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

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Abstract:

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). In order 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). When 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 neither 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.

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, five seems to be recurrent: t(11;14), t(6;14), t(4;14), t(14;16), and t(14;20). Whereas the two first deregulate cyclin D genes, the two latter deregulate two *MAF* genes, *c-MAF* and *MAFB*, respectively.^{1,2} These two genes are known oncogenes, whose deregulation might participate to 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 look for this abnormality in their diagnostic panel. Another more recent report from the University of

Arkansas⁵ suggested that MAF overexpression (that can be observed outside of the context of t(14;16))⁶ was associated with a shorter survival, even in patients treated with Total Therapy 3 program. In order 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.

Patients, Materials and Methods

Patient samples were all analyzed for fluorescence *in situ* hybridization (FISH) in a central laboratory in Nantes, France. Young patients (under 65 years of age) were treated in the IFM 99-02 and 99-04 trials,^{7,8} that 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, StemCell Technologies, Vancouver, Canada). After immuno-magnetic 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’s fixative. To test plasma cells for the t(14;16), we did use a specific *IGH-MAF* fusion probe (Abbott Molecular, Rungis, France). 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.

Results and Discussion

In order to assess the prognostic value of t(14;16), we did select patients with 3 conditions: (i) with clinical follow-up data, (ii) with a follow-up of at least 3 years for alive patients, and (iii) of course with 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% versus 1.5% in the control series). Their median age was 63 (45-75). 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. In order 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 cut-off, 4 or 5.5 mg/L), t(4;14), del(17p), and del(13) (Tables 1 and 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% versus 0%), no difference was observed for overall survival. This

difference with the Mayo's results may be due to the small numbers (15 patients in the Mayo's report, 30 patients in this series), but also to treatment differences. The Mayo's patients were treated with conventional chemotherapy, whereas 60% of ours received a double intensive regimen. Furthermore, in the Mayo 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. Also, 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 believe that the main explanation of the survival difference is related to other confounding poor prognostic factors in the Mayo experience. We cannot perform any comparison with the UAMS data, since 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 (due to 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

HAL, PM and SM designed the research; HAL and PM wrote the manuscript; FM and HAL performed the FISH experiments; LC performed statistical analyses; CS, BL, OD, TL, LL, JGF, MM, BC, PL, CH, CM, MA, TF, JLH and PM provided patients samples and clinical follow-up. The authors have no financial conflict of interest to disclose.

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Table 1

Prognostic factors (with a β 2-microglobulin cut-off at 4 mg/L)

Parameters	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 \geq 4 vs <4	2.02 (1.65-2.47)	<10 ⁻⁶	2.26 (1.74-2.93)	<10⁻⁶
t(4,14) pos vs neg	2.24 (1.72-2.92)	<10 ⁻⁶	2.63 (1.88-3.67)	<10⁻⁶
del(17p) \geq 60 vs <60	2.57 (1.88-3.50)	<10 ⁻⁶	2.51 (1.71-3.68)	<10⁻⁵
del13 >0 vs 0	1.63 (1.34-1.97)	<10 ⁻⁶	1.39 (1.05-1.83)	0.021
t(14,16) pos vs neg	1.28 (0.82-2.01)	0.281	1.24 (0.76-2.02)	0.388

Table 2

Prognostic factors (with a β 2-microglobulin cut-off at 5.5 mg/L)

Parameters	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 \geq5.5 vs <5.5	1.98 (1.60-2.45)	<10 ⁻⁶	2.16 (1.64-2.84)	<10⁻⁶
t(4,14) pos vs neg	2.24 (1.72-2.92)	<10 ⁻⁶	2.56 (1.83-3.58)	<10⁻⁶
del(17p) \geq 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)	0.030
t(14,16) pos vs neg	1.28 (0.82-2.01)	0.281	1.25 (0.76-2.03)	0.377