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6q deletion in Waldenström macroglobulinaemia negatively affects time to transformation and survival

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Abstract

Deletion of the long arm of chromosome 6 (del6q) is the most frequent cytogenetic abnormality in Waldenström macroglobulinaemia (WM), occurring in approximately 50% of patients. Its effect on patient outcome has not been completely established. We used fluorescence *in situ* hybridisation to analyse the prevalence of del6q in selected CD19+ bone marrow cells of 225 patients with newly diagnosed immunoglobulin M (IgM) monoclonal gammopathies. Del6q was identified in one of 27 (4%) cases of IgM-monoclonal gammopathy of undetermined significance, nine of 105 (9%) of asymptomatic WM (aWM), and 28/93 (30%) of symptomatic WM (sWM), and was associated with adverse prognostic features and higher International Prognostic Scoring System for WM (IPSSWM) score. Asymptomatic patients with del6q ultimately required therapy more often and had a shorter time to transformation (TT) to symptomatic disease (median TT, 30 months vs. 199 months, respectively, $P < 0{\cdot}001$). When treatment was required, 6q-deleted patients had shorter progression-free survival (median 20 vs. 47 months, $P < 0{\cdot}001$). The presence of del6q translated into shorter overall survival (OS), irrespective of the initial diagnosis, with a median OS of 90 compared with 131 months in non-del6q patients ($P = 0{\cdot}01$). In summary, our study shows that del6q in IgM gammopathy is associated with symptomatic disease, need for treatment and poorer clinical outcomes.

Keywords: 6q deletion, Waldenström macroglobulinaemia, IgM-MGUS, FISH, prognosis.

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Introduction

Waldenström macroglobulinaemia (WM) is an indolent B-cell clonal disorder mainly affecting elderly patients. It can be considered an entity that is intermediate between chronic lymphoproliferative disorders (LPDs), low-grade lymphomas and monoclonal gammopathies, which highlights the uncertainty about its pathogenesis.[1,2] Immunophenotypic and molecular studies have helped characterise the malignant clone and determine the origin of the disease.[3–6] More recently, whole-genome sequencing has identified the innate immune signal transduction adaptor (*MYD88*) L265P mutation as a unifying event present in most patients with WM, a result subsequently confirmed by allele-specific polymerase chain reaction (AS-PCR) in a larger series.[7,8] Cytogenetic studies in WM have been partially hampered by the low mitotic index of the tumour cells, which is typical of weakly proliferative diseases. Thus, there are reports from only a few series of patients concerning the karyotypic findings of WM. The frequency of cytogenetic abnormalities in these series was low (17–37%), the 6q deletion (del6q) being the most recurrent alteration, with a frequency of 6–16%.[9–14] Fluorescence *in situ* hybridisation (FISH) overcomes the disadvantages of traditional chromosome banding and, with its greater sensitivity, confirmed the presence of this abnormality in 24–63% of WM.[15–20]

At the clinical level, the disease is behaviourally very heterogeneous, ranging from indolent (i.e., immunoglobulin M-monoclonal gammopathy of undetermined significance [IgM-MGUS] and asymptomatic WM [aWM]), to highly symptomatic (symptomatic WM [sWM]) forms.[1,21–23] Around one-third of patients are asymptomatic at the time of diagnosis and their disease may remain indolent for years, showing no progression.[24] Within sWM, the evolution is also variable, with some cases displaying features of an aggressive disease that requires several lines of treatment, the patients tending to survive for <1 year.[21,25,26] Several models of the prognosis of patients with WM, mainly based on initial clinical features, have been proposed.[27–30] The one most frequently used in clinical practice is the International Prognostic Scoring System for WM (IPSSWM), which stratifies patients by age, and by haemoglobin, platelet, serum β_2-microglobulin (B2M) and monoclonal component levels.[31] This score has been revised recently, confirming its association with the duration of disease-specific survival.[32] However, all these factors rely on host features and tumour burden indicators, whereas genetic determinants of clinical behaviour have not yet been included in routinely used prognostic tools for symptomatic patients.

Del6q is associated with an aggressive clinical presentation, including anaemia, hypoalbuminaemia, high levels of B2M and IgM production, and a trend towards shorter treatment-free survival, although with no significant differences in overall survival (OS).[15,17,18,20] Moreover, fully clonal del6q is also correlated with C-X-C motif chemokine receptor 4 (*CXCR4*) mutational status, showing a mutual exclusivity that suggests a shared role for the two events.[33] Del6q leads to the loss of B-lymphocyte-induced maturation protein 1 (*BLIMP1*) and tumour necrosis factor alpha-induced protein 3 (*TNFAIP3*), a negative regulator of the nuclear factor kappa B (NF-κB) pathway.[9,13,34] This activates B-cell receptor (BCR) signalling and interleukin 21 receptor (IL21R) expression, which could explain the aggressive behaviour of 6q-deleted WM cases despite the absence of *CXCR4* mutations.[10,35]

In present study, we have analysed the prevalence of del6q in a large series of patients with IgM monoclonal gammopathies and examined how this was associated with clinical and biological characteristics, and with patient outcome.

Patients and methods

Patients and samples

Bone marrow samples from 225 patients consecutively diagnosed with IgM monoclonal disorders between 1994 and 2019 were included. All patients were studied at the University Hospital of Salamanca (Spain) and managed according to the recommendations of the Spanish Waldenström Macroglobulinaemia Group (SWMG). Diagnostic criteria were those established by the consensus panel of the Second International Workshop on Waldenström Macroglobulinaemia, and consisted of the presence of IgM paraprotein in the serum, and infiltration of the bone marrow by lymphoplasmacytic lymphoma, as revealed by a trephine biopsy.[1] Diagnosis of aWM required the absence of any symptom attributable to the tumour burden or the paraprotein, and ≥3 months without treatment after initial diagnosis. It was distinguished from IgM-MGUS because the latter does not feature bone marrow infiltration, and from sWM by the presence of symptoms that made therapy necessary. When a trephine biopsy was not available, diagnosis was based on lymphoplasmacytic involvement, the bone marrow aspirate immunophenotype and, in the case of sWM, clinical features consistent with WM.

Using these criteria, 27 patients were diagnosed with IgM-MGUS, 105 with aWM and 93 with sWM. The median (interquartile range [IQR]) follow-up of the cohort was 8·8 (5·2–12·7) years. Clinical and biological characteristics are summarised in Table I. Patients were stratified according to IPSSWM score assigned to three established risk categories.[31]

The study and all procedures were performed in accordance with the Helsinki Declaration for research on human subjects, and approved by the University Hospital of Salamanca Review Board.

Flow cytometry study

Immunophenotype was evaluated by conventional methods, as previously described by our group,[36,37] and following the

Table I. Clinical and biological characteristics of the 225 monoclonal gammopathies included in the study

Characteristic	IgM-MGUS and aWM (n = 132)	sWM (n = 93)	P
Sex = Female, n (%)	47 (35·6)	20 (21·5)	0·03
Age, years, median (IQR)	70 (62–77)	71 (62–76)	0·7
LDH, n (%)			0·04
≥Upper limit of normal	6 (5)	11 (13·3)	
<Upper limit of normal	113 (95)	72 (86·7)	
Adenopathy or splenomegaly, n (%)			<0·001
Yes	10 (8·5)	24 (30·4)	
No	107 (91·5)	55 (69·6)	
Haemoglobin, g/l, n (%)			<0·001
≥115	113 (89·7)	24 (27·3)	
<115	13 (10·3)	64 (72·7)	
Platelets, x10^9/l (%)			0·006
≥100	124 (98·4)	79 (89·8)	
<100	2 (1·6)	9 (10·2)	
IgM, mg/dl, n (%)			<0·001
≥2000	35 (27·6)	72 (81·8)	
<2000	92 (72·4)	16 (18·2)	
B2M, mg/l, n (%)			<0·001
≥3	31 (27·7)	48 (59·3)	
<3	81 (72·3)	33 (40·7)	
Albumin, g/l, n (%)			<0·001
≥35	97 (80·2)	42 (48·8)	
<35	24 (19·8)	44 (51·2)	
ESR, mm/h, median (IQR)	43 (26–85)	118 (93–126)	<0·001
CRP, mg/l, median (IQR)	8 (3–28)	28 (10–65)	<0·001
Ig light chain, n (%)			0·2
κ	88 (71)	67 (79·8)	
λ	36 (29)	17 (20·2)	
MYD88 L265P, n (%)			0·2
Wild-type	21 (19·8)	9 (12)	
Mutated	85 (80·2)	66 (88)	
CXCR4 S338X, n (%)			0·5
Wild-type	86 (84·3)	54 (80·6)	
Mutated	16 (15·7)	13 (19·4)	
IPSSWM score, n (%)			<0·001
1	40 (35·4)	15 (18·3)	
2	69 (61·1)	30 (36·6)	
3	4 (3·5)	37 (45·1)	

Unavailable data were considered as missing and therefore not shown, for ease of reading the table. For most clinical parameters, a cut-off based on published data, if available, was established.
aWM, asymptomatic Waldenström macroglobulinaemia; B2M, β_2-microglobulin; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinaemia; IQR, interquartile range; LDH, lactate dehydrogenase; MGUS, monoclonal gammopathy of uncertain significance; sWM, symptomatic Waldenström macroglobulinaemia.

general recommendations of the EuroFlow group for evaluating haematological malignancies.[38–40] Data were acquired in a FACSCalibur flow cytometer (Becton Dickinson Biosciences, San Jose, CA, USA) using a two-step acquisition procedure for total and CD19+-only events. Data were analysed using Infinicyt software (Cytognos, Salamanca, Spain).

Immunophenotyping was performed to detect light chain restriction, presence of pan-B antigens (CD79a and CD20) in the tumour cells and expression of CD38 in the plasma cell population. WM, IgM-MGUS and other B-cell LPDs were distinguished based on the expression of other markers (CD5, CD10, CD23).

Fluorescence in situ *hybridisation (FISH) and molecular studies*

Deletion of 6q was assessed in all 225 patients by interphase FISH analysis performed on cell nuclei from CD19-positive B cells ($n = 174$) or whole bone marrow samples ($n = 51$), according to our previously published techniques.[41] Del6q was evaluated with a commercially available probe for 6q21 (Kreatech, Amsterdam, The Netherlands). A minimum of 200 cells were analysed in all samples and the cut-off point for the identification of the alteration was set at ≥10% cells with abnormal signal.

For molecular studies, DNA was extracted by conventional methods, either manually with the DNAzol reagent (MRC, Cincinnati, OH, USA), or automatically with the Maxwell® system (Promega Corp., Madison, WI, USA). *MYD88* L265P mutation was assessed by AS-PCR, as described elsewhere,[42] and *CXCR4* S338X was also assessed by AS-PCR with in-house primers.

Statistical analysis

Groups were compared using chi-square and Wilcoxon–Mann–Whitney tests, for categorical and continuous variables, respectively. Clinical outcomes were analysed as time-to-event data using the Kaplan–Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated from Cox proportional hazards models. Statistical analyses were done using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria) with a 5% level of significance. For asymptomatic cases, time to transformation (TT) was defined as the time between diagnosis and progression to sWM. Progression-free survival (PFS) was the time between beginning any anti-tumour therapy and the date of progression or death. OS was the length of time patients remained alive after diagnosis. Time to next treatment (TNT) was considered as the time between first- and second-line initiation.

Results

Cytogenetic and molecular studies

The 6q21 region, detected by FISH, was deleted in 38/225 (17%) patients, with important differences with respect to the underlying disease: one case of IgM-MGUS (one of 27,

Table II. Comparative clinical and biological characteristics of IgM monoclonal gammopathies, by del6q status

Characteristic	6q normal (n = 187)	Del6q (n = 38)	P
Diagnosis, n (%)			<0·001
IgM-MGUS and aWM	122 (65·2)	10 (26·3)	
sWM	65 (34·8)	28 (73·7)	
Sex = Female, n (%)	55 (29·4)	12 (31·6)	0·8
Age, years, median (IQR)	71 (62–77)	71 (62–76)	0·9
Symptoms, n (%)			0·02
Yes	28 (16·9)	11 (34·4)	
No	138 (83·1)	21 (65·6)	
LDH, n (%)			0·03
≥Upper limit of normal	11 (6·5)	6 (18·2)	
<Upper limit of normal	158 (93·5)	27 (81·8)	
Adenopathy or splenomegaly, n (%)			0·5
Yes	27 (16·5)	7 (21·9)	
No	137 (84·5)	25 (78·1)	
Haemoglobin, g/l, n (%)			<0·001
≥115	123 (69·5)	14 (37·8)	
<115	54 (30·5)	23 (62·2)	
Platelets, $x10^9$/l, n (%)			0·7
≥100	167 (94·4)	36 (97·3)	
<100	10 (5·7)	1 (2·7)	
IgM, mg/dl (%)			<0·001
≥2000	78 (43·6)	29 (80·6)	
<2000	101 (56·4)	7 (19·4)	
B2M, mg/l, n (%)			<0·001
≥3	56 (35·2)	23 (67·6)	
<3	103 (64·8)	11 (32·4)	
Albumin, g/l, n (%)			0·01
≥35	122 (70·9)	17 (48·6)	
<35	50 (29·1)	18 (51·4)	
ESR, mm/h, median (IQR)	72 (73–102)	118 (102–125)	<0·001
CRP, mg/l, median (IQR)	11 (3–34)	63 (10–99)	0·02
Ig light chain, n (%)			0·2
κ	125 (72·7)	30 (83·3)	
λ	47 (27·3)	6 (16·7)	
MYD88 L265P, n (%)			0·08
Wild-type	28 (18·8)	2 (6·3)	
Mutated	121 (81·2)	30 (93·7)	
CXCR4 S338X, n (%)			1
Wild-type	116 (82·9)	24 (17·2)	
Mutated	24 (17·1)	5 (82·8)	
IPSSWM score, n (%)			0·01
1	50 (31·1)	5 (14·7)	
2	83 (51·5)	16 (47·1)	
3	28 (17·4)	13 (38·2)	
Required therapy, n (%)			<0·001
Yes	94 (50·3)	37 (97·4)	
No	93 (49·7)	1 (2·6)	

Unavailable data were considered as missing and therefore not shown, for ease of reading table.

aWM, asymptomatic Waldenström macroglobulinaemia; B2M, β_2-microglobulin; CRP, C-reactive protein; Del6q, 6q deletion; ESR, erythrocyte sedimentation rate; Ig, immunoglobulin; IPSSWM, International Prognostic Scoring System for Waldenström Macroglobulinaemia; IQR, interquartile range; LDH, lactate dehydrogenase; MGUS, monoclonal gammopathy of uncertain significance; sWM, symptomatic Waldenström macroglobulinaemia.

4%), nine patients with aWM (nine of 105, 9%), and 28 cases of sWM (28/93, 30%). Therefore, del6q was significantly more frequent in patients with symptomatic than indolent IgM gammopathies (28 [30%] vs. 10 [8%], $P < 0{\cdot}001$, Table II).

MYD88^{L265P} and *CXCR4*^{S338X} mutations were assessed by AS-PCR in 181 and 169 patients, respectively. In this series, 151/181 (83%) patients carried the *MYD88* mutation, while 29/169 (17%) were *CXCR4*-mutated (Table I). No relationship was found between the presence of del6q and these alterations. Five of 29 (17%) patients with del6q also had the *CXCR4*^{S338X} mutation (Table II). All were symptomatic and received active treatment, three of them including at least two lines (Table SI).

Association with clinical characteristics

To evaluate the impact of del6q on disease presentation, we examined the clinical and biological baseline information of the enrolled patients. Patients with del6q more frequently presented with high levels of B2M (68% vs. 36%, $P < 0{\cdot}001$) and lactate dehydrogenase (LDH, 18% vs. 7%, $P = 0{\cdot}03$), anaemia (62% vs. 31%, $P < 0{\cdot}001$), B-symptoms (34% vs. 17%, $P = 0{\cdot}02$), and hypoalbuminaemia (51% vs. 29%, $P = 0{\cdot}01$). The quantity of paraprotein, which is also of prognostic influence in WM, was greater in patients with del6q compared with patients without the deletion (median, 31.1 g/l; [IQR] 24.9-43.7 g/l vs. 17.0 g/l, [IQR] 8.2-32.6 g/l, $P < 0{\cdot}001$). Two other features of interest had significantly higher values in patients with del6q: the erythrocyte sedimentation rate (ESR) (median [IQR] 118 [102–125] vs. 72 [33–102] mm/h, $P < 0{\cdot}001$) and the level of C-reactive protein (CRP) (median, 0.063 g/l, [IQR] 0.01-0.099 g/l vs. 0.011 g/l, [IQR] 0.003-0.034 g/l, $P = 0{\cdot}02$). There were no differences related to sex, age, presence of lymphadenopathy and/or splenomegaly, or type of light chain (kappa vs. lambda) (Table II).

We then analysed the correlation between del6q and the IPSSWM score, evaluated at the time of diagnosis, for WM. The distribution of risk groups differed significantly between patients carrying del6q and those without it: 15%, 47% and 38% vs. 31%, 51% and 18%, for low-, intermediate- and high-risk patients, respectively ($P = 0{\cdot}02$, Table II).

Prognostic impact of del6q on monoclonal gammopathies

There was a higher frequency of del6q in patients receiving therapy (37/131, 28%) than in untreated patients (one of 94, 1%) ($P < 0{\cdot}001$, Table II) as the alteration was more common in the symptomatic disease (30% vs. 8%) but also in asymptomatic patients progressing to sWM. In this series, 38/132 patients with asymptomatic disease (IgM-MGUS or aWM) at the time of initial diagnosis progressed to symptomatic WM and needed therapy, nine of whom had del6q (nine of 38, 24%). By contrast, in the group of non-

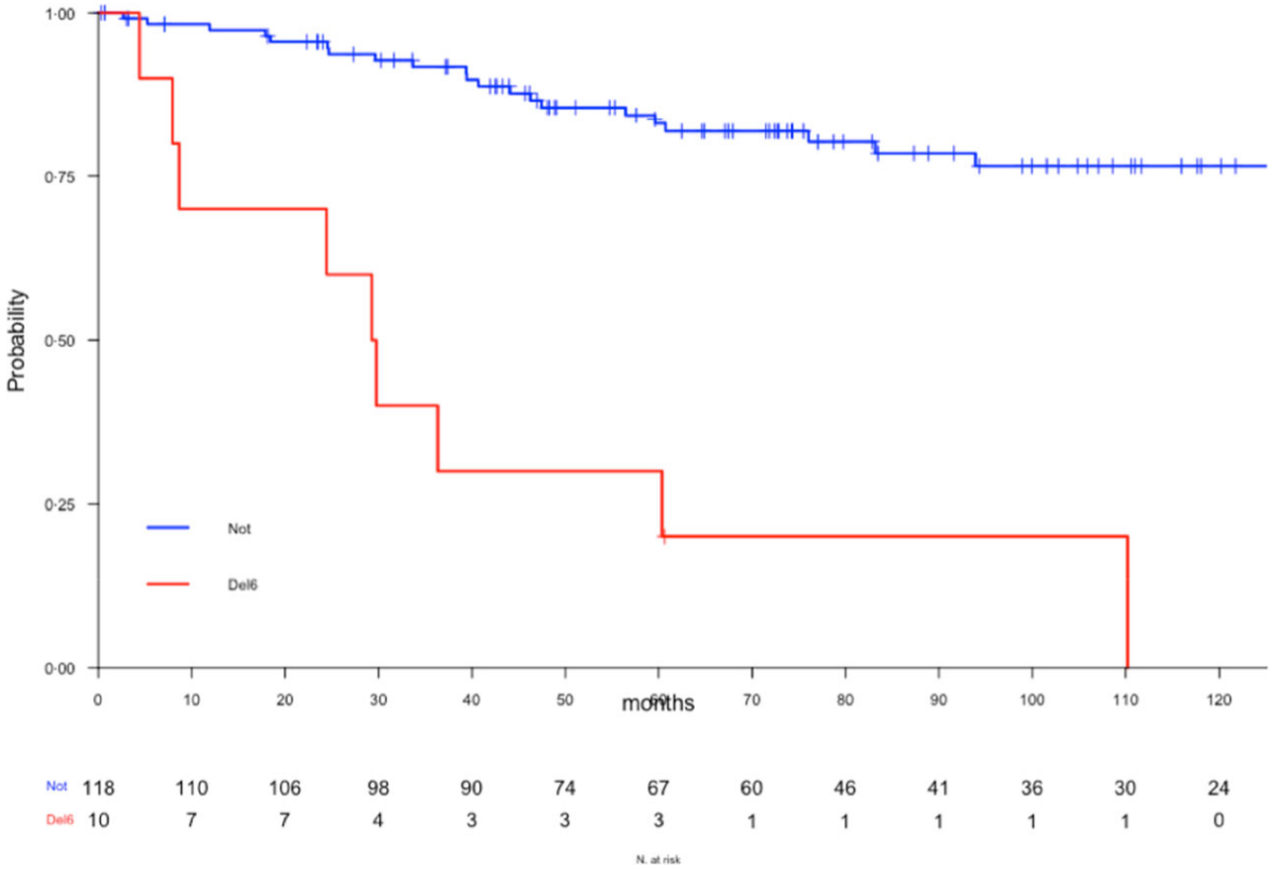

Fig 1. Time to transformation (TT) for patients with indolent monoclonal gammopathies, by 6q status. Patients with 6q deletion (red line) required treatment sooner than those without 6q deletion (blue line). [Colour figure can be viewed at wileyonlinelibrary.com]

progressing patients, there was only one case with the alteration (one of 94, 1%, $P < 0{\cdot}001$, Table SI). Consistent with the above, asymptomatic patients with del6q had a shorter TT than patients without the deletion (median 30 vs. 199 months, $P < 0{\cdot}001$, Fig 1). Thus, at 5 years, TT probability was 85% (95% CI 78–92%) and 30% (95% CI 12–77%) for patients with and without the deletion, respectively.

Of the patients who received treatment at any time, PFS was significantly shorter for those with the del6q alteration (median PFS 20 vs. 47 months, $P < 0{\cdot}001$, Fig 2). The PFS probabilities at 5 years were 34% (95% CI 24–50%) and 5% (95% CI 1–34%) for patients without and with the del6q alteration, respectively. To confirm that worse-risk patients were in the del6q group, we introduced del6q and diagnosis in a multivariate Cox regression model. Analysis showed that the impact of del6q was maintained irrespective of the initial diagnosis, with a HR of 2·6 for deletion (95% CI 1·6–4·3, $P < 0{\cdot}01$) and a HR of 1·3 for diagnosis (95% CI 0·7–2·3, $P = 0{\cdot}5$, Fig. 2). Considering only cases with sWM at diagnosis, TNT was longer for patients without del6q, although the difference was not statistically significant (median 48 vs. 28 months, $P = 0{\cdot}06$, Fig 3). Finally, OS was shorter for patients with del6q, irrespective of the initial diagnosis in the univariate analysis, with a median of 90 months (95% CI 52–154 months) compared with 131 months (95% CI 113–170 months) for patients without the deletion ($P = 0{\cdot}01$, Fig 4). The OS probability was 89% (95% CI 79–100%) vs. 93% (95% CI, 90–97%) at 2 years, 63% (95% CI 48–82%) vs. 79% (95% CI 72–85%) at 5 years, and 37% (95% CI 22–62%) vs. 56% (95% CI 48–66%) at 10 years, for patients with and without del6q, respectively. However, in the multivariate Cox regression model only an initial diagnosis of sWM was significantly associated with an increased risk of death (HR 2·6, 95% CI 1·7–4·0; $P < 0{\cdot}01$, Fig 4).

Discussion

Information about cytogenetic abnormalities in WM is very limited because it is difficult to obtain tumour metaphases for karyotype studies and the disease is rare. Therefore, studies of the associations between the cytogenetic profile and the clinical outcome of patients with WM are complex and require the use of aggregate data from multiple institutions, and in many cases the expected prognostic impact is not found. Some groups have observed that patients with del6q have poor prognostic features, but found no clear correlation between this abnormality and survival outcomes.[15,18,20]

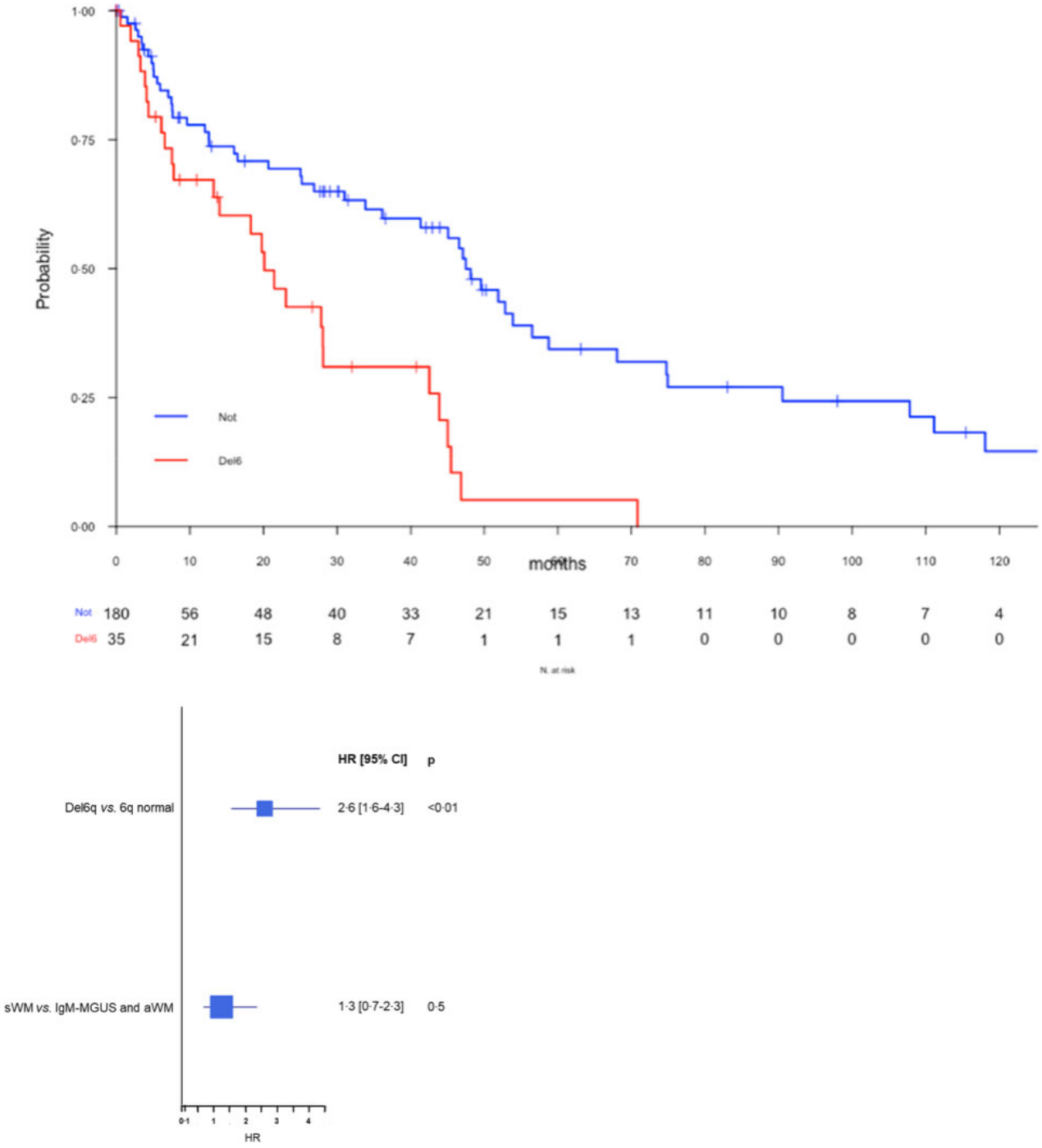

Fig 2. Progression-free survival (PFS) of patients with IgM monoclonal gammopathies by 6q deletion (del6q), and forest plot for diagnosis and del6q. Patients with del6q (red line) had significantly poorer PFS than patients with without the deletion (blue line). Forest plot was done to test the effect on the outcome of individual variables (diagnosis and del6q). Hazard ratios were calculated comparing first vs. second group of each variable. aWM, asymptomatic Waldenström macroglobulinaemia; CI, confidence interval; HR, hazard ratio; Ig, immunoglobulin; MGUS, monoclonal gammopathy of uncertain significance; sWM, symptomatic Waldenström macroglobulinaemia. [Colour figure can be viewed at wileyonline library.com]

In the present series, del6q was present in 17% of patients with IgM monoclonal gammopathies, as revealed by FISH analysis. Previous reports had already shown, by conventional cytogenetics[9–14] or FISH,[15–20] that deletion of chromosome 6q is the most common cytogenetic abnormality in WM. Furthermore, del6q is known to be a marker associated with WM, although not exclusively, as it has also been detected in several B-cell neoplasms, including multiple

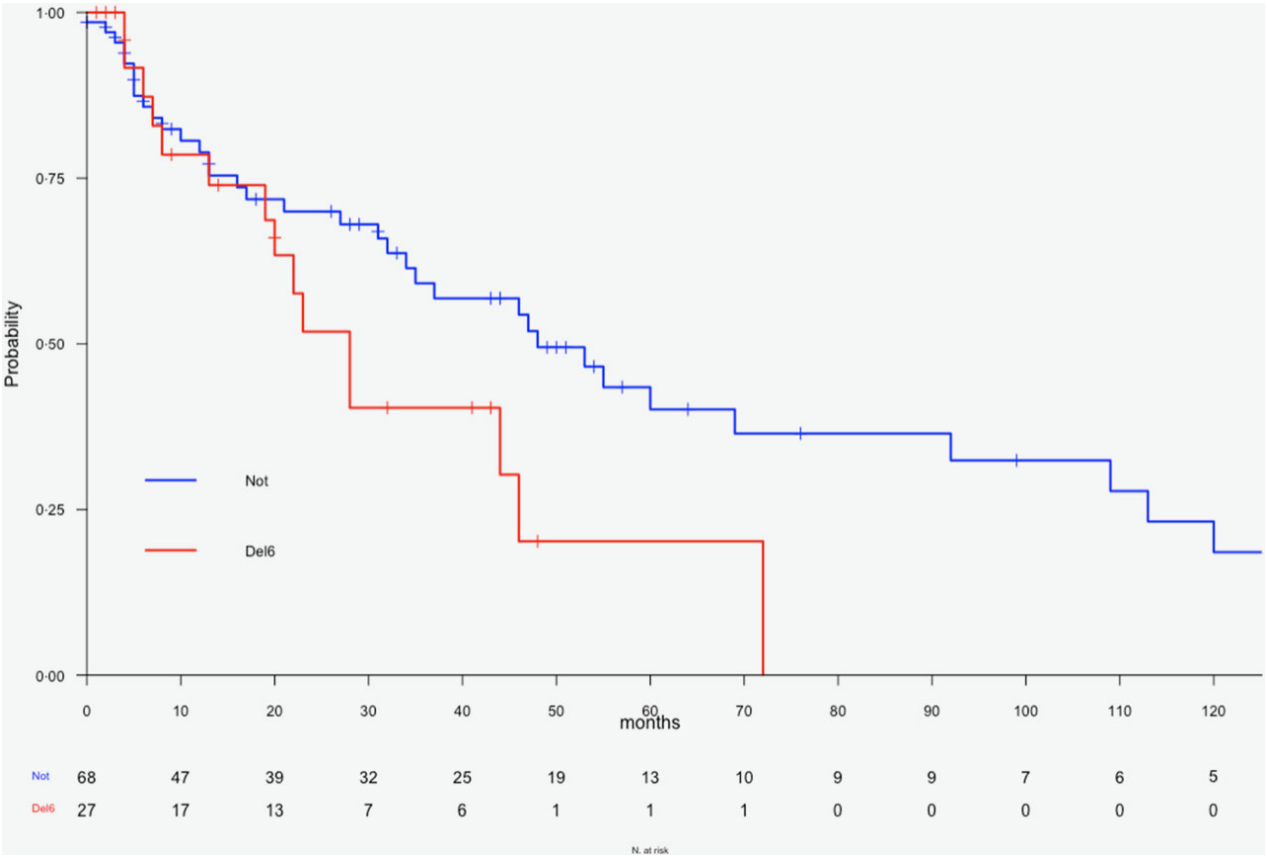

Fig 3. Time to next treatment (TNT) for patients with symptomatic Waldenström macroglobulinaemia at diagnosis with respect to 6q deletion (del6q). A trend towards shorter TNT is observed for patients with del6q (red line) compared to patients without del6q (blue line). [Colour figure can be viewed at wileyonlinelibrary.com]

myeloma and marginal zone lymphoma.[43–46] Specifically, in the case of IgM gammopathies, we observed a much higher frequency in symptomatic forms of the disease (30% vs. 4% and 9% for sWM vs. IgM-MGUS and aWM, respectively). In addition, asymptomatic patients carrying the alteration were more likely to progress to sWM (24% vs. 1%), consistent with the findings of other studies that concluded that del6q is a secondary event associated with the transition from IgM-MGUS to WM.[17,47,48] However, a detailed mapping study has shown that a minimal 6q region is deleted in most WMs, including asymptomatic forms,[33] suggesting that only large deletions detected by FISH are associated with disease aggressiveness. Although the timing of del6qs and the mechanism driving disease progression are unknown, it would be worthwhile assessing the 6q status of patients with asymptomatic forms of IgM monoclonal gammopathies.

With regard to disease presentation, patients with del6q displayed clinical features associated with adverse prognosis, such as anaemia or high levels of B2M and paraproteinaemia. Accordingly, the distribution of IPSSWM scores was disproportionally shifted towards the high-risk group in patients with del6q. Acute phase reactants, like CRP or ESR, also showed higher levels in patients with del6q, probably due to the disease-driven inflammatory state. All these observations are consistent with those of previous studies,[15,20,49] so careful follow-up of patients harbouring del6q would be of considerable value. Biologically, loss of key regulators of apoptosis, BCR and NF-κB signalling may be responsible for the more aggressive behaviour. The MYD88/interleukin 1 receptor-associated kinase (IRAK)1,4 complex and the NF-κB pathway, which is highly deregulated in patients with del6q, could be targets for future combined treatment strategies.[10,35]

Fully clonal del6qs, assessed by real-time PCR, and *CXCR4* mutations are known to be mutually exclusive in WM.[33] However, other groups have found a greater frequency of del6q, analysed by FISH, in *CXCR4*-mutated than in wild-type patients.[49] In our present cohort, 13% of patients with the del6q showed both alterations concomitantly, although the clonality of del6q was not evaluated.

Overall, we have shown for the first time that del6q is associated with shorter survival, measured as PFS and OS, in a series of patients with WM. This finding could be explained by the long follow-up (8·8 years) of the study and the homogeneous management of the patients. It seems beyond doubt that, at least in asymptomatic patients, del6q

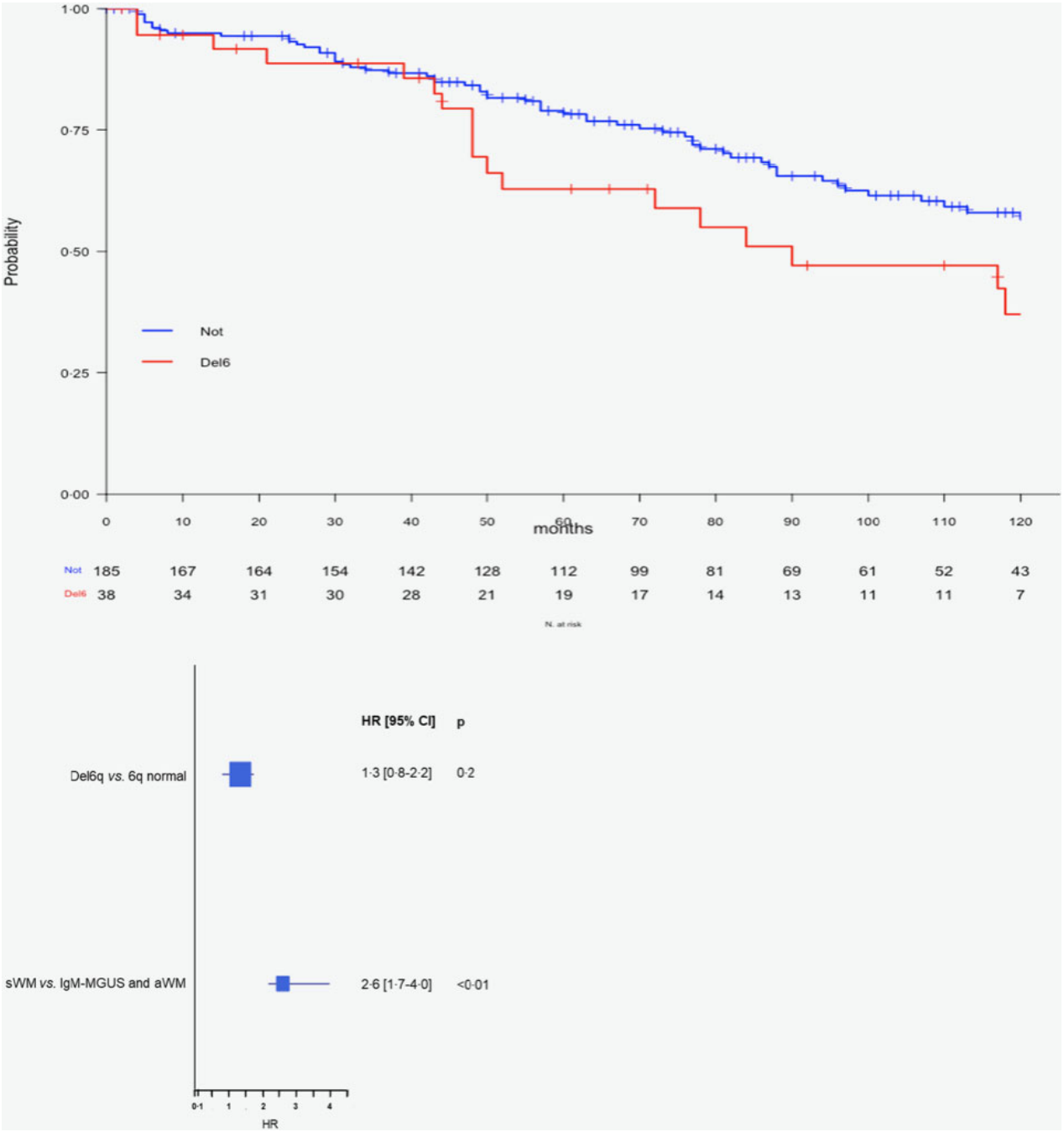

Fig 4. Overall survival (OS) in IgM monoclonal gammopathies with respect to 6q deletion (del6q), and forest plot for diagnosis and del6q. Patients with del6q (red line) had a significantly worse OS than those without del6q (blue line), regardless of diagnosis. Forest plot was done to test the effect on the outcome of individual variables (diagnosis and del6q). Hazard ratios were calculated comparing first vs. second group of each variable. aWM, asymptomatic Waldenström macroglobulinaemia; CI, confidence interval; HR, hazard ratio; Ig, immunoglobulin; MGUS, monoclonal gammopathy of uncertain significance; sWM, symptomatic Waldenström macroglobulinaemia. [Colour figure can be viewed at wile yonlinelibrary.com]

at diagnosis is indicative of inferior outcome, as these patients will more likely evolve to symptomatic WM. The expected association, confirmed by our present study, indicates that integration of complex biological data with clinical risk factors is one of the upcoming challenges in translational medicine. Moreover, for longitudinal and large studies, data quality and retrievability become critically important.[50] This will allow a personalised and comprehensive interpretation of

patient data, which will influence treatment algorithms and determine the nature of the follow-up.

In summary, our present results show that detection of del6q in IgM monoclonal gammopathies is necessary and easily achieved in clinical practice, and combined with clinical and biological data, may improve risk stratification and outcome prediction, leading to a more personalised approach to patient management.

AUTHORSHIP CONTRIBUTIONS

Ramón García-Sanz, Irene Dogliotti, Cristina Jiménez and Gian Maria Zaccaria wrote the paper; Cristina Jiménez and Irene Dogliotti performed the molecular studies; Enrique María Ocio, Norma Carmen Gutiérrez and Noemí Puig were responsible for the immunophenotyping and cytogenetic analyses; Ramón García-Sanz and Miguel Alcoceba designed the database for the analysis; María García-Álvarez, Alejandro Medina, María del Carmen Chillón and María Eugenia Sarasquete collected the data; Gian Maria Zaccaria and Irene Dogliotti performed the statistical analyses; the clinicians Ramón García-Sanz, Araceli Rubio, Ilda Murillo, Fernando Escalante, Carmen Aguilera, Alejandro Medina, Alfonso García de Coca, Roberto Hernández, Julio Dávila, Noemí Puig, Verónica González de la Calle, Marcos González and Norma Carmen Gutiérrez were responsible for the patients and performed clinical evaluations; all the authors revised the manuscript.

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Conflicts Of Interest

The authors declare that they have no potential conflicts of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Clinical and biological characteristics of the patients stratified by initial diagnosis and del6q status.

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