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Multiple Myeloma

Baseline Tc^{99}-MIBI scanning predicts survival in multiple myeloma and helps to differentiate this disease from monoclonal gammopathy of unknown significance

We performed baseline Tc^{99}-MIBI scanning in 43 patients with multiple myeloma (MM) and in 31 with monoclonal gammopathy of unknown significance (MGUS) patients. We identified two groups of MM patients whose actuarial survival correlated with low or high MIBI scores. MGUS patients had normal or very low scores.

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The ability of Tc^{99}-MIBI scanning to detect bone marrow involvement in MM has been known since 1996[1] but is scarcely used. The aim of this prospective study was to determine whether Tc^{99}-MIBI uptake can be used as a prognostic factor in MM and whether it can differentiate between MM and MGUS.

We studied 43 MM and 31 MGUS patients (33 men and 41 women), aged between 43 and 83 years (mean 69±7.9). Tc^{99}-MIBI scanning and plain X-rays were peformed before any therapy. The median follow-up was 57 and 44 months in the MM and MGUS groups, respectively. The Tc^{99}-MIBI scans were scored for intensity and pattern according to Pace;[2] there were four possible intensity levels (normal, +, ++ and +++) and four possible patterns (normal (N), focal (F), diffuse (D) and focal + diffuse (F+D). Two specialists in nuclear medicine, blind to the patients' diagnosis, evaluated the patterns and scores. We also received the percentage of bone marrow cells and biochemical data related to prognosis: β2-microglobulin (0.7-1.8 μg/mL), C-reactive protein (0.01-0.5 mg/dL), albumin (3.4-4.8 g/dL), creatinine (0.5-1.3 mg/dL) and lactate dehydrogenase (80-480 U/L). The units and normal ranges in our laboratory are given in brackets. All symptomatic patients with active disease but two received VBCMP/ VBAD as first line therapy. Radiotherapy and/or autologous stem cell transplantation were applied when appropriate.

The patients were categorized into groups according to Tc^{99}-MIBI uptake and MIBI pattern and the differences between groups were analyzed with the Kruskal-Wallis test and stepwise multiple regression. We used the Kaplan-Meier method for survival analysis, and log rank (Mantel-Cox), Breslow-Gehan-Wilcoxon, Tarone-Ware, Peto-Peto-Wilcoxon and Harritong-Fleming tests to investigate differences between groups. In cases of a p value <0.05 in any test we assumed a difference in survival and the significance was checked with the post-hoc Bonferroni-Dunn test. MM and MGUS groups were analyzed separately and together. Table 1 shows the variables correlated with MIBI uptake and pattern with the Kruskal-Wallis test (A), and with multiple step-wise regression (B). Only β-2-microglobulin, C-reactive-protein and lactate dehydrogenase were selected by multiple regression in MM patients. The percentage of bone marrow plasma cells was also selected if all the patients were considered together. Twenty-eight of the 31 MGUS patients had negative MIBI scores. Of the three cases with positive scores, two had a very low intensity (+) diffuse pattern and one a very low intensity (+) focal pattern

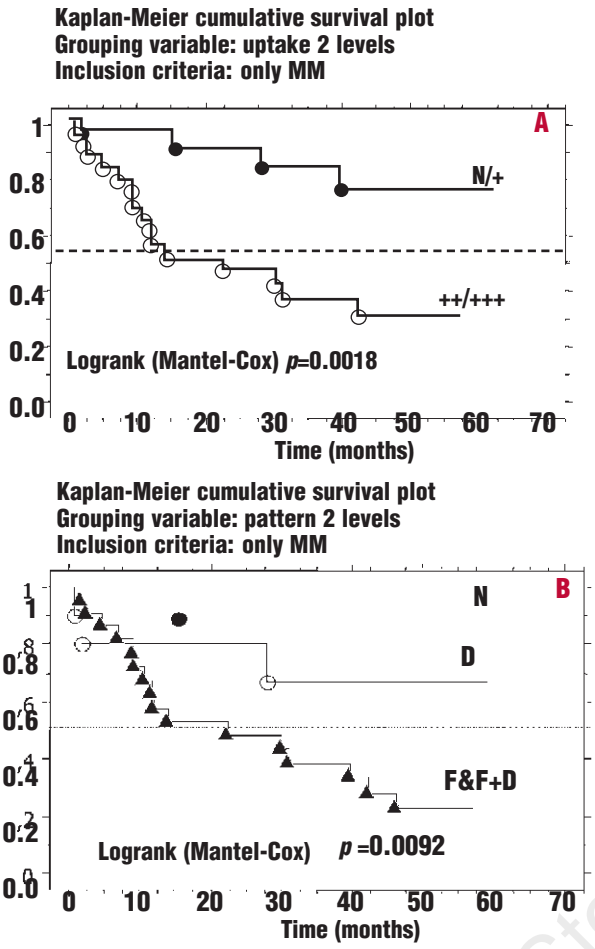

Figure 1. A. Multiple myeloma patients were categorized in two groups with good and poor prognosis. In a previous analysis (not shown) the survival curves of patients with ++ and +++ scores were almost identical and those with the normal and + scores were similar. **B.** Multiple myeloma patients were categorized into three groups according to scan patterns. In a previous analysis (not shown) the survival curves of patients with Focal and Focal+Diffuse patterns were similar.

(localized in a joint affected by active rheumatoid arthritis).

There was a significant difference in survival among MM patients depending on the intensity of MIBI uptake (p=0.0264). The patients with ++ or +++ scores had a similar poor prognosis. If the MM patients were categorized into two groups (normal/+ and ++/+++), the significance was even greater (p=0.0018) and the probability of survival at 57 months was 74%±11.5 in the former group and 26.1%±10.2 in the latter (Figure 1A). The difference in survival between these two groups was confirmed with the post-hoc Bonferroni-Dunn test (p=0.0072).

There was also a difference in survival among MM patients depending on the pattern of the scan, but this difference was at the borders of statistical significance (p slightly less than 0.05 in four tests, but 0.0608 in the Breslow-Gehan-Wilcoxon test). We categorized MM patients into three groups according to Tc^{99}-MIBI pattern: normal; diffuse; focal together with focal and diffuse

Table 1A. Kruskal-Wallis test for MIBI uptake.

	MIBI uptake				*MIBI pattern*			
	MM		*ALL*		*MM*		*ALL*	
	h	*p*	*h*	*p*	*h*	*p*	*h*	*p*
Moncl. Ig (serum)	2.75	n.s.	18.850	0.0008	3.7	n.s.	15.38	0.0015
Moncl. Ig (urine)	3	n.s.	8.4	0.037	3.4	n.s	9.47	0.0237
β2 µg	8.9	0.03	15.25	0.0016	9.514	0.0232	15.55	0.0014
C protein	9.23	0.026	14.87	0.0028	15.99	0.0011	20.85	0.0001
Albumin	2.2	n.s.	3.97	n.s.	2.062	n.s.	3.81	n.s.
Creatinin	9.25	0.026	4.82	n.s.	2.554	n.s.	5	n.s.
Lactate dehydrogenase	7.4	n.s..	6.96	n.s.	8.093	0.0441	6.3	n.s.
B.M. plasma cells	6.2	n.s.	26.1	0.0001	4.416	n.s.	24.08	0.0001

MM: only multiple myeloma patients; ALL: MGUS and MM patients; h: h corrected for ties; p: tied p-value.; n.s.: no significance. β-2-microglobulin and C-reactive protein show significantly different means in both MM and all patients. Bone marrow plasma cells and monoclonal component only are different if all patients were considered together.C protein: C reactive protein.

Table 1B. Step-wise multiple regression. Variables in model.

	MIBI uptake	
	Step 1	*Step 2*
MM & MGUS	Plasma cells p<0 .0001	–
Only MM Lactate dehydrogenase	β2-microglobulin p=0 .0059	p=0.0343

	MIBI pattern	
	Step 1	*Step 2*
MM & MGUS Plasma cells	C-reactive protein p<0.0001	p< 0.0001
Only MM	C-reactive protein p=0.0042	–

(Figure 1B); the three groups are clearly separated and the statistical significance reaches the level of p=0.0203 in the log rank Mantel-Cox test.

In previous studies Tc^{99}-MIBI has proven to be more sensitive than Tc^{99}-methylene diphosphonate and X-ray, and at least as sensitive as computed tomography, magnetic resonance imaging and positron emission tomography, with some discordant results regarding magnetic resonance.[3-9] However the prognostic significance of Tc^{99}-MIBI scanning has not been analyzed. Our results suggest that baseline Tc^{99}-MIBI scanning has prognostic significance, and that scores of marked intensity (++, +++) or advanced patterns (F and F+D) in the absence of inflammation or other pathologies exclude the diagnosis

of MGUS. Furthermore we have confirmed a previously reported correlation[10] between Tc^{99}-MIBI scanning results and laboratory data: β-2-microglobulin, C-reactive protein and lactate dehydrogenase. It would be incorrect to do a Cox-regression test in this small series to check whether these variables are independent of Tc^{99}-MIBI. Further studies should be done to establish the utility of Tc^{99}-MIBI in prognosis, staging and response to therapy in MM.

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Key words: multiple myeloma monoclonal gammopathy, prognosis, M protein, technetium Tc^{99} Sestamibi, radionucelide imaging.

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Chronic Lymphocytic Leukemia

Low-dose intravenous alemtuzumab therapy in pretreated patients affected by chronic lymphocytic leukemia. A single center experience

We report the efficacy and safety of intravenous low-dose alemtuzumab (10 mg three times weekly for 10 weeks) in 12 patients with relapsed or refractory chronic lymphocytic leukemia. Low-dose alemtuzumab induced significant responses in these patients (16% complete remission, 25% partial remission), with mild hematologic and extrahematologic side effects and a low rate of infections, even in the presence of long-lasting severe immunosuppression.

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Several studies have reported the efficacy of standard-dose alemtuzumab (30 mg three times weekly, administered by either the intravenous or the subcutaneous route) in previously treated patients with chronic lymphocytic leukemia (CLL), with overall response rates (ORR) ranging from 33% to 42%.[1-3] Although the response rates were high, standard dose alemtuzumab in refractory patients was associated with considerable hematologic and extrahematologic toxicity.[4,5]

Recently, a pilot study with low-dose subcutaneous alemtuzumab (10 mg three times weekly for 18 weeks) in refractory CLL patients showed a high response rate (ORR: 50%) and a favorable toxicity profile.[6] We therefore administered low-dose alemtuzumab to 12 patients with pretreated CLL. We evaluated the efficacy (NCIWG criteria) of the treatment, the duration of response, the overall survival, the safety, the incidence of infectious complications and the immune recovery. All patients had been previously treated with at least two lines of chemotherapy (range 2-5). In four patients treatment with fludarabine was not attempted because of autoimmune hemolytic anemia or refusal. The median time from the last treatment to initiation of alemtuzumab therapy was 4 months (range 2-24 months) (Table 1).

Alemtuzumab was given intravenously at a dose of 3 mg on day 1; from day 3 the target dose was raised to 10 mg three times weekly for 30 administrations. Treatment was stopped if disease progressed or grade IV thrombocytopenia, infections or cytomegalovirus (CMV) reactivation occurred. Therapy was withheld if the neutrophil count fell below 500/μL, although granulocyte colony-stimulating factor was administered for grade IV neutropenia. CMV screening was conducted by weekly analysis of antigenemia and CMV DNA. Immunological subsets ($CD3^+$, $CD4^+$, $CD8^+$, CD16/56, $CD19^+$) were studied before and after the end of treatment on days 60, 120, 180 and 240. Of the 12 patients, two (16%) obtained a CR and three (25%) achieved a PR, with an ORR of 41% (Table 2). The ORR was 83% in stage A/progressive or B/II disease compared to 0% in stage C/IV disease (p=0.01). The ORR was 50% in patients with mutated V_H genes and 29% in patients with unmutated V_H genes (p=ns). However, both CR were achieved in patients with mutated V_H genes and minimal residual disease was not detectable in these two patients. Five patients who were refractory to previous chemotherapy did not achieve any response to alemtuzumab. The