected from various potential prognostic factors both because they showed statistical power when used in various models and as simple, widely available and inexpensive tests.

The purpose of this study was to assess the correlation between the ^{99m}Tc-MIBI scan findings and the above prognostic factors in MM patients' according to the ISS.

Patients and methods

Twenty-five MM patients, 13 females and 12 males, (mean age: 64.2±13.9, range: 26-87)

were included in the study. The onset of the disease ranged from 0-70 months (25±23 months) before the study. Salmon's and Durie's criteria were used for initial staging regarding the tumour burden, and Bataille's staging system was used for disease activity [13]. Eighteen patients had received or were presently having chemotherapy and seven patients were newly diagnosed. According to the results of the staging procedure, 20 patients had active disease and five patients were in complete clinical remission. Patients with monoclonal component (MC) reduction of more than 75% and bone marrow plasma cells less than 5% were characterized as in complete remission.

Based on SA and the $S\beta_2M$ levels, measured within a week before the ^{99m}Tc-MIBI scan, patients were staged according to the recently described ISS for MM. Thus, patients with $S\beta_2M$ of less than 3.5 mg/L and SA more or equal to 3.5 g/dL were scored as stage I. Patients with $S\beta_2M$ of less than 3.5 mg/L and SA of less than 3.5 g/dL or $S\beta_2M$ 3.5-5.5 mg/L regardless of SA levels were scored as stage II and, patients with $S\beta_2M$ of more than 5.5 mg/L as stage III [12]. These data are summarized in Table 1.

Imaging protocol

The ^{99m}Tc-MIBI (Cardiolite®, Bristol Myers Squibb GmbH, Regensburg, Germany) was prepared according to the manufacturers instructions. Six hundred and sixty MBq of ^{99m}Tc-MIBI were injected intravenously in each patient and the scans were obtained 10 min post injection. All scintiscans were carried out on a single-head γ camera (Sophycamera DS7; Sopha Medical Vision International, Buc Cedex, France) equipped with a high-resolution parallel hole collimator connected to a dedicated computer (Sophy NxT; Sopha Medical Vision International, Buc Cedex, France). Spot images of the whole body were obtained in a 256 x 256 matrix, using a 20% window centered at 140 keV.

Image interpretation

Two experienced nuclear medicine physicians blinded to the patient's overall disease status reported the scintigraphic findings. Disagreement was resolved by consensus. The ^{99m}Tc-MIBI scans were classified as: a) Normal (N), when only normal physiological uptake was present b) Diffuse (D), when diffuse bone marrow uptake was observed c) Focal (F), when areas of focal bone marrow uptake of the tracer were evident and d) Diffuse and focal (D+F), when both D and F patterns were observed. Pattern N was considered as a negative study, while patterns D, F and D+F as positive studies.

The ^{99m}Tc-MIBI scans were scored according to intensity (I) and extension (E) of the radiopharmaceutical uptake [14]. Intensity of the ^{99m}Tc-MIBI uptake was scored as follows: I = 0: no evidence of bone marrow uptake; I = 1: bone marrow uptake less than in the myocardium; I = 2: bone marrow uptake of the same intensity as in the myocardium; I = 3: bone marrow uptake higher than in the myocardium. Extension was scored as follows: E = 0: no evidence of bone marrow uptake; E = 1: uptake limited to the spine and/or pelvis; E = 2: uptake in the spine, pelvis and ribs or the proximal long bone epiphyses; E = 3: uptake in the spine, pelvis ribs and the distal long bone epiphyses. A summed score (S) of E and I, ranging from 0 to 6, was thereafter calculated for each patient. The above scoring system was applied in both focal and diffuse patterns of involvement.

Statistical analysis

Statistical analysis was based on the application of rank methods after correcting for ties. Kendall's rank correlation coefficient τb was calculated for testing the null hypothesis of no relationship between uptake scores and serum variables. Kruskal-Wallis test was used to assess differences in uptake scores, SA and $S\beta_2M$ levels among stages I-III. In order to test for a trend for increasing uptake scores across the three stages, a Wilcoxon-type test for trend was applied [15]. Mann-Whitney U test was applied to assess differences in uptake scores between the group of patients who had died (Group D) and the group of patients still alive at the end of the follow-up period (Group A). A probability $P<0.05$ (two-tailed) was consider as statistically significant. Analysis was performed using STATA/SE 8.0 for Windows statistical package.

Results

Patients with normal and abnormal uptake of the ^{99m}Tc-MIBI scans are described in Table 2. In the same table are also described median values of uptake scores, $S\beta_2M$ and SA levels as well as the results of Kruskal-Walis test. Figures 1 to 3 show various examples of scintigraphic patterns observed in the three stages.

A statistically significant negative correlation between E, I, S uptake scores and SA levels, as well as a statistically significant positive correlation between E, S scores and $S\beta_2M$ levels was detected (Table 3). A statistically significant difference of median SA and $S\beta_2M$ levels was detected among MM patients of stages I to III using Kruskal-Wallis test. This test also revealed a statistically significant difference for E and S uptake scores but not for I scores among patients of stages I to III. Furthermore, the application of a non-parametric test for trend across ordered groups [15] provided evidence of increasing uptake E and S (but not I) scores across the three stages (P=0.003, 0.021 and 0.083 for E, S and I scores, respectively).

Of the 25 patients included in the study, seven patients died during a follow-up period of 15 ± 9 months (4 patients of stage I and 3 patients of stages II and III patients, group D). ^{99m}Tc-MIBI pattern was D in 4/7 patients and D+F in the remaining 3/7 patients. The remaining 18 patients, still alive at the end of the same follow-up period were in group A. Mann-Whitney U test showed that median E, and S uptake scores but not the median I scores differ significantly between groups A and D (P=0.007, 0.028 and 0.082 respectively).

The median E, I and S uptake scores of the seven untreated patients (four in stage I, one in stage II and two in stage III, all still alive), were 2, 1 and 4, respectively.

Table 1. *Serum albumin, serum β_2 microglobulin and ISS staging of the MM patients at the time of scintigraphic study*

	Patients (n)
Serum albumin (g/dl)	
< 3.5	4
> or = 3.5	21
Serum β_2 microglobulin (mg/l)	
< 3.5	18
= 3.5 – 5.5	3
> 5.5	4
ISS staging	
Stage I	18
Stage II	3
Stage III	4

Table 2. *Overview of the scintigraphic data and the results of the non-parametric one way analysis of variance among stages*

		Total patients	Stage I	Stage II	Stage III
^{99m}Tc-MIBI pattern	D	7	1	2	4
	F	6	6	0	0
	F+D	No 5	4	1	0
	N	7	7	0	0
^{99m}Tc-MIBI median score	E	2	1	3	3
				P=0.007	
	I	1	1	2	2
				P=0.082	
	S	3	2	5	5
				P=0.024	
Median Sb2M (mg/L)		2.90	2.05	4.30	8.50
				P=0.001	
Median SA (g/dL)		4.00	4.15	3.40	3.45
				P=0.028	

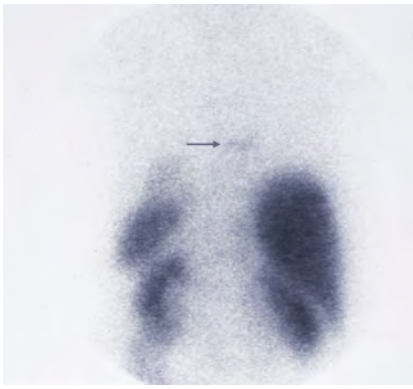

Figure 1. A 52 y.o. female patient with focal ^{99m}Tc-MIBI pattern (arrow – posterior view of lumbar region). SA = 4.1 g/dl and Sb2M = 2.2 mg/L (stage I). E, I and S uptake scores were 1, 1 and 2 respectively

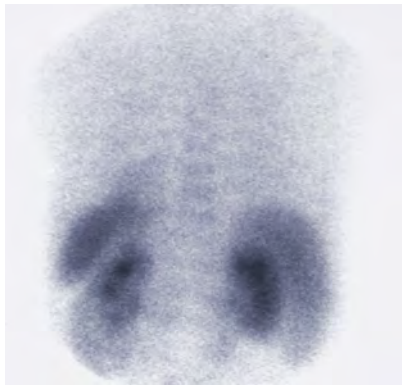

Figure 2. A 78 y.o. female patient with diffuse ^{99m}Tc-MIBI pattern (posterior view of thorax and upper lumbar region). SA = 3.3 g/dl and Sb2M = 3.5 mg/L (stage II). E, I and S uptake scores were 3, 2 and 5 respectively

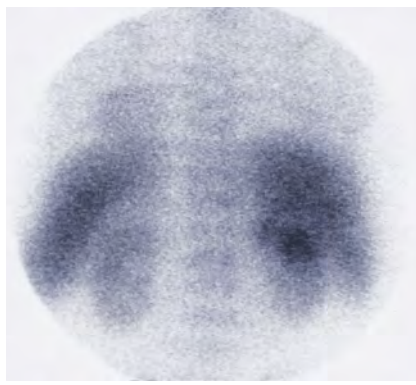

Figure 3. A 78 y.o. male patient with diffuse ^{99m}Tc-MIBI pattern (posterior view of thorax and upper lumbar region). SA = 3.2 g/dl and Sb2M = 10mg/L (stage III). E, I and S uptake scores were 3, 2 and 5 respectively

Table 3. *Kendall's rank correlation coefficient τ_b between uptake scores and serum variables in patients with MM*

	Extension score	Intensity score	Summed score
Serum beta2-microglobulin	0.40	0.29	0.33
	(P=0.012)	(P=0.062)	(P=0.032)
Serum albumin	-0.46	-0.32	-0.37
	(P=0.004)	(P=0.049)	(P=0.018)

Discussion

^{99m}Tc-MIBI scintigraphy was shown to be useful in the evaluation of patients with MM [5, 6, 14, 16-18]. In particular, a relationship was shown between scintigraphic patterns of ^{99m}Tc-MIBI uptake and both clinical status and stages [14]. It is considered that ^{99m}Tc-MIBI uptake by malignant tissues is due to its accumulation in the mitochondria of viable tumor cells [19]. Previous studies have reported high sensitivity and specificity of ^{99m}Tc-MIBI scintigraphy in patients with MM [5, 14, 17]. This scintigraphic approach, was shown by others to be superior to the X-rays in identifying sites of active MM disease [17,19] and its possible role in the follow-up of these patients was anticipated [6]. Pace et al. (2001) [20], found an association between ^{99m}Tc-MIBI scintigraphic findings and the observed clinical status of MM patients.

The significance of Sβ_2M and SA levels in MM disease was suggested by Bataille et al. [21], since 1986. Durie et al. (1990) [22], concluded that Sβ_2M is the most powerful prognostic factor available for MM and that it can be used alone or in combination with other variables, such as SA, for pretreatment stratification. There has been much debate as to whether these were sufficient prognostic factors or whether better prognostic factors were required [23–25]. However, in the absence of other prognostic factors suggested, further analyses of the significance of Sβ_2M and SA levels were conducted. This led to a Sβ_2M and SA staging system developed by the Southwest On-

cology Group [26]. Recently these two factors were included in the ISS system [12]. In the present study, the possible role of ^{99m}Tc-MIBI scintigraphy in predicting and assessing variations in staging MM patients according to the ISS criteria showed an association between the results of the scintigraphic study and the dominant predictive factors of ISS, $S\beta_2M$ and SA. There was a positive correlation between S score and $S\beta_2M$ and an inverse correlation between S score and SA.

In this study, we have found that ^{99m}Tc-MIBI uptake was highly elevated in stages II & III as compared to stage I, despite the relatively small number of patients in stages II and III. Scores from the scintigraphic studies were associated with prognosis. Since ^{99m}Tc-MIBI accumulates in the malignant cells in a way analogous to their metabolic rate [27], the absence of correlation between the intensity of ^{99m}Tc-MIBI uptake and $S\beta_2M$ and SA levels may be explained as follows: $S\beta_2M$ levels would logically be correlated with total tumour volume which on the ^{99m}Tc-MIBI scan is expressed as extensive marrow involvement or as focal bone deposits indicating the extent of the disease. The intensity of ^{99m}Tc-MIBI uptake is related to mitochondrial density which is not necessarily related to $S\beta_2M$ production. It may however reflect the aggressiveness of the tumour or in part be a reflection of multidrug-resistant activity. Due to the small number of patients we have studied, no definite conclusions could be drawn concerning sensitivity and specificity of our procedure. It should be noted though that from 4/18 patients from stage I with E score equal to 3, three patients died in the follow up period. Moreover, the low scores found in the untreated patients that were all still alive, even if it cannot be evaluated statistically, constitutes a clue to the prognostic value of this indicator.

The relatively small number of patients studied precluded a survival analysis. However, the present data provide evidence of a satisfactory correlation between the results of ^{99m}Tc-MIBI scintigraphy score and MM prognostic factors, particularly the extension of the disease. If these findings are confirmed in larger series of patients, the results of ^{99m}Tc-MIBI scintigraphy could be included among the parameters used to describe the stage and plan the most appropriate induction and consolidation treatment for patients with MM.

In conclusion, this study provides additional evidence that ^{99m}Tc-MIBI scan not only reflects myeloma disease activity in bone marrow but it is also well correlated with $S\beta_2M$, SA and the new International Staging System.

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