[CANCER RESEARCH 59, 4546–4550, September 15, 1999]

Advances in Brief

14q32 Translocations and Monosomy 13 Observed in Monoclonal Gammopathy of Undetermined Significance Delineate a Multistep Process for the Oncogenesis of Multiple Myeloma[1]

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Abstract

Clonal plasma cells in monoclonal gammopathy of undetermined significance (MGUS) have been shown to bear copy number chromosome changes. To extend our knowledge of MGUS to structural chromosomal abnormalities, we have performed fluorescence *in situ* hybridization experiments with probes directed to the 14q32 and 13q14 chromosomal regions in 100 patients with either MGUS or smoldering multiple myeloma (SMM). 14q32 abnormalities were observed in at least 46% of patients with MGUS/SMM, with these abnormalities being present in the majority of clonal plasma cells. Whereas t(11;14)(q13;q32) occurs in 15% of MGUS/SMM patients, an incidence similar to that of overt multiple myeloma (MM) patients, translocation t(4;14)(p16;q32) is observed in only 2% of these cases [$P = 0.002$ for difference with t(11;14)], as compared with 12% in MM patients ($P = 0.013$). Monoallelic deletions of the 13q14 region were found in 21% of patients, with two types of situations. In half of the evaluable patients, and especially in patients with SMM, the deletion is present in the majority of clonal plasma cells, as in MM, whereas in the other half of the evaluable patients (essentially in MGUS patients), it is observed in subclones only. These data enable us to elaborate a plasma cell oncogenesis model from MGUS to MM.

Introduction

MGUS[3] is a condition defined by the detection of a monoclonal protein (the M-component) in the serum without evidence of any causal disease, such as MM, Waldenstrom macroglobulinemia, primary amyloidosis, or any related disorder (1). This situation is not unusual, because it represents the first cause of monoclonal gammopathy, corresponding to 1% of the population over 50 years of age, and 3% of the population over 70 years of age (2). However, as an exclusion diagnosis, MGUS is probably not a unique entity. This heterogeneity is evident when analyzing the evolution of these individuals. Some may remain asymptomatic for decades, whereas others evolve to highly malignant conditions in less than 1 year. The overall incidence of MM transformation is estimated to be 1–2% per year (2, 3), but thus far, no clear-cut prognostic parameter has been identified.

The origin of MGUS is largely unknown. Whereas malignant PCs accumulate within the bone marrow in MM, bone marrow examination is frequently normal in MGUS. However, serial studies usually show a plasmacytosis increase, making it difficult to distinguish early-stage MM from advanced-stage MGUS. Recent immunophenotypic studies have shown that PCs displayed similar phenotypic abnormalities, and that the only difference between these two conditions was the persistence of normal PCs in MGUS (4). What about chromosomal changes? Although most (if not all) MM patients have large numbers of aneuploid PCs, chromosomal abnormalities are found in only 30–50% of the patients (5–8). The situation is even more dramatic in MGUS, for which only one successful cytogenetic analysis has been reported thus far (9). This scarcity is explained mainly by the low proliferative index of PCs in MGUS. To circumvent this problem, some authors have used FISH on interphase cells (10–12). Using only four centromeric probes, they have demonstrated that the incidence of trisomy for at least one chromosome was between 43% and 68%. Moreover, serial analyses revealed that most individuals without trisomy at first evaluation acquired numerical chromosomal changes on subsequent examinations (12). These studies suggest that, as in MM, most patients with MGUS display numerical chromosomal changes in their clonal PCs.

More recently, we and others have demonstrated that structural chromosomal changes also occur in the PCs of individuals with MGUS (13, 14). Nishida *et al.* (14) first reported the presence of 14q32 abnormalities in three of five MGUS patients. More recently, we demonstrated in a preliminary analysis that 14q32 abnormalities were present in 11 of 19 patients with MGUS (15). These data suggest that structural chromosomal abnormalities could be as frequent in MGUS as in MM. To confirm this hypothesis, we conducted a study on a series of 100 individuals with either MGUS or SMM using interphase FISH to determine: (*a*) the incidence of 14q32 rearrangements; (*b*) the frequency of the main partner chromosomal regions; and (*c*) the incidence of deletion/monosomy 13 in MGUS. These results were then compared with those of 102 patients with overt MM at diagnosis (15).

Patients and Methods

Patients. We selected a cohort of 100 consecutive individuals with either MGUS or SMM seen at one of the three hematology departments participating in this study. Nineteen of these patients have been reported previously (15). Diagnosis of MGUS and SMM was performed according to the criteria described by Kyle and Lust (1) and Kyle and Greipp (16), respectively. MGUS was assessed when individuals had serum monoclonal protein lower than 30 g/liter and bone marrow plasmacytosis lower than 10% in the absence of clinical symptoms, lytic bone lesions, anemia, hypercalcemia, and renal function impairment. Patients with SMM fulfilled the same criteria, except that the M-component was higher than 30 g/liter and/or bone marrow plasmacytosis was higher than 10%. In this series, there were 79 patients with MGUS and 21 patients with SMM. The median age at diagnosis for individuals with MGUS (44 males and 35 females) was 64 years (range, 33–86 years), whereas the

Received 6/14/99; accepted 7/30/99.

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[1] Supported by grants from the Fondation de France and the Comité Départemental de la Loire-Atlantique de la Ligue contre le Cancer.

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[3] The abbreviations used are: MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; PC, plasma cell; SMM, smoldering MM; FISH, fluorescence *in situ* hybridization.

Table 1 *Characteristics of patients with an illegitimate IGH rearrangement*

Patient status	% of PCs with a 14q32 abnormality	Specific translocation[a]	Trisomies 3, 9, 11, or 15	% of clonal PCs[b]
MGUS	19	No	3, 9, and 15	23
MGUS	20	No	3 and 11	18
MGUS	34	No	3 and 15	39
MGUS	39	No	No	
MGUS	43	No	3, 9, and 15	41
MGUS	46	No	9 and 11	46
MGUS	52	t(11;14)	3	64
MGUS	53	No	9 and 15	49
MGUS	59	No	3	62
MGUS	63	t(11;14)	9	65
MGUS	65	No	3, 9, 11, and 15	67
MGUS	67	No	11 and 15	70
MGUS	68	No	No	
MGUS	68	No	9, 11, and 15	69
MGUS	69	t(11;14)	No	
MGUS	69	No	3, 9, 11, and 15	68
MGUS	69	No	3 and 11	65
MGUS	70	t(11;14)	No	
MGUS	71	No	No	
MGUS	71	No	No	
MGUS	72	t(11;14)	No	
MGUS	72	t(11;14)	No	
MGUS	72	No	11 and 15	70
MGUS	73	No	15	78
MGUS	74	No	3 and 11	71
MGUS	75	No	No	
MGUS	78	No	No	
MGUS	82	No	9, 11, and 15	81
MGUS	82	t(4;14)	No	
MGUS	86	No	15	81
MGUS	88	No	3 and 15	92
MGUS	89	t(11;14)	No	
MGUS	91	t(11;14)	No	
MGUS	92	t(11;14)	15	87
MGUS	93	t(11;14)	No	
MGUS	95	No	3, 9, 11, and 15	89
SMM	61	No	3, 9, and 11	67
SMM	78	t(11;14)	3	74
SMM	79	No	3 and 9	83
SMM	82	t(4;14)	9	78
SMM	85	No	3	82
SMM	93	t(11;14)	No	
SMM	93	No	9	91
SMM	96	t(11;14)	9	91
SMM	97	t(11;14)	No	
SMM	99	t(11;14)	No	

[a] Specific translocation refers to the detection of one of the three specific rearrangements, *i.e.*, t(4;14), t(8;14), and t(11;14).

[b] The percentage of PCs with at least one trisomy. In case of more than one trisomy, the highest percentage of clonal PCs was chosen.

median age of SMM patients (11 males and 10 females) was 65 years (range, 37–78 years). Within the MGUS population, M-component was Gκ in 44 cases, Gλ in 26 cases, Aκ in 8 cases, and Aλ in only 1 case. In the SMM population, the corresponding numbers of cases were 12, 3, 4, and 2, respectively. No patient with only light chain excretion was analyzed in this series. The median follow-up of patients with MGUS and SMM was 25 months (range, 3–168 months) and 16 months (range, 6–180 months), respectively. The control population, *i.e.*, patients with overt MM, was defined according to the criteria of Durie and Salmon (17). A total of 102 consecutive patients with stage I, II, or III MM were analyzed using the same strategy. These patients have been reported previously (15). There were 17 patients with stage I disease, 27 patients with stage II disease, and 58 patients with stage III disease.

PC Selection. Because of the scarcity of PCs in individuals with MGUS (by definition less than 10%, and very often 0–2%), we chose to positively select them. This selection was based on CD138 expression, as described previously (13). Because CD138 is specific for PC within bone marrow, we used an immunomagnetic method with an anti-CD138 antibody (Miltenyi Biotec, Auburn, CA). Briefly, bone marrow mononuclear cells were separated using gradient density (Ficoll-Hypaque) and then incubated with anti-CD138-coated magnetic beads. Cells were passed through columns, allowing us to sort PCs. Recovery and purity of PCs were evaluated by morphology. PCs were then fixed in methanol:acetic acid (3:1 v/v and dropped on slides for FISH analysis.

FISH Experiments. FISH was performed as described previously (13). Probes used in this study have been reported previously (13). Briefly, the *IGH* gene was analyzed in a first attempt using the Y6 and Ig10 probes, which were kindly provided by Dr. Matsuda (Kyoto University, Japan) and Dr. Rabbits (Medical Research Council, Cambridge, United Kingdom), respectively. Each lot of probes was validated on 1000 bone marrow cells obtained from healthy donors, and cut-off values were determined for each lot. Illegitimate *IGH* rearrangements (defined by any situation other than two colocalized green and red signals) were considered when present in more than 10–16% of cells (mean + three SDs). Patients with illegitimate *IGH* rearrangements were then analyzed for the presence of the three main partner chromosomal regions, *i.e.*, 11q13 (*CCND1*), 4p16 (*FGFR3/MM-SET*), and 8q24 (*MYC*). The *CCND1* and *FGFR3* probes have been reported previously (13). The *MYC* locus was analyzed using a YAC probe described recently (18). Patients were also analyzed using centromeric probes specific for chromosomes 3, 9, 11, and 15 (Vysis, Downers Grove, IL) to evaluate the percentage of clonal PCs. These four probes were selected based on the high frequency of trisomies 3, 9, 11, and 15 in MM and MGUS patients. The thresholds for trisomy were determined for each probe by analyzing 2000 nuclei from five normal bone marrow specimens (healthy donors). Cut-off values (mean + three SDs) were 1.7%, 2.4%, 2.1%, and 3.4% for centromere 3, 9, 11, and 15 probes, respectively. Finally, chromosome 13 was analyzed using a probe specific for the *D13S319* locus at 13q14 (Vysis). The deletion cut-off was fixed at 5.3%, as described previously (15).

Results

Illegitimate *IGH* Rearrangements Are Detected in 46% of the Patients in the Majority of Clonal PCs. An abnormal configuration of 14q32 probes was observed in 46 (36 patients with MGUS and 10 patients with SMM) of 100 patients. This abnormal configuration was mainly a separation of the two probes, corresponding to probable translocations involving the *IGH* gene. These results were slightly lower than those of patients with overt MM, showing 61 of 102 (60%) patients with an illegitimate *IGH* rearrangement ($P = 0.068$; Ref. 15). Among the 46 patients with MGUS/SMM who had a 14q32 abnormality, the median percentage of cells displaying the abnormality was 72% (range, 19–99%). Twenty-nine of these patients were aneuploid for one of the tested centromeric probes. The median percentage of aneuploid cells was 70% (range, 18–96%), in good agreement with the percentage of cells with illegitimate *IGH* rearrangement. The results are described in Table 1. Specimens with a normal 14q32

Table 2 *Characteristics of patients with monosomy 13*

Patient status	% of PCs with monosomy 13	% of clonal PCs[a]	14q32 abnormality[b]
MGUS	14		No
MGUS	19		No
MGUS	19	82	No
MGUS	21	63–65	t(11;14)
MGUS	25		No
MGUS	28		No
SMM	29	74–78	t(11;14)
MGUS	33	73	Yes (UIP)
MGUS	33		No
MGUS	34		No
MGUS	34	70	t(11;14)
MGUS	38	87	No
MGUS	40	86	Yes (UIP)
MGUS	52		No
MGUS	66	60	Monosomy 14
SMM	68		No
MGUS	73	75	Yes (UIP)
SMM	78	82	t(4;14)
SMM	82	88	Yes (UIP)
MGUS	83	82	t(4;14)
SMM	89	93	Yes (UIP)

[a] The percentage of clonal PCs was determined as the percentage of PCs with a 14q32 abnormality and/or the percentage of PCs with at least one trisomy 3, 9, 11, or 15.

[b] UIP, unidentified partner; PCs present an illegitimate *IGH* rearrangement involving a chromosomal region different than 4p16, 8q24, and 11q13.

Table 3 *Results of 14q32 analysis in patients with MGUS, SMM, and overt MM*

	MGUS		SMM		Overt MM
Overall	36/79	NS[a]	10/21	NS	61/102
t(11;14)(q13;q32)	10/79	NS	5/21	NS	16/102
t(4;14)(p16;q32)	1/79	NS	1/21	NS	12/102
			$P = 0.026$		

[a] NS, nonsignificant.

configuration, *i.e.*, two yellow signals corresponding to the fusion of the VH and CH probes, could be interpreted in two different ways. These patients could lack any illegitimate *IGH* rearrangement in their clonal PCs or the percentage of clonal PCs could be above the cut-off threshold for the detection of 14q32 abnormalities, *i.e.*, 10–16%. To answer this important question, we analyzed these patients with chromosome 3, 9, 11, and 15 centromeric probes to estimate the percentage of clonal PCs. Among the 54 patients with a normal *IGH* configuration, at least one trisomy was detected in 32 patients (15 patients displayed two trisomies, 5 patients displayed three trisomies, and 2 patients were trisomic for the four probes). The median percentage of clonal PCs (defined as cells presenting at least one trisomy) was 58% (range, 6–97%). Combining the results of both analyses using centromeric probes, slightly but not significantly different results were found in patients with MGUS and patients with SMM: whereas the median percentage of clonal PCs was 71% in patients with MGUS, it was 88% in patients with SMM.

Whereas the Incidence of t(11;14)(q13;q32) in MGUS/SMM Is Similar to That of MM, t(4;14)(p16;q32) Is Rare in MGUS/SMM. Patients with an illegitimate *IGH* rearrangement were then analyzed using the *CCND1*, *FGFR3*, and *MYC* probes in combination with probes specific for the constant *IGH* domain, as reported previously (13). No specific translocation was found in patients lacking illegitimate *IGH* rearrangement, as determined by the interphase FISH assay. Translocation t(11;14) was observed in 15 patients (10 patients with MGUS and 5 patients with SMM). This incidence is similar to that observed in MM (13). In each case, only one *CCND1-IGH* fusion was observed in MGUS/SMM. This situation is strikingly different from that observed in MM, where multiple fusions are observed in a significant number of patients (13). In contrast to t(11;14), t(4;14)(p16;q32) occurs in a significantly lower number of patients: only two patients displayed this translocation [one individual with MGUS and one patient with SMM; $P = 0.002$ for difference with t(11;14)]. This incidence is significantly lower than that found in MM (12%; $P = 0.013$; Ref. 13). No patient displayed t(8;14)(q24;q32).

Monosomy 13 Is Observed in 21% of Patients, but Usually Only in Subclones. Using the 13q14 probe, significant percentages of PCs with only one signal were observed in 21 patients (5 patients with SMM and 16 patients with MGUS). The results are summarized in Table 2. Whereas 14q32 abnormalities were observed in the large majority of clonal PCs, deletion 13q14/monosomy 13 was usually present in a lower percentage of cells (median, 34%; range, 14–89%). Only seven patients displayed a high percentage of PCs with monosomy 13, *i.e.*, 66–89% of PCs, as observed in patients with overt MM. Of note, four of these seven patients had SMM. Thus, whereas 4 of 21 patients with SMM presented 13q14 deletion in a majority of clonal PCs, only 3 of 79 patients with MGUS had this feature ($P = 0.051$). The median percentage of clonal PCs (defined by the percentage of PCs with another 14q32 abnormality or trisomy for one of the centromeric probes) could be evaluated in 13 of these patients and was 75% (range, 36–93%). In 7 of these 13 evaluable patients, the percentage of PCs with monosomy 13 was significantly lower (Table 2).

Discussion

Chromosomal analysis of clonal PCs in MGUS is a difficult challenge, and very few cases have been reported. Several reasons may explain the poor literature on this topic. The two main explanations are the low number of clonal PCs within the bone marrow (usually less than 2%) and the low proliferation index of these PCs. Even in MM, in which the number of clonal PCs is much higher, chromosomal analyses remain a difficult art, and clonal chromosomal abnormalities are found in only 30–50% of patients (5–8), although 90–100% of them display aneuploidy in tumor cells, as shown by DNA index or interphase FISH analyses (19–23). In MGUS, very few studies dedicated to chromosome analysis have been reported. Three main reports using interphase FISH with four centromeric probes identified numerical chromosomal changes in 50–84% of patients with MGUS (10–12). These percentages (although on a low number of patients) are similar to those found in MM. Very few data are available regarding structural chromosomal abnormalities. Using conventional cytogenetics, only one report described the occurrence of chromosome changes in 25% of patients with MGUS (9). However, these changes are strikingly different from those found in MM, especially by the lesser degree of complexity (usually a single chromosomal change). Apart from this study, no other cytogenetic study has been published. Using interphase FISH, Nishida *et al.* (14) reported the presence of 14q32 abnormalities in three of five patients with MGUS. We recently preliminarily reported 14q32 and 13q14 abnormalities in 11 of 19 MGUS patients (patients included in this study; Ref. 15). To our knowledge, no other study reporting structural chromosomal changes in MGUS has been published.

In this study, we looked for both types of chromosomal changes, *i.e.*, numerical (chromosomes 3, 9, 11, and 15) and structural (13q14 and 14q32 chromosomal regions). Moreover, we also analyzed the most frequent specific chromosomal translocations involving the 14q32 region: (*a*) t(11;14)(q13;q32); (*b*) t(4;14)(p16;q32); and (*c*) t(8;14)(q24;q32). First of all, this study confirmed previous reports on the incidence of chromosome gains in MGUS/SMM (67% of patients; Refs. 10–12). Because the analysis was performed on purified PCs, a larger number of cells could be analyzed, and more precise percentages of clonal PCs could be defined. The median percentage of clonal PCs in patients with MGUS was 71% and 88% in patients with SMM. This percentage of clonal PCs in patients with MGUS is higher than those reported previously using FISH (10–12) but is similar to that described by Ocqueteau *et al.* (4) using an immunophenotypic analysis. This difference might be explained by the higher number of PCs analyzed and, moreover, by the fact that most of our patients were not studied at diagnosis, but at various times after diagnosis. This finding, associated with the even higher percentage of clonal PCs in patients with SMM, supports the hypothesis of a sequential increase of clonal PCs with MGUS evolution.

Table 4 *Incidence of deletion 13q14 in patients with MGUS, SMM, and overt MM*

	MGUS		SMM		Overt MM
Overall	16/79	NS[a]	5/21	NS	41/102
			$P < 0.01$		
In majority of PCs (*i.e.*, >60%)	3/79	$P = 0.05$	4/21	NS	41/102
			$P < 0.000001$		
In subclones only	13/79	NS	1/21	NS	0/102
			$P < 0.0001$		

[a] NS, nonsignificant.

For the first time, we showed on a large series of patients that structural chromosomal abnormalities are present in a high proportion of patients with MGUS/SMM. We focused our study on two of the most recurrent changes found in MM, *i.e.*, 14q32 rearrangements and 13q14 deletions. Illegitimate *IGH* rearrangements were observed in 36 of 79 patients with MGUS (46%) and 10 of 21 patients with SMM (48%). These incidences are lower than that found in overt MM (61%). This difference could reflect a continuous mutational process in PCs, as shown by VH mutation analysis. However, it could also be interpreted as not significant, because of the possible inclusion of patients with very few clonal PCs, leading to a misclassification of these patients as nonprearranged (false-negative patients). The analysis of clonality using centromeric probes in patients lacking 14q32 abnormalities showed that some informative specimens contained only a small percentage of clonal PCs (6%, and possibly less). Because the cut-off for determination of illegitimate *IGH* rearrangements varied between 10% and 16%, we may have missed some patients with a 14q32 abnormality. Thus, the conclusion of this 14q32 study is that at least 46% of patients with MGUS/SMM display an illegitimate *IGH* rearrangement. We cannot rule out the hypothesis of an identical incidence in MGUS, SMM, and overt MM.

The second part of this 14q32 analysis was the search for specific translocations. We have previously shown that two translocations were highly recurrent in MM, *i.e.*, t(11;14) and t(4;14), respectively, found in 16% and 12% of patients. To a lesser degree, t(8;14) was also recurrent (3% of MM patients). Surprisingly, t(11;14) was observed in 15 patients, an incidence similar to that of overt MM. Based on published data (24, 25), this translocation was described as a poor prognostic cytogenetic abnormality and thus was not expected in this series of patients with MGUS/SMM. Other poor prognostic abnormalities (such as monosomy 13) might be responsible for the outcome of the patients reported previously. This similar incidence favors the hypothesis of a similar incidence of 14q32 abnormalities in MGUS/SMM and overt MM, rather than an ongoing acquisition during PC evolution.

In contrast, the second highly recurrent 14q32 abnormality, *i.e.*, t(4;14), was observed in only two patients. This lower incidence might be interpreted in two ways: (*a*) either it occurs later in PC oncogenesis; or (*b*) this specific translocation directly precipitates the PCs in a true myeloma cell. Hypothesizing a similar incidence of 14q32 abnormalities in MGUS/SMM and MM, we favor the second theory. Interestingly, the two patients bearing the t(4;14) have monosomy 13 in a large number of PCs. This association between the two chromosomal abnormalities is in agreement with the results found in MM. Apart from these 2 patients, deletion 13q14 or monosomy 13 was observed in 19 other patients. In contrast to the 14q32 abnormalities observed in the majority of clonal PCs, deletion 13q14 was often present in a subset of clonal PCs. Among the 21 patients with deletion 13q14, 13 were evaluable for clonality. Six patients displayed deletion 13q14 in the majority of clonal PCs, and seven patients presented deletion 13q14 only in subclones of PCs (Table 2). Of note, this latter finding was observed in six of nine evaluable patients with MGUS and in only one of four evaluable patients with SMM. This situation differs from MM, in which deletion 13q14 is usually observed in the large majority of clonal PCs. The presence of deletion 13q14 in patients with MGUS/SMM was also unexpected. This abnormality has been clearly associated with a poor outcome in MM (23, 26) and represents one of the most powerful prognostic factors in MM. However, the incidence of deletion 13q14 is twice as low in MGUS/SMM as in MM. Moreover, we have recently shown that deletion 13q14 was tightly associated with post-MGUS MM. These data, together with the higher percentage of clonal PCs bearing deletion 13q14 in SMM than in MGUS, support the hypothesis of a possible acquisition of deletion 13q14 during MGUS evolution. This chromosomal change could be involved in the transition between MGUS and MM. In this regard, the evolution of these patients with deletion 13q14 will be very interesting.

In conclusion, the analysis of this large series of patients demonstrated for the first time the presence of structural chromosomal changes in MGUS/SMM. Moreover, the comparison of the results obtained in MGUS, SMM, and overt MM (Tables 3 and 4) enables us to construct a theoretical model of PC oncogenesis. Whereas 14q32 abnormalities are early events, deletion 13q14 is involved in the transition of MGUS to MM. Although other oncogenetic changes could be implicated in this transition, a close survey of our MGUS/SMM patient cohort will be of great value in validating (or invalidating) this model.

References

1. Kyle, R. A., and Lust, J. A. Monoclonal gammopathies of undetermined significance. Semin. Hematol., *26:* 176–200, 1989.
2. Kyle, R. A. "Benign" monoclonal gammopathy: after 20 to 35 years of follow-up. Mayo Clin. Proc., *68:* 26–36, 1993.
3. Blade, J., Lopez-Guillermo, A., Rozman, C., Cervantes, F., Salgado, C., Aguilar, J. L., Vives-Corrons, J. L., and Montserrat, E. Malignant transformation and life expectancy in monoclonal gammopathy of undetermined significance. Br. J. Haematol., *81:* 391–394, 1992.
4. Ocqueteau, M., Orfao, A., Almeida, J., Blade, J., Gonzalez, M., Garcia-Sanz, R., Lopez-Berges, C., Moro, M. J., Hernandez, J., Escribano, L., Caballero, D., Rozman, M., and San Miguel, J. F. Immunophenotypic characterization of plasma cells from monoclonal gammopathy of undetermined significance patients. Implications for the differential diagnosis between MGUS and multiple myeloma. Am. J. Pathol., *152:* 1655–1665, 1998.
5. Dewald, G. W., Kyle, R. A., Hicks, G. A., and Greipp, P. R. The clinical significance of cytogenetics studies in 100 patients with multiple myeloma, plasma cell leukemia or amyloidosis. Blood, *66:* 380–390, 1985.
6. Gould, J., Alexanian, R., Goodacre, A., Pathak, S., Hecht, B., and Barlogie, B. Plasma cell karyotype in multiple myeloma. Blood, *71:* 453–456, 1988.
7. Laï, J. L., Zandecki, M., Mary, J. Y., Bernardi, F., Izydorczyk, V., Flactif, M., Morel, P., Jouet, J. P., Bauters, F., and Facon, T. Improved cytogenetics in multiple myeloma: a study of 151 patients including 117 patients at diagnosis. Blood, *85:* 2490–2497, 1995.
8. Sawyer, J. R., Waldron, J. A., Jagannath, S., and Barlogie, B. Cytogenetics findings in 200 patients with multiple myeloma. Cancer Genet. Cytogenet., *82:* 41–49, 1995.
9. Calasanz, M. J., Cigudosa, J. C., Odero, M. D., Ferreira, C., Ardanaz, M. T., Fraile, A., Carrasco, J. L., Sole, F., Cuesta, B., and Gullon, A. Cytogenetic analysis of 280 patients with multiple myeloma and related disorder: primary breakpoints and clinical correlations. Genes Chromosomes Cancer, *18:* 84–93, 1997.
10. Drach, J., Angerler, J., Schuster, J., Rothermundt, C., Thalhammer, R., Haas, O. A., Jager, U., Fiegl, M., Geissler, K., Ludwig, H., and Huber, H. Interphase fluorescence *in situ* hybridization identifies chromosomal abnormalities in plasma cells from patients with monoclonal gammopathy of undetermined significance. Blood, *86:* 3915–3921, 1995.
11. Zandecki, M., Obein, V., Bernardi, F., Soenen, V., Flactif, M., Laï, J. L., Francois, M., and Facon, T. Monoclonal gammopathy of undetermined significance: chromosome changes are a common finding within plasma cells. Br. J. Haematol., *90:* 693–696, 1995.
12. Zandecki, M., Laï, J. L., Genevieve, F., Bernardi, F., Volle-Remy, H., Blanchet, O., Francois, M., Cosson, A., Bauters, F., and Facon, T. Several cytogenetic subclones may be identified within plasma cells from patients with monoclonal gammopathy of undetermined significance, both at diagnosis and during the indolent course of this condition. Blood, *90:* 3682–3690, 1997.
13. Avet-Loiseau, H., Li, J. Y., Facon, T., Brigaudeau, C., Morineau, N., Maloisel, F., Rapp, M. J., Talmant, P., Trimoreau, F., Jaccard, A., Harousseau, J. L., and Bataille, R. High incidence of translocations t(11;14)(q13;q32) and t(4;14)(p16;q32) in patients with plasma cell malignancies. Cancer Res., *58:* 5640–5645, 1998.
14. Nishida, K., Tamura, A., Nakazawa, N., Ueda, Y., Abe, T., Matsuda, F., Kashima, K., and Taniwaki, M. The Ig heavy chain gene is frequently involved in chromosomal translocations in multiple myeloma and plasma cell leukemia as detected by *in situ* hybridization. Blood, *90:* 526–534, 1997.
15. Avet-Loiseau, H., Li, J. Y., Morineau, N., Facon, T., Brigaudeau, C., Harousseau, J. L., Grosbois, B., and Bataille, R., on behalf of the Intergroupe Francophone du Myélome. Monosomy 13 is associated with the transition of monoclonal gammopathy of undetermined significance to multiple myeloma. Blood, *94:* 1999.
16. Kyle, R. A., and Greipp, P. R. Smoldering multiple myeloma. N. Engl. J. Med., *302:* 1347–1349, 1980.
17. Durie, B. G. M., and Salmon, S. E. Multiple myeloma, macroglobulinaemia and monoclonal gammopathies. *In:* A. V. Hoffbrand, M. C. Brain, and J. Hirsh (eds.), Recent Advances in Haematology, pp. 243–261. Edinburgh, London, New York: Churchill Livingstone, 1977.
18. Rack, K. A., Delabesse, E., Radford-Weiss, I., Bourquelot, P., Le Guyader, G., Vekemans, M., and Macintyre, E. A. Simultaneous detection of *MYC*, *BVR1*, and

PVT1 translocations in lymphoid malignancies by fluorescence *in situ* hybridization. Genes Chromosomes Cancer, *23:* 220–226, 1998.
19. Barlogie, B., Alexanian, R., Dixon, D., Smith, L., Smallwood, L., and Delasalle, K. Prognostic implications of tumor cell DNA and RNA content in multiple myeloma. Blood, *66:* 338–342, 1985.
20. Zandecki, M., Bernardi, F., Laï, J. L., Facon, T., Izydorczyk, V., Bauters, F., and Cosson, A. Image analysis in multiple myeloma at diagnosis: correlation with cytogenetic study. Cancer Genet. Cytogenet., *74:* 115–119, 1994.
21. Flactif, M., Zandecki, M., Laï, J. L., Bernardi, F., Obein, V., Bauters, F., and Facon, T. Interphase fluorescence *in situ* hybridization (FISH) as a powerful tool for the detection of aneuploidy in multiple myeloma. Leukemia (Baltimore), *9:* 2109–2114, 1995.
22. Drach, J., Schuster, J., Nowotny, H., Angerler, J., Rosenthal, F., Fiegl, M., Rothermundt, C., Gsur, A., Jaeger, U., Heinz, R., Lechner, K., Ludwig, H., and Huber, H. Multiple myeloma: high incidence of chromosomal aneuploidy as detected by interphase fluorescence *in situ* hybridization. Cancer Res., *55:* 3854–3859, 1995.
23. Perez-Simon, J. A., Garcia-Sanz, R., Tabernero, M. D., Almeida, J., Gonzalez, M., Fernandez-Calvo, J., Moro, M. J., Hernandez, J. M., San Miguel, J. F., and Orfao, A. Prognostic value of numerical chromosome aberrations in multiple myeloma: a FISH analysis of 15 different chromosomes. Blood, *91:* 3366–3371, 1998.
24. Laï, J. L., Michaux, L., Dastugue, N., Vasseur, F., Daudignon, A., Facon, T., Bauters, F., and Zandecki, M. Cytogenetics in multiple myeloma: a multicenter study of 24 patients with t(11;14)(q13;q32) or its variant. Cancer Genet. Cytogenet., *104:* 133–138, 1998.
25. Fonseca, R., Witzig, T. E., Gertz, M. A., Kyle, R. A., Hoyer, J. D., Jalal, S. M., and Greipp, P. R. Multiple myeloma and the translocation t(11;14)(q13;q32): a report on 13 cases. Br. J. Haematol., *101:* 296–301, 1998.
26. Seong, C., Delasalle, K., Hayes, K., Weber, D., Dimopoulos, M., Swantkowski, J., Huh, Y., Glassman, A., Champlin, R., and Alexanian, R. Prognostic value of cytogenetics in multiple myeloma. Br. J. Haematol., *101:* 189–195, 1998.