Advances in Brief

High Incidence of Translocations t(11;14)(q13;q32) and t(4;14)(p16;q32) in Patients with Plasma Cell Malignancies

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Abstract

Abnormalities involving the 14q32 region are recurrent chromosomal changes in plasma cell malignancies. Recent preliminary molecular analyses found IGH rearrangements in almost 100% of human myeloma cell lines and in 75% of patients. However, no systematic study analyzing the nature of the partner chromosomal regions have been reported thus far. To define the exact incidence of illegitimate IGH rearrangements and the respective incidence of partner genes cloned to date, we analyzed 141 patients with either multiple myeloma (MM, n = 127) or primary plasma cell leukemia (PCL, n = 14) using fluorescence in situ hybridization. The overall incidence of illegitimate recombinations was 57% (80 of 141 patients). Analysis of this incidence according to Durie and Salmon stage, patients’ status, i.e., MM versus primary PCL and diagnosis versus relapse, immunoglobulin type and subtype, and β2-microglobulin value, did not show any correlation. To analyze the nature of the partner chromosomal region, we selected probes specific for the following genes: FGFR3, and CCND1. A recent study available (12), CCND1 remains a very good candidate. We investigated four HMCLs and five MM patients with t(11;14) and found overexpression of CCND1 in all these nine cases.5 Other identified partner genes include MYC (8q24), BCL2 (18q21), FGFR3 (4p16), IRF4 (6p25; Refs. 13 and 14), and more recently MAF (16q23; Ref. 15).

Recently, analyses of the IGH gene using Southern blotting (1) and FISH (10) have shown that illegitimate recombinations occur in almost 100% of HMCLs and 75% of 42 MM patients, from the only study available (10). In contrast to other B-cell malignancies, MM presents IGH breakpoints that occur in the constant regions and that usually involve switch regions (1). Consequently, these illegitimate recombinations are supposed to occur during the isotypic switch process. The discrepancy between cytogenetic and molecular incidences of IGH illegitimate rearrangements might be due to cryptic translocations, as shown recently with the t(4;14) (13, 16), or the t(14;16) (15). However, the role of these translocations in the pathogenesis of MM remains unclear. Actually, the multiplicity of the partner chromosomal regions does not support the hypothesis that the deregulated partner gene would be responsible of the MM genesis. Another possibility could be that the illegitimate switch itself would deregulate plasma cell differentiation and cause MM. However, this theory would suppose that illegitimate recombinations occur in 100% of the patients, which does not seem to be the case (10). Another explanation could be that these genetic changes would play a key role in tumor progression. Depending on the nature of the partner gene, the disease course would be more or less aggressive.

Using FISH, we have conducted an analysis of 141 patients with either MM or primary PCL to address the following questions: (a) what is the exact incidence of IGH illegitimate rearrangements? (b) what is the respective incidence of the partner chromosomal regions, with analysis of the 4p16, 8q24, 11q13, 16q23, and 18q21 regions? and (c) Is there any correlation between the presence or not of such rearrangements and the main prognostic features at diagnosis?

Patients and Methods

Patients. We have analyzed 101 consecutive previously untreated patients with MM diagnosed in the clinical departments participating in the study. Furthermore, 14 patients with a primary PCL and 26 patients at first relapse were included. The diagnostic criteria of MM were those of the Southwest

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4 The abbreviations used are: IGH, immunoglobulin heavy chain; MM, multiple myeloma; PCL, plasma cell leukemia; HMCL, human myeloma cell line; FISH, fluorescence in situ hybridization; YAC, yeast artificial chromosome; MUGS, monoclonal gammopathy of undetermined significance.

Oncology Group (17). Primary PCL was diagnosed in cases with more than 20% malignant plasma cells in peripheral blood (or more than 2 × 10⁹/μL). Monoclonal isotype was IgG in 72 patients, IgA in 49 patients, and light chains or other rare variants in 6 patients. In MM, there were 27 patients with stage I, 26 with stage II, and 48 with stage III. For the 71 first patients, conditions for enrolling in the study were the presence of numerical abnormalities on karyotype or on the FISH screening with 10 centromeric probes (1, 3, 7, 8, 11, 15, 17, 18, and X) and a bone marrow plasmacytosis of at least 10%. Patients without detectable numerical abnormality, but with >50% plasma cells in the sample, were also included (three patients). Interphase FISH was performed on cytogenetic preparations. Malignant plasma cell nuclei were identified on the basis of aneuploidy (monosomy or trisomy) for the control probe. For the 70 last patients, no restrictive condition was used because the chromosome evaluation was performed on highly purified malignant plasma cells. Plasma cells were sorted using an immunomagnetic method (MACS; Miltenyi Biotec, Auburn, CA). Plasma cells were labeled with the B-B4 monoclonal antibody as described previously (18) and isolated on columns, according to the manufacturer’s instructions. After purification, cells were cytocentrifuged, and purity was assessed based on morphology. Cells were then fixed in methanol:acetic acid until analysis.

HMCLs. Detection of illegitimate IGH recombinations using interphase FISH was validated on HMCLs with documented rearrangements (JJN3, U266, NCI-H929, OPM2, XG1, XG2, XG5, LP1, and AMO1). The XGs HMCLs were established by ourselves (19). OPM2, LP1, and NCI-H929 were purchased from DSM (Braunschweig, Germany) and U266 from American Type Culture Collection (Rockville, MD). JJN3 was a generous gift from Dr. Van Camp (VUB, Brussels, Belgium), and AMO1 was from Dr. Minowada (Fujisaki Cell Center, Okayama, Japan).

Probes. α-Satellite probes specific for chromosomes 3, 7, 8, 11, 15, 17, and 18 were obtained from American Type Culture Collection, whereas probes specific for chromosome 1 heterochromatin and chromosome X centromere were kindly provided by Dr. Kuo (UCSF Cancer Center, San Francisco, CA). The IGH locus was analyzed using three probes (Fig. 1): the Y6 YAC probe was a kind gift from Dr. Matsuda (Kyoto University, Kyoto, Japan) and Ig10 cosmid probe was kindly provided by Dr. Rabbits (Medical Research Council, Cambridge, United Kingdom). A BAC clone (158A2) was isolated by screening of a BAC library (generously provided by Dr. Batzer, Stanley Scott Cancer Center, New Orleans, LA), using a JH-specific cDNA probe (20). The FGFR3 locus was analyzed using the PAC probe described by Chesi et al. (13). The MAF locus was analyzed using a pool of 3 YACs described by Chesi et al. (15). A BCL2-specific YAC clone (922E7) was obtained by screening of the CEPH mega-YAC library using a BCL2 cDNA probe. The MYC locus was analyzed using two YAC probes (12 and P72), generously provided by Dr. Veronese (Jefferson Cancer Institute, Philadelphia, PA). These different probes were labeled using standard nick translation, with biotin-dUTP (Boehringer Mannheim, Germany), FITC-dUTP, coumarin-dUTP (NEN, Germany), and SpectrumOrange-dUTP (Vysis, Downers Grove, IL). The CCND1 probe was provided by Vysis.

FISH. After labeling, 50 ng of each probe were mixed with 1 μg of Cot-1 DNA, precipitated, and resuspended in 10 μl of Hybrisol VII (Oncor, Gaithersburg, MA). After denaturation and preannealing for 15 min at 37°C, the hybridization mixture was placed on slides (previously denatured in 70% formamide) at 37°C. After overnight hybridization at 37°C, slides were washed in 2× SSC at 73°C for 5 min and rinsed in 2× SSC/0.1% Triton X-100. Slides hybridized with biotin-labeled probes were then incubated with avidin-FITC (BioAtlantic, Nantes, France) at 37°C for 10 min and rinsed in 2× SSC/0.1% Triton X-100. Nuclei were then counterstained with 4′,6-diamidino-2-phenylindole in an antifade solution.

Results

Validation of Probes. FISH using the IGH-specific probes (Y6, Ig10, and 158A2) gave two strong well-defined signals on control metaphase spreads and interphase lymphocyte nuclei (Fig. 2). Detection of illegitimate IGH recombinations using interphase FISH was validated on HMCL with documented rearrangements (JJN3, U266, NCI-H929, OPM2, XG1, XG2, XG5, LP1, and AMO1). Using differentially labeled Y6 and Ig10 probes on interphase nuclei, illegitimate recombinations were shown by absence of at least one fusion signal (i.e., separated green and red signals, or only a green signal corresponding to the Ig10 probe; Fig. 3B). Specific translocations
Fig. 3. A, hybridization of the Y6 (red), Ig10 (green), and chromosome 1 (purple) probes on a plasma cell. This patient displayed a germ-line configuration (colocalization of the red and green signals) and a trisomy 1q (three purple signals), enabling the positive identification of malignant plasma cells. B, hybridization of the Y6 (red), Ig10 (green), and chromosome 1 (purple) probes on a plasma cell. This patient displayed an illegitimate IGH rearrangement (split of the Y6 and Ig10 probes) and a trisomy 1q (three purple signals). C, hybridization of the 158A2 (green), Ig10 (green), CCND1 (red), and chromosome 3 centromere (purple) probes on a plasma cell of a patient with trisomy 3 and a t(11;14)(q13;q32). The two fused signals (white) correspond to the duplication of der(14), whereas the green signal corresponds to the normal chromosome 14 and the red signal to the normal chromosome 11. D, hybridization of the 158A2 (green), Ig10 (green), and FGFR3 (red) probes on a plasma cell of a patient with a t(4;14)(p16;q32). The white fused signal corresponds to der(14), the green signals to the normal chromosome 14, and der(14) and the red signal to the normal chromosome 4.

involving the IGH gene were detected using combination of the Ig10 and 158A2 probes. The t(11;14)(q13;q32) was shown by a fusion of the 14q32 and CCND1 probes on the der(14) (Fig. 3C), with usually a split of the CCND1 probe and occasionally a split of the 14q32 probes. This probe set has been validated on mantle cell lymphomas and on the XG1 and XG5 HMCLs, shown to share a t(11;14) by cytogenetics. The t(4;14)(p16;q32) was shown by a fusion of the 14q32 and FGFR3 probes on the der(14) (Fig. 3D) and was validated on the OPM2 and NCI-H929 HMCLs, according to published data (13). In both HMCLs, we have observed a fusion signal on the der(14) without a split of the FGFR3 probe. The t(8;14)(q24;q32) was detected as a fusion of the 158A2-Ig10 and I2-P72 probes on der(14), with usually a split of the MYC-specific probes. This probe combination has been validated on 10 patients with Burkitt's lymphoma and a t(8;14). The t(14;16)(q32;q23) was detected as a fusion of the MAF probes and the Y6 probe. In fact, because the YAC probes described by Chesi et al. (15) are centromeric to most breakpoints reported until now, we chose to detect the fusion signal on der(16). This set of probes was validated on the JJN3 cell line, according to Chesi et al. (15). Finally, the t(14;18)(q32;q21) was shown by a fusion of the 14q32 and YAC E7 probes. These probes have been validated on the Karpas 422 cell line, established from a follicular lymphoma and obtained from DSM and on 10 follicular lymphoma samples.7

6 H. Avet-Loiseau, personal data.

7 H. Avet-Loiseau, unpublished data.
**Delineation of IGH Rearrangements and Aneuploidy.** To detect illegitimate IGH rearrangements, we combined the Ig10 cosmid probe (labeled with biotin and detected with avidin-FITC) and the Y6 YAC probe (labeled with SpectrumOrange). On control cells (mononuclear bone marrow cells from six healthy donors), this probe combination appeared as two yellow (Y) or connected green (G) and orange (O) signals (Fig. 2B). Illegitimate rearrangements were defined as any variation of this feature. To diagnose an illegitimate configuration, the cutoff value was 8.7% (mean + 3 SD) on 2000 normal bone marrow cells. In patients, the most common rearrangement was a dissociation of one of the two fused probes (i.e., one Y, one G, and one O) but also the absence of one orange signal (YG), which corresponds to a deletion of the telomeric part of IGH or a loss of the derivative chromosome.

Aneuploidy was determined using repetitive probes, specific for chromosomes 1, 3, 7, 8, 9, 11, 15, 17, 18, and X. The cutoffs for trisomy were determined on 2000 normal bone marrow cells and were equal to 2.3, 5, 2.6, 3, 2.7, 4.9, 5.7, 3.2, 4.1, and 4.4%, respectively (mean + 3 SD). These 10 probes were used for determination of aneuploidy in patients without numerical abnormality on karyotype. For patients with several aneuploidies, we chose the probe with the lowest cutoff as a control.

**Patients.** Among patients for whom we did not sort plasma cells, 13 were excluded because of either absence of numerical chromosomal abnormality (3 patients) or <10% plasma cells (10 patients). For the last 70 patients included in the study, we were able to purify enough cells for analysis in each case. Morphological analysis of sorted cells showed a >97% purity. The analysis of the unsorted fraction showed absence of any plasma cell in each case.

**FISH.** At least 100 nuclei were analyzed in each patient. Two patients could not be analyzed for IGH interphase FISH because of repeated unsuccessful hybridization and were excluded from the analysis. In three patients, we found a unique fusion signal (Y configuration), presumably corresponding to monosomy 14. These three patients were considered nonrearranged, despite the abnormal configuration. A rearrangement was found in 60 of 101 previously untreated MM patients (59%) and 10 of 14 PCL patients (71%) at diagnosis and in 10 of 26 patients at relapse (38%). Among 80 patients with IGH rearrangement, 68 have a YGO configuration, 8 a YG configuration, 2 a YO configuration, and 2 a GGGO configuration (corresponding to a biallelic illegitimate recombination). No intrachromosomal variability was found, because the illegitimate rearrangement was detected in the large majority of cells (mean, 92%; range, 85–100). Of note, no statistically significant difference appears in IGH rearrangement incidence between stages I, II, and III, and neither between MM and primary PCL patients (Table 1).

Patients with an IGH rearrangement were then analyzed to characterize the partner region with FGFR3, MYC, CCND1, MAF, and BCL2 probes. Because illegitimate IGH rearrangements have been shown to involve switch regions, we combined the 158A2 and Ig10 probes to cover the entire constant region. One hundred thirty-five of the 141 patients could be analyzed for these specific translocations (no more available cells for 6 patients). Of note, none of the patients without illegitimate IGH rearrangement (as determined with Y6 and Ig10 probes) displayed a specific translocation. Twenty-three patients had an IGH-CCND1 fusion (19 MM and 4 primary PCL). One of these patients had a second illegitimate rearrangement involving an unknown partner. In 11 cases (8 MM and 3 primary PCL patients), more than one fusion signal was found (two to four; Fig. 3C). To further analyze these IGH-CCND1 fusions, we performed FISH experiments combining the Ig10 and CCND1 probes. In each case, we detected an equal number of fused signals with both probe combinations. These data strongly favor the hypothesis of der(14) duplication. An IGH-FGFR3 fusion was found in 17 patients (15 MM and 2 primary PCL; Fig. 3D). More than two FGFR3 signals (corresponding to a probable split of the FGFR3 probe) was present in 5 of 17 cases. To further analyze these five patients, we performed FISH using a chromosome 4 α-satellite probe. In all five cases, only two signals were observed. Although it is not a direct demonstration, this finding favors the hypothesis of a FGFR3 probe split. One patient displayed a biallelic illegitimate rearrangement: one IGH-FGFR3 fusion and one IGH-MYC fusion. Two other patients displayed an IGH-MYC fusion, and a single patient displayed an IGH-MAF fusion. No patient displayed an IGH-BCL2 fusion. Using metaphase FISH, three other specific translocations were identified: t(X;14)(q28;q32), t(9;14)(p13;q32), and t(12;14)(q24;q32).

**Correlations with Bioclinical Features.** As outlined in Table 1, we then analyzed FISH data according to the principal features available: stage, immunoglobulin type and subtype, C-reactive protein, and β2-microglobulin. At diagnosis, the incidence of IGH rearrangements was not statistically different in patients with stage I (17 of 27), stage II (17 of 26), stage III MM (26 of 48), or primary PCL (10 of 14). The incidence was also similar in patients at diagnosis (70 of 115) or at relapse (10 of 26). We then looked at correlations between IGH rearrangements and isotype. No statistically significant difference was found. We then compared this incidence with the β2-microglobulin value, and this analysis was restricted to patients at diagnosis. According to data published previously, the cutoff value of β2-microglobulin to discriminate good versus poor prognosis patients is 6 mg/l. The β2-microglobulin value was recorded for 97 of 115 previously untreated patients. We separated the patients within two groups: patients with a β2-microglobulin <6 mg/l and patients with a β2-microglobulin equal or superior to 6 mg/l. We then analyzed FISH data within these two groups. No statistically significant difference was found between patients with or without any IGH rearrangement.

**Discussion**

Chromosome 14q32 rearrangements were detected in 57% (80 of 141) and 71% (10 of 14) of patients with MM and primary PCL, respectively. This incidence is higher than that described in published cytogenetic (10–40%; Refs. 2, 3, and 5–7) or molecular (24%; Ref. 16) studies and similar to that published recently by Nishida et al. (10) using FISH (31 of 42). In stage I and II MM, illegitimate translocations occur with a similar incidence to that of stage III MM, primary PCL, and relapse cases, ruling out the hypothesis that these chromosomal abnormalities might be associated with tumor progression. To definitely confirm this observation, analysis of patients with a MGUS would be of major interest. If the same incidence is found in MGUS patients, it would confirm that these illegitimate rearrangements occur during the switch recombinatorial process, presumably during the first steps of MM genesis. Thus far, only a few patients with MGUS have

| Table 1 Detailed results of FISH analysis in 141 patients with either MM or primary PCL |
|---------------------------------|------------------|
| **Patient statusa** | **Illegitimate IGH rearrangement** | **No IGH abnormality** | **Overall** |
| MM | 70 | 57 | 127 |
| Diagnosis | 60 | 41 | 101 |
| Stage I | 17 | 10 | 27 |
| Stage II | 17 | 9 | 26 |
| Stage III | 26 | 22 | 48 |
| Relapse | 10 | 16 | 26 |
| Primary PCL | 10 | 4 | 14 |
| Overall | 80 | 61 | 141 |

*a* No statistically significant difference was found within these groups.

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been analyzed using this technique, showing evidence of illegitimate IGH rearrangements in three of five samples (10).

Nevertheless, our study enables the investigation of structural chromosomal changes in low cell mass MM stages. Thus far, cytogenetic studies were hampered by the low proliferative index of malignant plasma cells. In stage I, abnormal clones are usually found in <10% of patients. Using FISH, numerical chromosomal abnormalities have been demonstrated in the majority of these early stage MM patients. Thus, we have now demonstrated that structural abnormalities are present in minimally symptomatic or even asymptomatic MM patients.

In patients with IGH illegitimate rearrangements, we then investigated the incidence of the four major partner regions described thus far, i.e., FGFR3, MYC, CCND1, MAF, and BCL2. For this purpose, we selected and validated probes enabling the assessment of these specific recombinations on interphase cells. As expected, no patient with a normal interphase IGH configuration displayed a specific translocation. Among the 80 patients with an illegitimate IGH rearrangement (as shown by interphase FISH) and analyzed for these specific abnormalities, 42 (53%) displayed one rearrangement, and 2 patients had two rearrangements. In 23 cases, a fusion IGH-CCND1 was identified. This high incidence confirms that the t(11;14) is the most frequent translocation involving IGH in plasma cell malignancies (at least for the specific translocations identified thus far). Whereas an association between t(11;14) and an especially aggressive disease evolution has been suggested (21), we did not find any correlation with stage, immunoglobulin subtype, or β2-microglobulin level. Longer follow-up will be needed to correlate this specific abnormality with outcome.

The second most frequent specific rearrangement was the t(4;14)(p16;q32). Our study is the first evaluation of the incidence of this genetic abnormality in a large series of patients with either MM or primary PCL. Thus far, this abnormality has been found in HMCL and a few patients using molecular technologies (13, 16). For the first time, we demonstrate that this translocation occurs in about 12% (17 of 141) of patients with plasma cell malignancies. Molecular consequences of this abnormality are not yet completely clarified. The juxtaposition of FGFR3 and IGH sequences is supposed to deregulate the FGFR3 transcriptional control, with finally overexpression of the FGFR3 protein. Moreover, the translocation seems to be sometimes associated with activating gene mutations (13, 16). Thus far, the role of this FGFR3 up-regulation in MM genesis is not known. Regarding the high incidence of t(4;14) in MM, elucidation of the functions of this receptor in plasma cell regulation represents a major challenge for the future.

As opposed to these two specific and recurrent chromosomal changes, t(8;14) and t(14;18) seem to be rather infrequent. A MYC-IGH fusion was found in only three patients, whereas no BCL2-IGH fusion was observed. This low incidence of t(8;14) is in disagreement with cytogenetic series that reported this specific abnormality in a significant number of patients (3, 6, 7, 22). This discrepancy may be the consequence of the proliferative advantage conferred by up-regulation of MYC. Because proliferation is correlated with a higher proportion of abnormal karyotypes, cytogenetic studies may preferentially recruited patients with this specific abnormality. We did not find any t(14;18) in our series. This abnormality has been occasionally described in cytogenetics studies (8), and the absence of any BCL2-IGH fusion in our patients does not appear to be a significant discrepancy. This specific rearrangement is probably rather exceptional in MM patients. Recently, Chesi et al. (15) described a high incidence of IGH-MAF fusion in HMCLs. Moreover, they also reported overexpression of MAF in 8 of 22 MM patients. In our series, only one patient was found to harbor a t(14;16). This discrepancy might be explained by different mechanisms of MAF up-regulation (mutations, translocation with other loci, and others). Nevertheless, MAF does not seem to be frequently involved in IGH illegitimate recombinations.

Besides these 42 patients with specific recurrent translocations, 38 patients displayed a rearrangement but with other partner chromosomal regions. In three cases, metaphase FISH enabled to identify the partner chromosome (Xq28, 9p13, or 12q24). In the remaining 35 patients, we do not know the nature of the chromosome. Although we cannot exclude the possibility that a recurrent specific region would be involved (such as 4p16), these data are consistent with the apparent extreme variability of IGH partner in plasma cell malignancies.

What is the significance of these illegitimate IGH rearrangements in the MM genesis or progression? Because these chromosomal changes are not found in 100% of patients, they cannot be implicated as the primary event of plasma cell malignancies. They could play a role in the progression of the disease. Depending on the nature of the partner gene, the up-regulation of this gene by the translocation may confer proliferative or survival advantages to plasma cells already transformed by other still unknown factors. According to this concept, the partner chromosome would participate in the progression of the disease. Thus, we can speculate that the t(11;14), i.e., by up-regulating the CCND1 gene in most cases, will induce a higher proliferation and possibly a more aggressive form of the disease.

FISH data were then compared with the main bioclinical features at diagnosis, i.e., immunoglobulin isotype and β2-microglobulin level (which is one of the major biological prognostic factor at diagnosis). No correlation was found between IGH rearrangement incidence and immunoglobulin isotype. A more precise analysis looking at the type of IGH rearrangement (specific translocations, loss of the Y6 probe) failed to establish any correlation. Comparison of these results with β2-microglobulin levels did not show any correlation. This absence of correlation does not mean that IGH rearrangements do not have any prognostic value, but that they do not correlate with presently defined prognostic parameters. A longer follow-up will be necessary to answer this important question.

This study is the largest series analyzing the incidence of illegitimate IGH rearrangements in plasma cell malignancies. These events are found in ~60% of patients and seem to occur early in MM patients’ evolution. For the first time, we have generated data about the partner chromosomes independently of the presence of clonal metaphases. We have shown that two major translocations (covering one-half of the rearrangements) occur, i.e., t(11;14) and t(4;14). This latter translocation has never been evaluated previously in a MM patients series and was found in 12% of our cases. Illegitimate IGH rearrangements do not correlate with any bioclinical feature at diagnosis (stage, immunoglobulin type and subtype, and β2-microglobulin). Correlations with outcome will require a longer observation time.

References

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