The t(14;20) is a poor prognostic factor in myeloma but is associated with long-term stable disease in monoclonal gammopathies of undetermined significance

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ABSTRACT

A large series of plasma cell dyscrasias (n=2207) was examined for translocations which deregulate the *MAF* genes, t(14;20)(q32;q12) and t(14;16)(q32;q23), and their disease behavior was compared to a group characterized by the t(4;14)(p16;q32) where CCND2 is also up-regulated. The t(14;20) showed low prevalence in myeloma (27/1830, 1.5%) and smoldering myeloma (1/148, <1%) with a higher incidence in MGUS (9/193, 5% *P*=0.005). Strong associations with del(13) (76%), non-hyperdiploidy (83%) and gain of 1q (58%) were seen but no association with an IgA M-protein or absence of bone disease was noted. All three translocations were associated with poor outcome in myeloma, but strikingly all t(14;20) MGUS/smoldering myeloma cases (n=10) had stable, low level disease. In contrast, the 10 t(14;16) and 25 t(4;14) MGUS/smoldering myeloma cases were associated with both evolving and non-evolving disease. None of the associated genetic abnormalities helped to predict for progression from MGUS or smoldering myeloma. *(Clinicaltrials.gov identifier: ISRCTN 68454111; UKCRN ID 1176)*

Key words: plasma cell, myeloma, MGUS, chromosome abnormality, disease progression.

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Introduction

Approximately half of myeloma (MM) cases are characterized by translocations into the immunoglobulin heavy chain locus (IgH). Each translocation subgroup is associated with deregulation of a D group cyclin either directly, such as occurs with the t(11;14) (cyclin D1) and t(6;14) (cyclin D3) or indirectly, such as occurs with the t(4;14) or in the MAF translocation group.[1] The MAF translocation group includes the t(14;16) and t(14;20), both of which are rare in myeloma, but are thought to be associated with poor prognosis.[2] The mechanism of this poor outcome is thought to involve the consequences of MAF upregulation, which include upregulation of cyclin D2, effects on cell interaction and upregulation of apoptosis resistance.[3] As upregulation of cyclin D2 is also seen in the t(4;14) group where poor prognosis is well established,[4-8] it may be deregulation of this D group cyclin which is important in this respect. MM cases with t(4;14) show an excess of IgA M-protein type[9] and have been reported to be less likely to present with bone disease (1) but it is not clear whether this also applies to the other cyclin D2 dysregulating translocations, t(14;16) and t(14;20) cases.

MGUS is a benign premylomatous condition lacking the clinical sequelae of myeloma, but with a rate of transformation to myeloma of approximately 1% per year.[10] This relationship has led to the generation of disease models of myeloma based on the multistep progression of normal to MGUS through to myelomatous plasma cells.[11] In these models, initial genetic hits result in an immortalized plasma cell clone and additional changes lead to its transformation to clinical myeloma. With the recent recognition that essentially all myeloma cases have a pre-existing asymptomatic phase,[12-13] it becomes even more important to recognize which abnormalities affect the rate of progression.

The t(4;14) has been reported to be rare in MGUS and smoldering/asymptomatic MM (SMM), leading to the suggestion that it is associated with an aggressive disease process effectively bypassing this stage.[9,14] However, there are reports

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of several cases of stable MGUS and SMM with t(4;14), which argues against this hypothesis.[9,15-17] We report here the prevalence, genetic associations and outcome of patients with the t(14;20) and t(14;16) in a large series of MM, MGUS, and SMM cases and compare these to cases with a t(4;14). Particular emphasis has been placed on t(14;20) cases due to the almost complete absence of published information.

Design and methods

Patients

Bone marrow (BM) samples were received from UK hospitals with informed consent for cytogenetic testing. Adequate material was received from 2207 patients between January 2001 and November 2007. The diagnoses (made on standard criteria[18] with central revue of values but not slides) were MM 1,830 (with 1,695 diagnostic samples), plasma cell leukemia (PCL) 10, SMM 149, MGUS 192, amyloidosis (AL) not meeting the criteria for MM 26. The age range was 23 to 93 (MM, median 65 with 21% ≥75, MGUS median 69, SMM median 68, AL median 58, PCL median 59) with 1,284 male and 923 female patients. MGUS cases showed a slight excess of females (98F:94M). MM patients were treated with a variety of UK standard therapies; 1,020 were in the MRC myeloma IX trial[19] and the majority of younger patients received at least one autologous transplant.

FISH

Plasma cell purification and fluorescence *in situ* hybridization (FISH) studies using probes for 13q, IgH break-apart, t(11;14), t(4;14), t(14;16), MAFB break-apart, CCND3 break-apart, t(8;14), 17p deletion, enumeration of chromosomes 5, 9, 15 and 3, 7 and 22 was performed as described previously[20,21] with the addition of BAC RP11307C12 for CKS1B at 1q21, and confirmation that split IgH and MAFB indicated t(14;20) by hybridization of a single color (red) MAFB probe along with the FGFR3/IgH probe, resulting in fusions in all cases. One hundred cells were scored for each probe and the European Myeloma Network FISH workshop recommendations used for cut-offs (fusion/break-apart probes 10%, numerical abnormalities 20%). Ploidy was primarily deduced from the 5/9/15 probe combination[22] but all results were taken into account where only one of the 5/9/15 probes was gained.

Statistical analysis

Median follow-up was 31.7 months (range 4–290). Kaplan-Meier survival curves were calculated using MINITAB 14. Survival from diagnosis of MM was accepted for primary IgH translocations and ploidy regardless of the time of FISH testing as these are early changes. Analysis for deletions of 13q, 16q and 17p were only performed on patients studied at diagnosis. Incidences of genetic abnormalities and clinical associations were compared using Fisher's exact test.

Results and Discussion

Prevalence

In this series, overall, the MAF translocations have a prevalence of approximately 5%, making them a clinically significant subgroup of patients (Table 1). The t(14;20) is rare in MM or SMM with a prevalence of 1.5 and <1% respectively, but was unexpectedly higher (5%) in MGUS (P=0.005). This finding is consistent with a single report in a smaller number of cases.[23] Both the MM and MGUS cases showed the translocation in at least 70% of cells. The t(14;16) showed a prevalence of 3% (n=67) with a consistent distribution in each of the major disease subgroups. The prevalence of t(4;14) in MM was 11%, which is at the lower end of the range described (11-20%).[5-8] Nevertheless this appears to be an accurate reflection of the incidence of t(4;14) in UK MM patients. We have shown that the rate of IgH translocations is inversely proportional to age[20] and when only patients under the age of 66 are considered the incidence of t(4;14) in MM rose to 13%. In keeping with previous reports[9;14] the t(4;14) was significantly less frequent in MGUS than in MM or SMM (P=0.0002 and P=0.001 respectively).

Association with other factors

The t(14;20) is similar in its genetic associations to the t(14;16) and t(4;14). Of 37 patients with t(14;20), 28 (76%)

Table 1. Prevalence of t(14;20), t(4;14) and t(14;16) in different plasma cell dyscrasias and associations with other factors.

Abnormality	Diagnosis	Prevalence		del(13q)		NHRD**		del(17p)		del(16q)		1q gain		IgA		Bone disease at diagnosis	
		n/n	%	n/n	%	n/n	%	n/n	%	n/n	%	n/n	%	n/n	%	n/n	%
t(14;20)*	MM	27/1830	1.5	23/27	85	20/26	77	2/27	7	4/22	18	13/20	65	3/23	13	14/23	61
	SMM	1/149	<1	1/1		1/1		0/1		0/1		0/1		0/1			
	MGUS	9/192	5	4/9	44	9/9	100	0/9	0	0/9	0	1/4	25	0/9	0		
t(4;14)*	MM	198/1830	11	176/197	89	163/196	83	26/189	14	17/171	10	110/150	73	82/180	46	98/170	58
	SMM	19/148	13	15/19	79	15/19	79	2/19	11	2/18	11	10/12	83	5/19	26		
	MGUS	6/193	3	5/6	83	5/6	83	0/6	0	0/5	0	3/5	60	2/6	33		
t(14;16)*	MM	55/1830	3	41/54	76	52/54	96	4/53	8	8/55	15	26/38	68	19/49	39	23/40	58
	SMM	4/148	3	3/4	75	3/4	75	0/4	0	0/4	0	2/4	50	1/4	25		
	MGUS	6/193	3	4/6	67	6/6	100	0/6	0	0/6	0	3/6	50	1/6	17		
total	MM	1830		825/1819	45	748/1776	42	145/1765	8	305/1540	20	570/1379	41	388/1621	24	1026/1499	68
cases	SMM	149		56/149	37	62/144	43	2/146	1	15/123	12	42/109	39	23/96	24		
	MGUS	193		45/191	24	107/188	57	5/183	3	10/162	6	28/127	22	28/153	18		

** In addition there were 10 PCL patients, one with t(4;14) and 2 with t(14;16), and 26 AL amyloidosis patients, one of whom had a t(4;14); **NHRD = non-hyperdiploid.*

also had a del(13q) ($P<0.0001$ cf total del(13) cases). There was a strong association with a non-hyperdiploid (NHRD) karyotype (30/36, $P<0.0001$ cf total NHRD cases). Fewer cases could be tested for 1q. There was a strong association between 1q and all three translocations in MM but t(14;20) MGUS cases did not show an excess of 1q gain, although the difference from t(4;14) or t(14;16) cases was not significant.

The t(14;16), like the t(4;14) (Ref. #9 and Table 1; $P<10^{-7}$), has a higher prevalence in IgA myeloma (19/49 cf 388/1621 in total MM cases, $P=0.02$). No association with IgA isotype was seen with t(14;20) (only 3/23 cases IgA, 13%). Interestingly, none of the translocations showed an IgA excess in MGUS/SMM. The incidence of bone disease at diagnosis (Table 1) was significantly lower in t(4;14) and t(14;16) cases (both 58%) than for MM overall (68%, $P=0.006$ and $P=0.05$ respectively). Although the trend was also lower for t(14;20) at 61% (14/23) this was not significantly different from the overall incidence ($P=0.19$) which may be due to the small numbers.

Table 2. Genetic abnormalities, patient's characteristics and disease course in smoldering/asymptomatic MM and monoclonal gammopathies of undetermined significance patients with t(4;14), t(14;16) or t(14;20)

Translocation and diagnosis	Pt #	Age	Sex	PP	Other genetic changes			Stable	Time to progression or length of FU (months)	Median FU
					del(13)	*HRD*	*gain of 1q*			
t(4;14) MGUS	1230	56	F	IgAκ	√	-	-	lost	n/a	
	2715	65	F	IgGκ	√	-	√	yes	25	
	2664	42	M	IgGκ	√	-	nd	yes	31	
	1390	39	M	IgGλ	√	-	-	yes	57	44
	58	62	M	IgGλ	√	-	nd	yes	98	
	1275	58	M	IgAκ	-	√	√	no	44	
t(14;16) MGUS	1494	39	F	IgGλ	√	-	√	yes	17	
	2941	53	M	IgAλ	-	-	√	yes	23	34
	2190	66	M	IgGκ	√	-	√	yes	45	
	1189	63	F	IgGκ	-	-	√	yes	120*	
	837	47	F	IgGλ	√	-	√	no	44	61
	551	57	F	IgGλ	√	-	√	no	76*	
t(14;20) MGUS	2285	69	F	IgGκ	√	-	nd	yes	43	
	1655	50	M	IgG	-	-	nd	yes	46	
	1862	43	M	IgGλ	-	-	nd	yes	53	
	823	74	F	free λ	-	-	nd	yes	54	60
	976	78	M	IgGκ	√	-	-	yes	67**	
	842	75	M	IgGλ	-	-	-	yes	60	
	367	46	F	IgGλ	√	-	√	yes	77	
	630	58	M	IgGκ	-	-	-	yes	78	
	417	84	F	IgGλ	√	-	-	yes	74	
t(4;14) SMM	1342	65	M	IgGλ	√	-	√	yes**	9	
	508	61	F	IgGκ	√	√	-	yes	14	
	1252	56	M	IgGκ	√	-	-	yes	24	
	1516	77	M	IgGκ	√	√	√	yes	32	32
	1134	37	F	IgGκ	√	-	√	yes	52	
	1385	63	F	IgAκ	√	-	-	yes	60	
	1107	50	F	IgGκ	√	√	-	yes	67	
	1509	46	M	IgAλ	√	-	-	no	6+	
	105	68	M	IgGκ	√	-	√	no	7	
	2295	42	M	IgAκ	√	√	-	no	8	
	1597	63	F	IgGκ	√	√	√	no	11+	
	2543	58	F	IgGλ	√	-	√	no	15	
	1836[@]	60	F	IgAκ	√	-	√	no	16	
	2849	69	F	IgGκ	√	-	√	no	21	18.5
	1925	60	F	IgG	√	-	√	no	33	
	331	71	F	IgGκ	√	√	√	no	33	
	3269	36	F	IgGλ	√	-	nd	no	34	
	259	30	F	IgAκ	-	-	-	no	53	
	579	78	M	IgGκ	√	-	nd	no	78*	
t(14;16) SMM	1073	67	F	IgG	√	-	√	yes	55	61.5
	2198	60	F	IgGλ	√	-	-	yes	68	
	582	56	F	IgAκ	-	√	-	no	15	32
	1315	60	F	IgGλ	√	-	√	no	49	
t(14;20) SMM	866	44	F	IgG	√	-	-	yes	71	

**Pts 1189, 551 and 579 were studied at 86, 66 and 27 months after diagnosis; +pts 1509 and 1597 also had deletion of 17p, [@]pt 1836 also had a t(8;14); ** died of unrelated disease. SMM: smoldering/asymptomatic MM; MGUS: monoclonal gammopathies of undetermined significance.*

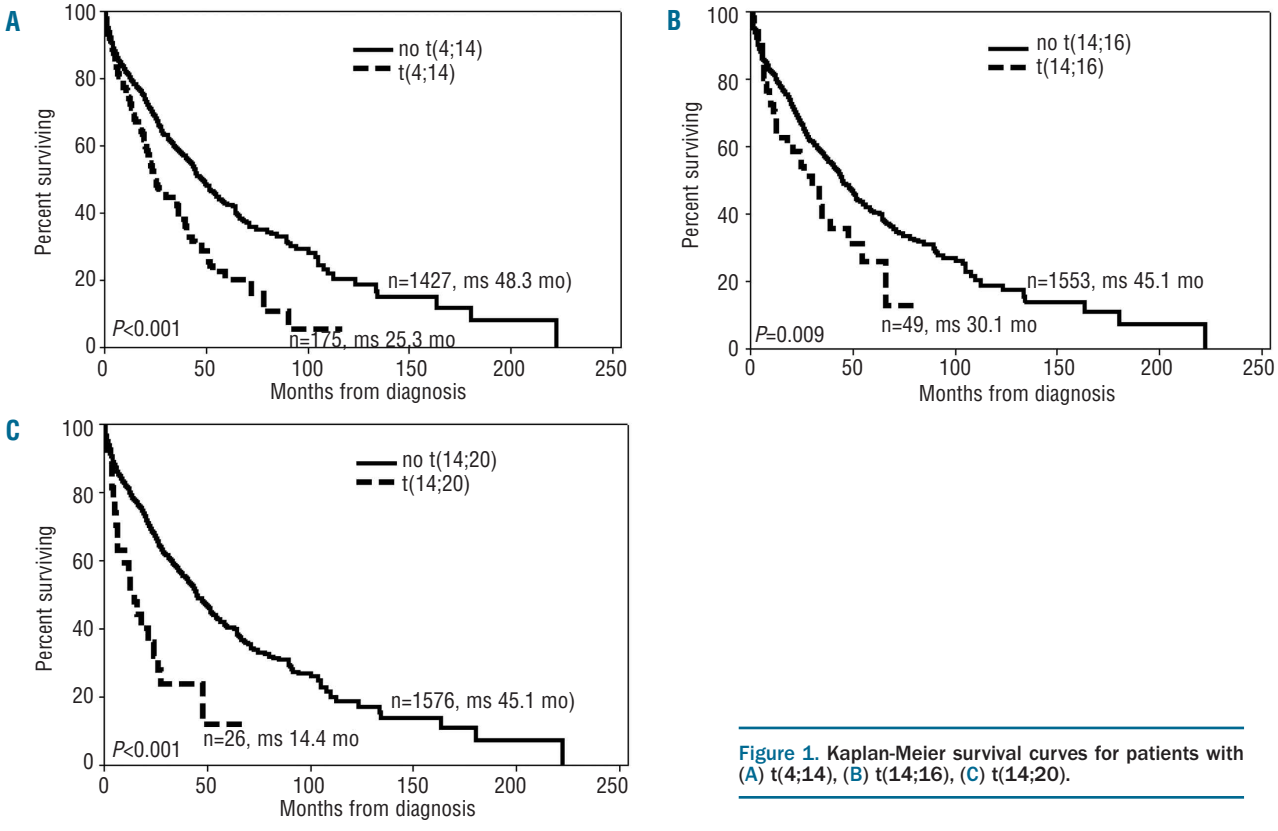

Figure 1. Kaplan-Meier survival curves for patients with (A) t(4;14), (B) t(14;16), (C) t(14;20).

The survival curves for t(4;14), t(14;16) and t(14;20) are shown in Figure 1 A-C, which make it clear that all three translocations are associated with a poor prognosis in MM. The t(14;20) patients had a short median survival of only 14.4 months.

In contrast to myeloma patients, the t(14;20) MGUS/SMM patients appear to do particularly well. All are alive with stable paraprotein levels and no evidence of progression from 43-78 months after diagnosis. This observation does not hold for t(4;14) and t(14;16) MGUS patients, who constitute a less uniform group (Table 2) with one of 5 t(4;14) and 2 of 6 t(14;16) MGUS cases having progressed (follow-up range 17-120 months from diagnosis). Not surprisingly, SMM cases show a higher progression rate, with 12/19 t(4;14) and 2/4 t(14;16) cases progressing. There appeared to be two patterns of progression with 7 patients showing steadily increasing M-protein and requiring treatment by less than 1.5 years from presentation, and the remainder having a longer indolent period followed by a sudden rise in M-protein or onset of other symptoms of end organ damage, thus conforming to both the evolving and non-evolving patterns suggested by Rosinol *et al.*[24] The range of time to progression of the latter group was 33 to 78 months. Overall only 11 of 27 t(4;14) and t(14;16) MGUS and SMM patients with follow-up of at least three years required treatment.

Conclusions

These results provide important information about the impact of these three translocations on the etiology and outcome of myeloma. While they are associated with short survival in MM the translocations alone cannot be responsible for this clinical behavior and additional events must be required. Cases characterized by these translocations, particularly the t(14;20), can be stable as either MGUS or SMM for years before progression occurs. All three translocations are strongly associated with deletion of 13q, NHRD and gain of 1q, but none of these additional markers are sufficient to distinguish the clinical behavior of t(4;14), t(14;16) or t(14;20) cases.

Authorship and Disclosures

FMR was the principal investigator and takes primary responsibility for the paper. LC, GPD, RKMP, DMS, and MTD performed the laboratory work for this study. AJS participated in the statistical analysis, FMR, NCPC, CJH and GJM co-ordinated the research. All authors contributed to the final version of the paper.

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