Active multiple myeloma suppresses and typically eliminates coexisting MGUS

John P Campbell[1,2,9], Jennifer L J Heaney[1,9], Sankalp Pandya[1], Zaheer Afzal[1], Martin Kaiser[3], Roger Owen[4], J Anthony Child[4], Walter Gregory[5], Gareth J Morgan[6], Graham H Jackson[7], Chris M Bunce[8] and Mark T Drayson*,[1]

[1]Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham B15 2TT, UK; [2]Department for Health, University of Bath, Bath BA2 7AY, UK; [3]Institute of Cancer Research, London SM2 5NG, UK; [4]St James's University Hospital, Leeds LS9 7TF, UK; [5]Clinical Trials Research Unit, University of Leeds, Leeds LS2 9NL, UK; [6]The Myeloma Institute, University of Arkansas for Medical Sciences, Little Rock, AR 72205, USA; [7]University of Newcastle, Newcastle upon Tyne NE1 7RU, UK and [8]School of Biosciences, University of Birmingham, Birmingham B15 2TT, UK

Background: Myeloma is consistently preceded by premalignant monoclonal gammopathy of undetermined significance (MGUS). In >5% of MGUS patients there is a second MGUS clone (biclonal gammopathy of undetermined significance; BGUS), yet, at myeloma diagnosis, presentation of biclonal gammopathy myeloma (BGMy) is considered less frequent, implying that myeloma eradicates coexisting MGUS.

Methods: In the largest study of its kind, we assessed BGMy frequency amongst 6399 newly diagnosed myeloma patients enrolled in recent UK clinical trials.

Results: Compared to expected prevalence (i.e., >5% of MGUS have BGUS), only 58 of 6399 (0.91%) newly diagnosed myeloma patients had BGMy, indicating myeloma typically eliminates coexistent MGUS. In these 58 BGMy cases, the MGUS plasma cell clone was greatly suppressed in size compared to typical levels observed in conventional MGUS; contrarily, the MGUS clone did not inhibit the myeloma plasma cell clone in BGMy.

Conclusion: Myeloma eliminates the majority of competing MGUS, and when it does not, the MGUS clone is substantially reduced in size.

Myeloma and the asymptomatic precursor that consistently precedes it, monoclonal gammopathy of undetermined significance (MGUS) (Landgren *et al*, 2009; Weiss *et al*, 2009), are characterised by monoclonal plasma cells (PCs) in the bone marrow and monoclonal antibody (MAB) in blood. In a population-based study of 12 482 persons, prevalence of MGUS was 3.7% in blacks, 2.3% in whites and 1.8% in Hispanics, and within these MGUS populations, the prevalence of two MGUS clones–termed biclonal gammopathy of undetermined significance (BGUS) (Kyle *et al*, 1981)–was 15.4%, 6.8% and 12.8%, respectively (Landgren *et al*, 2014). A proportion of new myeloma diagnoses also exhibit two MABs in immunofixation electrophoresis (IFE), termed myeloma

with biclonal gammopathy (BGMy). This represents progression of one BGUS clone to active myeloma and the continued presence of a secondary MGUS clone (Kyle *et al*, 1981; Kyle *et al*, 2003). Given that the prevalence of MGUS in the general population–at the mean age of myeloma diagnosis–is ~5% (Dispenzieri *et al*, 2010; Wadhera and Rajkumar, 2010), and prevalence of BGUS amongst all MGUS is >5% (Landgren *et al*, 2014), one would also expect more than 5% of myeloma cases to be BGMy. The frequency of BGMy remains uncertain (Kyle *et al*, 1981; Nilsson *et al*, 1986; Riddell *et al*, 1986; Guastafierro *et al*, 2012; Garcia-Garcia *et al*, 2015). In a review of 1027 myeloma diagnoses in one centre, 2% of cases were BGMy (Kyle *et al*, 2003). This lower than expected figure

warrants validation as it implies that when myeloma arises in an individual with BGUS, the malignant myeloma clone eliminates the competing MGUS clone. Here, in the largest study of its kind, we assessed 6399 newly diagnosed myeloma patients entered into three multicentre UK clinical trials to determine the frequency, and MAB sizes of, BGMy at myeloma diagnosis.

MATERIALS AND METHODS

Trial patients. The BGMy patients were identified from 6399 newly diagnosed myeloma patients enrolled in one of the following multicentre, phase III trials: the UK MRC Myeloma IX trial ($N = 1693$; ISRCTN68454111); the CRUK Myeloma XI trial up to an induction randomisation date of 23 July 2015 ($N = 3880$; ISRCTN49407852); or the UK NIHR TEAMM Trial up to a randomisation date of 23 July 2015 ($N = 826$; ISRCTN51731976). All patients gave written informed consent. The study was approved by the institutional review boards of the participating centres and was conducted according to the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice.

Laboratory tests. The MABs in serum were identified by IFE (Sebia, Paris, France) and quantified by protein zone electrophoresis and densitometry (SPE; Interlab, Rome, Italy); please refer to Supplementary Information for more information. In patients with a light-chain (LC) MAB without a heavy-chain (HC) component (i.e., LC-only myeloma), MAB size was measured and monitored by involved free LCs (Binding Site, Birmingham, UK) expressed in $g l^{-1}$.

Statistical analyses. Differences between groups were analysed by one-way ANOVA for continuous variables (e.g., MAB size), and χ^2 for categorical variables and frequencies. One-sample t-tests were used to compare observed MAB sizes to previously observed mean MAB sizes in the literature; observed BGMy MAB sizes were compared to reported MAB sizes in MGUS (Turesson et al, 2014) and myeloma using a combined data set from MIX and MXI UK trials. Correlational analyses were conducted using Pearson's for normally distributed data and Spearman's Rank where data was skewed. Significance was accepted at $P < 0.05$. Data were analysed by IBM SPSS statistics version 21 (Armonk, NY, USA).

RESULTS

Frequency of BGMy and demographics of BGMy patients. A total of 58 patients had BGMy (from MIX = 18, MXI = 33 and TEAMM = 7) and 6341 had monoclonal gammopathy myeloma (MGMy) giving a BGMy frequency of 58 out of 6399 patients (0.91%; 99% confidence interval: ± 0.3%). Comparison of the 58 BGMy patients with MGMy patients in the same trials found no differences in age: BGMy median age (range) was 69 (45–86) years; and MGMy was 66 (28–90) years.

Distinguishing MGUS from myeloma MABs. The frequencies and concentrations of serum MABs in all 58 BGMy patients at trial entry are presented in Table 1; the largest MAB is classified as the myeloma MAB and is referred to as 'M1', whereas the smaller MAB was classified as the MGUS MAB and is referred to as 'M2'. In 4 patients with a FLC MAB $> 500 \, mg l^{-1}$ and intact

Table 1. Characteristics and frequencies of M1 and M2 in 58 BGMy patients at myeloma diagnosis, compared to expected frequencies and characteristics of MGMy and conventional MGUS

MAB 1						MAB 2							
HC isotype		Frequency (N)	Proportion (%)	Conc. (g l⁻¹) (median (range))	MGMy reference ranges[a]		HC isotype		Frequency (N)	Proportion (%)	Conc. (g l⁻¹) (median (range))	MGUS reference ranges[b]		
					Proportion (%)	Conc. (g l⁻¹) (median (range))						Kyle et al, 2006	Turesson et al, 2014	
													Proportion (%)	Conc. (g l⁻¹) (median ± s.d.)
IgG	Total	39	67.2	[c]36.1 (4.8–70.0)	59.9	34.4 (0.8–100.2)	IgG	Total	33	56.9	[d]2.6 (0.5–12.0)	68.9	68.8	7.0 ± 6.0
	IgGκ	26	66.7	32.6 (4.8–70.0)				IgGκ	17	51.5	2.5 (0.5–12.0)			
	IgGλ	13	33.3	39.7 (10.2–60.0)				IgGλ	16	48.5	2.8 (0.5–9.0)			
IgA	Total	14	24.1	[c]25.4 (1.8–60.0)	23.6	33.0 (0.2–96.6)	IgA	Total	11	19.0	[d]1.7 (0.5–11.6)	10.8	14.7	8.0 ± 5.0
	IgAκ	8	57.1	26.9 (1.8–60.0)				IgAκ	5	45.5	1.3 (0.5–3.9)			
	IgAλ	6	42.9	23.2 (3.9–53.0)				IgAλ	6	54.5	2.5 (0.5–11.6)			
IgD	Total	1	1.7	2.6 (2.6–2.6)	1.7	4.2 (0.2–36.9)	IgM	Total	14	24.1	[d]1.3 (0.5–6.0)	17.2	16.2	7.0 ± 6.0
	IgDκ	0	0.0	—				IgMκ	12	85.7	1.3 (0.5–6.0)			
	IgDλ	1	100	2.6 (2.6–2.6)				IgMλ	2	14.3	1.6 (0.6–2.7)			
FLC	Total	4	6.9	1.0 (0.5–1.9)	13.1	2.6 (0.02–46.7)								
	FLCκ	3	75.0	1.4 (0.5–1.9)										
	FLCλ	1	25.0	0.7 (0.7–0.7)										
LC isotype	Frequency (N)	Proportion (%)	Conc. (g l⁻¹) (median (range))	MGMy reference proportion[a] (%)			LC isotype	Frequency (N)	Proportion (%)	Conc. (g l⁻¹) (median (range))	MGUS reference proportion (%) Kyle et al, 2006			
κ	37	63.8	26.0 (0.5–70.0)	66.0			κ	34	58.6	1.8 (0.4–12.0)	62.0			
λ	21	36.2	27.0 (0.7–60.0)	34.0			λ	24	41.4	2.7 (0.5–11.6)	37.9			

Abbreviations: BGMy = biclonal gammopathy myeloma; Conc. = concentration; FLC = free light chain; HC = heavy chain; LC = light chain; MAB = monoclonal antibody; MGMy = monoclonal gammopathy myeloma; MGUS = monoclonal gammopathy of undetermined significance.
[a]Reference ranges aggregated from 3248 patients with MGMy diagnosed at entry into Myeloma IX and Myeloma XI trials; data set cutoff June 2013.
[b]Reference ranges derived from 728 MGUS patients (Turesson et al, 2014) or 694 MGUS patients (Kyle et al, 2006).
[c]Significant difference between M1 and M2 concentration (IgG $P < 0.001$; IgA $P < 0.001$).
[d]Significant difference between M2 concentration and expected MAB concentration in MGUS (IgG $P < 0.001$; IgA $P < 0.001$; IgM $P < 0.001$) (Turesson et al, 2014). No significant differences observed between M1 and expected MAB concentrations in MGMy ($P > 0.05$) based on observations from Myeloma IX and XI.

Table 2. Frequency of M1 and M2 combinations observed in BGMy

MAB 1	MAB 2	MAB 2 frequency		MAB 2 proportion	
		Observed BGMy frequency (*N*)	Expected MGUS[a] frequency (*N*)	Observed BGMy proportion (%)	Expected MGUS[a] proportion (%)
IgG κ (*N* = 26)	IgG κ	0[b]	12	0	46
	IgG λ	10	6	38	23
	IgA κ	3	3	12	10
	IgA λ	4	1	15	5
	IgM κ	7	3	27	11
	IgM λ	2	1	8	5
IgG λ (*N* = 13)	IgG κ	6	6	46	46
	IgG λ	0	3	0	23
	IgA κ	2	1	15	10
	IgA λ	2	1	15	5
	IgM κ	3	1	23	11
	IgM λ	0	1	0	5
IgA κ (*N* = 8)	IgG κ	5	4	63	46
	IgG λ	1	2	13	23
	IgA κ	0	1	0	10
	IgA λ	0	0	0	5
	IgM κ	2	1	25	11
	IgM λ	0	0	0	5
IgA λ (*N* = 6)	IgG κ	4	3	67	46
	IgG λ	2	1	33	23
	IgA κ	0	1	0	10
	IgA λ	0	0	0	5
	IgM κ	0	1	0	11
	IgM λ	0	0	0	5

Abbreviations: BGMy = biclonal gammopathy myeloma; FLC = free light chain; MAB = monoclonal antibody; MGUS = monoclonal gammopathy of undetermined significance. Because of low frequency, data not shown from one patient with IgD MAB 1 and four patients with FLC MAB 1.
[a]Reference range proportions obtained from Turesson *et al* (2014), with assumed 2 : 1 proportion of kappa : lambda for each heavy-chain isotype.
[b]χ^2-analyses revealed significant differences between the observed frequency of IgGκ pairs in BGMy compared to those expected in MGUS ($P < 0.001$; $\chi^2 = 15.60$). A trend ($P = 0.065$; $\chi^2 = 3.391$) was observed for frequency of observed IgGλ pairs in BGMy and those expected in MGUS.

Table 3. Comparison of M1 and M2 concentrations in BGMy with expected MAB sizes in conventional MGMy and in MGUS

Size	M1 proportion and frequency[a]	Expected proportion in MGMy (%)[b,c]	M2 proportion and frequency	Expected proportion in MGUS (%)[d]
< 4.99 g l^{-1}	7% (*N* = 4)	7	83% (*N* = 48)	24
5.00–9.99 g l^{-1}	7% (*N* = 4)	5	14% (*N* = 8)	19
10.00–14.99 g l^{-1}	7% (*N* = 4)	5	3% (*N* = 2)	33
15.00–19.99 g l^{-1}	7% (*N* = 4)	6	0% (*N* = 0)	18
20.00–24.99 g l^{-1}	13% (*N* = 7)	9	0% (*N* = 0)	5
> 25.00 g l^{-1}	57% (*N* = 31)	68	0% (*N* = 0)	1

Abbreviations: BGMy = biclonal gammopathy myeloma; MAB = monoclonal antibody; MGMy = monoclonal gammopathy myeloma; MGUS = monoclonal gammopathy of undetermined significance.
[a]Excludes four patients diagnosed with a FLC myeloma M1 (all four patients had a whole MAB < 4.99 g l^{-1}).
[b]Reference range represents aggregated data from patients with MGMy diagnosed at entry into Myeloma IX and Myeloma XI trials.
[c]Excludes patients with FLC myeloma and non-secretory myeloma.
[d]Reference range derived from 694 MGUS patients (Kyle *et al*, 2006).

immunoglobulin < 5 g l^{-1}, the FLC MAB was selected as M1. M1s were 10- to 20-fold larger than M2s with median M1 IgG 34.4 g l^{-1} compared to M2 IgG 2.6 g l^{-1}; and M1 IgA 33 g l^{-1} compared to M2 IgA 1.7 g l^{-1}.

M1 and M2 MAB combinations in BGMy are presented in Table 2 where it can be seen that 37 out of 58 BGMy (65%) combinations exhibited different LC isotypes; assessment of available serum FLC levels in these patients (illustrated in Supplementary Figure 1) demonstrated that elevated FLC levels were predominantly associated with the M1 clone.

In Table 2, we show that two independent IgG MABs was the most common M1 and M2 combination (16 out of 58 patients), but not as common as expected (27 out of 58), and we did not observe any patients with two IgG MABs with the same LC isotype (15 out of 58 expected; $P < 0.001$; $\chi^2 = 17.228$). In 6 BGMy patients with two IgG MABs, the electrophoretic mobilities of the MABs

were very similar and so these MABs were only reliably distinguishable by their different LC isotype. Accordingly, we may have missed a third of the 15 out of 58 expected IgG MAB pairs of the same LC isotype, because of electrophoretic mobility similarities.

MGUS MAB isotypes and levels in BGMy compared to conventional MGUS. The most frequent M2 was IgG (33 out of 58), and a quarter of M2 clones (14 out of 58) secreted IgM. The frequency of different M2 HC isotypes was closest to the patterns observed in two MGUS studies of 728 and 694 MGUS patients, rather than the different HC frequencies seen in myeloma (Kyle *et al*, 2006; Turesson *et al*, 2014) (Table 1). There were, however, less IgG M2s than would be expected in a typical MGUS population (33 *versus* 41) and more IgM and IgA isotypes (25 *versus* 16; trend observed: $P = 0.092$; $\chi^2 = 2.83$).

The level of the MGUS-associated MAB (M2) in BGMy was smaller than sizes reported in MGUS (Turesson *et al*, 2014) by 2.5-fold for IgG and 5-fold for IgA and IgM MABs ($P < 0.001$). Thus, whereas coexistent MGUS (i.e., M2) did not appear to suppress the myeloma clone (i.e., M1) in BGMy, the presence of myeloma (M1) significantly suppressed MGUS (M2) MAB levels. The magnitude of this suppression is illustrated in Table 3 where 83% of M2's were below 5 g l^{-1} compared to the observed 24% in a prior MGUS study.

Serum levels of myeloma MABs are the same in MGMy and BGMy. The most prevalent M1 was IgG, followed by IgA, FLC and then IgD; no IgM or IgE M1's were observed; please refer to Supplementary Information for more information. The HC frequencies were very similar to those of 3248 patients in the same clinical trials who had MGMy (Table 1). Notably, IgG and IgA M1 MAB concentrations were not significantly different to those observed in the MGMy patients from the same trials. This indicates that the presence of a second neoplastic PC clone (i.e., M2) does not competitively suppress the expansion of the neoplastic myeloma clone (i.e., M1) (Table 3).

DISCUSSION

This is the largest study of BGMy frequency in a large cohort of newly diagnosed myeloma patients, and demonstrates that

myeloma eliminates or greatly suppresses coexisting MGUS. As the prevalence of MGUS in the general population – at the typical age of myeloma diagnosis – is ~5% (Dispenzieri et al, 2010; Wadhera and Rajkumar, 2010) and the prevalence of BGUS amongst all individuals with MGUS is >5% (Landgren et al, 2014), it would also be expected that >5% of myeloma cases would be BGMy. However, despite rigorous central laboratory analysis, it was found to be just 0.91%.

This shortfall is unlikely to be the result of myeloma being fivefold more likely to arise in individuals with a single MGUS clone than from individuals with two MGUS clones. A recent study reported the rate of progression from BGUS to myeloma was ~1% per year, which is similar to the incidence of MGUS progression to myeloma (Mullikin et al, 2016). Thus, when myeloma arises from BGUS, in ~80% of cases, the other MGUS clone must be eliminated or suppressed below the limits of detection on IFE $(0.1\,g\,l^{-1})$.

In the BGMy cases reported herein, MGUS-associated MAB levels were smaller than expected levels typically observed in conventional MGUS (Turesson et al, 2014), by 2.5-fold for IgG and 5-fold for IgA and IgM. The degree of suppression of MGUS clones in BGMy appears comparative to the immunoparesis of non-malignant polyclonal PC that occurs in the majority of newly diagnosed myeloma patients (Pruzanski et al, 1980; Wangel, 1987; Wang and Young, 2001; Kastritis et al, 2014). Of 3248 MGMy patients from the same Myeloma IX and XI trials reported in this study, we found that polyclonal immunoglobulin levels were below the normal range in >80% of patients and levels were lower than the median level found in healthy controls by 2.5-fold for IgG and 7-fold for IgA and IgM. Despite their larger relative presence, MGUS clones appear to only compete effectively with polyclonal PC in ~20% of cases, as evidenced by incidence of immunoparesis in MGUS (Turesson et al, 2014). As only a fifth of MGUS clones exhibit competitiveness for the normal PC niche, we hypothesise that these are the only MGUS clones that survive when myeloma arises in the wider marrow environment and that they are subject to the same suppression of clonal size and antibody secretion as normal polyclonal PCs; this would also be applicable to the MGUS PC clone from which myeloma arose. In a separate observation, we observed in this study that two IgG MABs was the most common BGMy combination (16 out of 58 patients) but not as common as expected (27 out of 58) indicating that the presence of IgG myeloma PC clones suppresses IgG MGUS PC clones more than IgA or IgM PC clones. There is evidence from both MGUS and myeloma that neoplastic IgG PC clones exert a greater degree of suppression on normal polyclonal IgG PC than they do on IgA and IgM isotypes (Bradwell et al, 2013; Katzmann et al, 2013; Ludwig et al, 2016).

A limitation of our study is that we were unable to conduct longitudinal measurement of BGUS before myeloma diagnosis; this excluded the possibility of investigating elimination of MGUS clones at the time of myeloma clone proliferation. Future prospective studies may seek to explore differences between BGUS that progress to myeloma, and BGUS that do not progress to myeloma, and measurements should incorporate bone marrow tumour samples as well as stroma to investigate possible mechanisms of tumour eradication. In summary, our findings confirm that BGMy is rare, and the survival of a coexisting MGUS clone is hallmarked by reduced MAB size.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

JPC, CMB and MTD wrote the manuscript; MTD, JPC and JLJH designed the investigation into BGMy; JPC, JLJH, SP and ZA conducted the experiments; JPC, JLJH, SP and MTD interpreted the data; MK, RO, GJM, GHJ, AC and MTD designed the Myeloma IX, XI and/or TEAMM trials. All authors approved the manuscript.

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