Brief report

Translocation t(14;16) and multiple myeloma: is it really an independent prognostic factor?

Hervé Avet-Loiseau,[1] Florent Malard,[1] Loic Campion,[2] Florence Magrangeas,[1] Catherine Sebban,[3] Bruno Lioure,[4] Olivier Decaux,[5] Thierry Lamy,[6] Laurence Legros,[7] Jean-Gabriel Fuzibet,[8] Mauricette Michallet,[9] Bernadette Corront,[10] Pascal Lenain,[11] Cyrille Hulin,[12] Claire Mathiot,[13] Michel Attal,[14] Thierry Facon,[15] Jean-Luc Harousseau,[16] Stephane Minvielle,[1] and Philippe Moreau,[17] for the Intergroupe Francophone du Myélome

[1]Hematology Laboratory, University Hospital, and Inserm U892, Nantes, France; [2]Department of Statistics, Centre René Gauducheau, Nantes, France; [3]Hematology Department, Centre Léon Bérard, Lyon, France; [4]Hematology Department, University Hospital, Strasbourg, France; [5]Internal Medicine Department, University Hospital, Rennes, France; [6]Hematology Department, University Hospital, Rennes, France; [7]Hematology Department, University Hospital, Nice, France; [8]Internal Medicine Department, University Hospital, Nice, France; [9]Hematology Department, University Hospital, Lyon, France; [10]Hematology Department, University Hospital, Annecy, France; [11]Hematology Department, Centre François Baclesse, Rouen, France; [12]Hematology Department, University Hospital, Nancy, France; [13]Hematology Laboratory, Institut Curie, Paris, France; [14]Hematology Department, University Hospital, Toulouse, France; [15]Hematology Department, University Hospital, Lille, France; [16]Hematology Department, Centre René Gauducheau, Nantes, France; and [17]Hematology Department, University Hospital, Nantes, France

Many trials in myeloma are stratified on cytogenetic abnormalities. Among them, the most commonly chosen are the t(4;14), the del(17p), and the t(14;16). If data are well established for t(4;14) and del(17p), very few data support the use of t(14;16). To address this issue, we retrospectively analyzed 1003 patients with newly diagnosed myeloma for this abnormality. We identified 32 patients with the t(14;16). Compared with patients lacking the t(14;16), we did not observe any difference in overall survival ($P = .28$). Moreover, in multivariate analyses, the t(14;16) was not prognostic ($P = .39$). In conclusion, our data do not support the use of t(14;16)-specific probes in the diagnostic panels of multiple myeloma. (*Blood*. 2011; 117(6):2009-2011)

Introduction

As in other malignancies, multiple myeloma (MM) is characterized by a huge landscape of chromosomal abnormalities. Among this genetic chaos, a few random chromosomal changes have been identified, such as the *IGH* translocations, deletions 13q or 17p, or gains of 1q. Among the *IGH* translocations, 5 seems to be recurrent: t(11;14), t(6;14), t(4;14), t(14;16), and t(14;20). Whereas the 2 first deregulate cyclin D genes, the 2 latter deregulate 2 *MAF* genes, *c-MAF* and *MAFB*, respectively.[1,2] These 2 genes are known oncogenes, whose deregulation might participate in the MM oncogenic process.[3]

It has been reported in a pivotal study from the Mayo Clinic that the t(14;16)(q32;q23) was associated with a poor outcome.[4] Even though the series was small (only 15 patients with t(14;16)), most of the MM investigators (including us) did integrate this message and looked for this abnormality in their diagnostic panel. Another more recent report from the University of Arkansas[5] suggested that MAF overexpression, which can be observed outside of the context of t(14;16),[6] was associated with a shorter survival, even in patients treated with the Total Therapy 3 program. To try to confirm these data, we performed a retrospective study in a large series of patients (1003 patients), including 698 patients with a long follow-up.

Methods

Patient samples were all analyzed for fluorescence in situ hybridization in a central laboratory in Nantes, France. Young patients (younger than 65 years) were treated in the IFM 99-02 and 99-04 trials,[7,8] which used a VAD (vincristin-adriamycin-dexamethasone) induction, followed by a double-intensive melphalan course (735 patients). Older patients were treated within the IFM 99-06 trial,[9] which randomized MP (melphalan-prednisone), versus MPT (MP + thalidomide), versus double-intermediate-dose melphalan (233 patients). All patients signed an informed consent form in accordance with the Declaration of Helsinki, and all studies were approved by the University Hospital of Nantes. Upon receipt, bone marrow plasma cells were sorted using nanobeads and an anti-CD138 antibody (RoboSep, Stem Cell Technologies). After immunomagnetic sorting, the plasma cell suspension purity was verified, and only samples with at least 90% of plasma cells were kept. Cells were then fixed in Carnoy fixative. To test plasma cells for the t(14;16), we did use a specific *IGH-MAF* fusion probe (Abbott Molecular). Hybridizations were performed according to the manufacturer's instructions. For analysis, at least 100 plasma cells with correct signals were scored using a Zeiss epifluorescence microscope.

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Table 1. Prognostic factors (with a β_2-microglobulin cutoff of 4 mg/L)

Parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (n = 697)	1.03 (1.02-1.05)	< .0001	1.03 (1.01-1.05)	< .001
β_2-microglobulin ≥ 4 vs < 4	2.02 (1.65-2.47)	< .0001	2.26 (1.74-2.93)	< .0001
t(4,14) positive vs negative	2.24 (1.72-2.92)	< .0001	2.63 (1.88-3.67)	< .0001
del(17p) ≥ 60 vs < 60	2.57 (1.88-3.50)	< .0001	2.51 (1.71-3.68)	< .0001
del13 > 0 vs 0	1.63 (1.34-1.97)	< .0001	1.39 (1.05-1.83)	.021
t(14,16) positive vs negative	1.28 (0.82-2.01)	.281	1.24 (0.76-2.02)	.388

HR indicates hazard ratio; and CI, confidence interval.

Results and discussion

To assess the prognostic value of t(14;16), we did select patients with 3 conditions: (1) clinical follow-up data, (2) follow-up of at least 3 years for alive patients, and (3) stored plasma cells. We found frozen samples for 1084 patients. After slide preparation and hybridization, 81 patients were excluded because of lack of enough cells (69 patients) or hybridization failure (12 patients). Among the 1003 analyzable patients, a translocation t(14;16) was observed in 32 patients. This large series confirms the very low incidence of this chromosomal abnormality in MM (3.2%). These patients did not differ from the control population, except for a higher incidence of leukemic presentation (15% vs 1.5% in the control series). Their median age was 63 years (45-75 years). The control population was in agreement with previously published data,[10] with an incidence of t(4;14) of 15% and a del(17p) incidence of 10% (defined by presence in at least 60% of the plasma cells, as previously published).[9] As expected, no patient presented both t(14;16) and t(4;14). A del(17p) was observed in 3 patients with t(14;16). In contrast, a del(13) was observed in 78% of them.

Several prognostic comparisons were performed. To assess the prognostic value of t(14;16), we compared the outcome of 30 patients with t(14;16) and a full analysis of other parameters with that of 698 patients lacking t(14;16) but analyzed for all other parameters. In univariate analysis, t(14;16) was not prognostic ($P = .28$), in contrast to age, β_2-microglobulin level (tested with 2 different cutoff, 4 or 5.5 mg/L), t(4;14), del(17p), and del(13) (Tables 1-2). In multivariate analyses, the *P* value associated with t(14;16) was even less significant ($P = .39$). Despite a higher incidence of leukemic presentation in the patients with t(14;16) (14% vs 0%), no difference was observed for overall survival. This difference with the Mayo Clinic's results may be the result of the small numbers (15 patients in the Mayo Clinic's report, 30 patients in this series), but also to treatment differences. The Mayo Clinic patients were treated with conventional chemotherapy, whereas 60% of ours received a double-intensive regimen. Furthermore, in the Mayo Clinic study, a clear association with other prognostic parameters was found. For instance, the median β_2-microglobulin level was 5.4, versus 4.2 in our study, not different from the whole population. In addition, the incidence of del(17p) was 33% in the Mayo series versus 9% in our study, an incidence not different from that of the general population. Thus, we think that the main explanation of the survival difference is related to other confounding poor prognostic factors in the Mayo Clinic experience. We cannot perform any comparison with the University of Arkansas Medical School data because individual data from patients with MAF overexpression are not available.

In conclusion, we do not confirm the poor prognostic value of t(14;16). Even though this study is statistically limited by the relatively small number of patients (resulting from the low incidence of t(14;16), 3%), it will be difficult to obtain larger series. However, we encourage other groups to analyze this abnormality in prospective trials to confirm (or not) our data.

Authorship

Contribution: H.A.-L., F. Magrangeas, P.M., and S.M. designed the research; H.A.L. and P.M. wrote the manuscript; F. Malard and H.A.-L. performed the fluorescence in situ hybridization experiments; L.C. performed statistical analyses; and C.S., B.L., O.D., T.L., L.L., J.-G.F., M.M., B.C., P.L., C.H., C.M., M.A., T.F., J.-L.H., and P.M. provided patient samples and clinical follow-up.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Hervé Avet-Loiseau, Laboratoire d'Hématologie, Institut de Biologie, 9, quai Moncousu, 44093 Nantes, France; e-mail: havetloiseau@chu-nantes.fr.

Table 2. Prognostic factors (with a β_2-microglobulin cutoff of 5.5 mg/L)

Parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (n = 697)	1.03 (1.02-1.05)	$< 10^{-6}$	1.03 (1.01-1.05)	$< 10^{-3}$
β_2-microglobulin ≥ 5.5 vs < 5.5	1.98 (1.60-2.45)	$< 10^{-6}$	2.16 (1.64-2.84)	$< 10^{-6}$
t(4,14) positive vs negative	2.24 (1.72-2.92)	$< 10^{-6}$	2.56 (1.83-3.58)	$< 10^{-6}$
del(17p) ≥ 60 vs < 60	2.57 (1.88-3.50)	$< 10^{-6}$	2.47 (1.68-3.62)	$< 10^{-5}$
del13 > 0 vs 0	1.63 (1.34-1.97)	$< 10^{-6}$	1.36 (1.03-1.80)	.030
t(14,16) positive vs negative	1.28 (0.82-2.01)	.281	1.25 (0.76-2.03)	.377

HR indicates hazard ratio; and CI, confidence interval.

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