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Immunoglobulin isotypes in multiple myeloma: laboratory correlates and prognostic implications in total therapy protocols

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According to Mayo Clinic data concerning the immunoglobulin (Ig) isotype distribution in patients with multiple myeloma (MM), IgG accounts for 52%, IgA for 21% and only light chain secretion for 16%; IgD and IgM phenotypes are rare (2% and 0·5% respectively) (Kyle *et al*, 2003). The recently adopted International Staging System classification distinguishes three groups with significantly different survival outcomes based on serum beta-2-microglobulin (B2M) and albumin levels (Greipp *et al*, 2005). IgA and especially IgD phenotypes have been considered prognostically unfavourable (Blade *et al*, 1994; Krejci *et al*, 2005).

This study searched for possible associations of Ig heavy and light chain isotypes with prognostically relevant baseline laboratory features, especially with gene expression profiling (GEP)-defined molecular subgroup designation and prognostic risk scores that dominantly affect prognosis (Zhan *et al*, 2006; Shaughnessy *et al*, 2007). Our MM database was scrutinized for all patients previously enrolled in total therapy 1, 2 and 3 (TT1, TT2 and TT3) protocols for newly diagnosed patients with symptomatic or progressive disease. Details of protocol therapy and clinical outcomes have been previously reported (Barlogie *et al*, 1999, 2006, 2007). The current analysis was performed as of August 2008, encompassing median follow-up times of live patients of 14·3 years for TT1 (n = 231), 6·5 years with TT2 (n = 668), and 3·3 years with TT3 (n = 303). All protocols had been approved by the Institutional Review Board at the University of Arkansas for Medical Sciences and all patients had provided written informed consent in keeping with the Helsinki declaration and with Food and Drug Administration and National Cancer Institute guidelines. The various Ig heavy and light chain types were annotated at diagnosis, along with their serum levels and their urinary excretions. Clinical endpoints included complete response (CR, immunofixation analysis negative), duration of CR from response onset, as well as event-free survival (EFS) and overall survival (OS), both measured from initiation of protocol therapies. GEP data on CD138-purified plasma-cells were available for 626 patients enrolled in TT2 and TT3. GEP-defined risk score and molecular subgroup designation was performed as previously published (Zhan *et al*, 2006; Shaugh-nessy *et al*, 2007). Kaplan–

Authors' contributions

BN, BB designed and wrote paper. BN, SW contributed patients and analysed data. JDS performed gene array analyses. JS, JC performed statistical analyses.

Meier methods were used to generate survival distribution graphs and comparisons were made via the log-rank test. Stepwise selection and Cox proportional hazard regression modelling were applied for the multivariate analyses. Estimated R^2 values were calculated through the methods of O'Quigley and Xu (2001).

In our series of 1202 patients, IgG was present in 648 (54%), IgA in 268 (22%), IgD in 12 (1%); 194 had light chain only disease (16%); two were classified as having bi-clonal disease (0·2%); 28 (2%) were deemed to have non-secretory MM; and 50 had unknown disease type (4%). The kappa-to-lambda light chain ratio was 2·0 for IgG, 1·4 for IgA, 1·0 for IgD MM, and 1·2 among those with only light chain secretion ($P = 0·008$). Serum M-protein levels were higher in patients with IgG (median, 33 g/l; range, 0–97 g/l) than in those with IgA (median, 21 g/l; range, 0–87 g/l), while lowest levels were recorded in patients with IgD MM (median, 3 g/l; range, 0·01–45 g/l). The associated median daily urinary light chain excretions were 550·0 mg/d (range, 0–3120 mg/d) in case of kappa and 43·0 mg/d (range 0–2780 mg/d) in case of lambda for IgG; 465·0 mg/d (range, 0–3060 mg/d) in case of kappa and 70·0 mg/d (range, 0–1620 mg/d) in case of lambda for IgA; 162·0 mg/d (range, 0–584 mg/d) in case of kappa and 148·0 mg/d (range, 71–200 mg/d) in case of lambda for IgD; 164·0 mg/d (range 0·0–803·0 mg/d) for kappa and 95·0 mg/d (range, 0·0–216·0 mg/d) for lambda light chain among those with light chain only disease. In the 439 patients with serum free-light chain determinations, available at our centre since 2002, the median levels were 42·6 mg/l (range 0·1–38700 mg/l) for kappa and 12·8 mg/l (range 0·01–71200 mg/l) for lambda.

Among potentially significant associations of the different Ig phenotypes with baseline prognostic features examined, IgD isotype was uniquely associated with significantly higher frequencies of cytogenetic abnormalities (CA) and of elevated serum levels of lactate dehydrogenase (LDH), B2M, and C-reactive protein (CRP) (Table I). GEP data, introduced at our centre in 2000, were available prior to commencement of therapy in TT2 in 351 and in TT3 in 275. While GEP-defined high-risk MM appeared evenly represented among the various Ig subgroups ($P = 0·422$), IgD isotype was associated with the proliferation (PR) subgroup in 38% as opposed to 10% in the entire population ($P = 0·003$).

Median OS and EFS durations according to Ig subtypes were 83 and 49 months for IgA and 84 and 41 months for IgD, and thus tended to be shorter than the 99 and 58 months observed for the remainder ($P = 0·17$, $P = 0·14$). We next examined clinical outcomes in the context of baseline characteristics that included Ig isotypes (Table II). In the absence of GEP information, both OS and EFS were adversely affected by the presence of CA and elevated serum levels of B2M and LDH. IgA isotype was an additional adverse feature for EFS only. With added knowledge of GEP data, GEP-defined high-risk dominated both OS and EFS models, while CA, LDH and B2M remained independent adverse features. IgA was an additional poor prognosticator for both OS and EFS. Renal compromise was an added negative feature for EFS, while TT3 was the only positive variable associated with improved EFS.

Our results demonstrated that, in the era of highly effective combination therapy for multiple myeloma, CA, GEP-high-risk and elevated levels of LDH and B2M were the main and consistently adverse features associated with poor OS and EFS. IgA isotype additionally affected OS and EFS especially in the context of GEP data; IgD did affect EFS adversely although, due to its rare occurrence (1%), it did not contribute significantly in the context of R^2 statistics, portraying the variability of clinical outcomes that could be accounted for by baseline variables (see Table II). As delineated in Table I, IgD was strongly associated with high levels of LDH and B2M as well as the presence of CA and PR molecular subtype,

attesting to its highly proliferative potential which, in former times, may have explained the poorer outcome seen of such patients.

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Table I

Associations of immunoglobulin heavy and light chain types with baseline clinical features without and with gene expression profiling (GEP) data.

Factor	All TT Patients (Overall)	IgA	IgD	IgG	Bi-clonal	Free light chain	Non-secretory	Unknown	*P*-value
CA	371/1184 (31%)	102/266 (38%)	6/12 (50%)	198/639 (31%)	1/2 (50%)	47/191 (25%)	5/28 (18%)	12/46 (26%)	0·018★
Albumin <35 g/l	257/1198 (21%)	61/267 (23%)	2/12 (17%)	164/645 (25%)	0/2 (0%)	17/194 (9%)	2/28 (7%)	11/50 (22%)	<·001★
B2M ≥ 3·5 mg/l	474/1200 (40%)	118/268 (44%)	9/12 (75%)	229/647 (35%)	1/2 (50%)	93/194 (48%)	6/28 (21%)	18/49 (37%)	<·001★
B2M >5·5 mg/l	230/1200 (19%)	59/268 (22%)	3/12 (25%)	100/647 (15%)	1/2 (50%)	56/194 (29%)	3/28 (11%)	8/49 (16%)	0·001★
Creatinine ≥176 μmol/l	107/1188 (9%)	20/263 (8%)	1/12 (8%)	41/642 (6%)	1/2 (50%)	40/192 (21%)	0/27 (0%)	4/50 (8%)	<·001★
CRP ≥4 mg/l	662/1183 (56%)	161/264 (61%)	10/11 (91%)	339/643 (53%)	0/1 (0%)	117/193 (61%)	11/28 (39%)	24/43 (56%)	0·009★
CRP ≥8 mg/l	433/1183 (37%)	106/264 (40%)	8/11 (73%)	214/643 (33%)	0/1 (0%)	82/193 (42%)	6/28 (21%)	17/43 (40%)	0·009★
LDH ≥190 U/l	334/1199 (28%)	66/268 (25%)	5/12 (42%)	163/647 (25%)	1/2 (50%)	82/194 (42%)	6/26 (23%)	11/50 (22%)	<·001★
GEP†-defined-high risk MM	86/626 (14%)	23/157 (15%)	0/8 (0%)	42/342 (12%)	0/1 (0%)	18/106 (17%)	1/7 (14%)	2/5 (40%)	0·422★
GEP† PR subgroup	61/626 (10%)	17/157 (11%)	3/8 (38%)	21/342 (6%)	0/1 (0%)	18/106 (17%)	1/7 (14%)	1/5 (20%)	0·003★

★Sample size assumption for chi-square test is suspect.

n/N(%): *n*, number with factor, *N*-number with valid data for factor.

B2M, beta-2-microglobulin; CRP, C-reactive protein; TT, total therapy; LDH, lactate dehydrogenase; PR, proliferation; CA, cytogenetic abnormalities; MM, multiple myeloma; GEP, gene expression profiling.

Table II

Multivariate analysis of baseline parameters associated with clinical outcomes.

Endpoint	Variable	*n/N* (%)	HR (95% CI)	*P*-value	Cumulative R^2 (%)
OS (all patients)	CA	371/1180 (31%)	1·90 (1·59,2·28)	<0·001	10·76
	B2M >5·5 mg/l	226/1180 (19%)	1·66 (1·35,2·04)	<0·001	14·45
	LDH ≥190 U/l	328/1180 (28%)	1·52 (1·25,1·84)	<0·001	16·45
	IgA myeloma	266/1180 (23%)	1·18 (0·96,1·45)	0·122	16·52
	IgD myeloma	12/1180 (1%)	0·75 (0·31,1·81)	0·518	16·61
OS (with GEP data)	GEP-defined high-risk MM	86/625 (14%)	2·44 (1·71,3·47)	<0·001	18·95
	CA	207/625 (33%)	1·95 (1·44,2·64)	<0·001	25·07
	LDH ≥190 U/l	192/625 (31%)	1·85 (1·36,2·52)	<0·001	30·02
	B2M >5·5 mg/l	131/625 (21%)	1·62 (1·18,2·23)	0·003	33·06
	IgA myeloma	157/625 (25%)	1·24 (0·89,1·72)	0·213	33·19
	IgD myeloma	8/625 (1%)	1·41 (0·51,3·87)	0·508	33·22
EFS (all patients)	TT1 protocol	219/1180 (19%)	1·84 (1·54,2·20)	<0·001	4·95
	CA	371/1180 (31%)	1·64 (1·39,1·92)	<0·001	12·14
	B2M >5·5 mg/l	226/1180 (19%)	1·60 (1·34,1·93)	<0·001	15·24
	TT3 protocol	302/1180 (26%)	0·57 (0·44,0·73)	<0·001	20·48
	LDH ≥190 U/l	328/1180 (28%)	1·48 (1·25,1·75)	<0·001	22·81
	IgA myeloma	266/1180 (23%)	1·23 (1·03,1·48)	0·024	23·19
	IgD myeloma	12/1180 (1%)	1·42 (0·73,2·75)	0·301	23·25
EFS (with GEP data)	GEP-defined high-risk MM	85/616 (14%)	2·54 (1·85,3·49)	<0·001	15·27
	Creatinine ≥2 mg/dl	58/616 (9%)	1·97 (1·41,2·77)	<0·001	18·79
	CA	205/616 (33%)	1·60 (1·23,2·07)	<0·001	22·38
	TT3 protocol	275/616 (45%)	0·58 (0·43,0·77)	<0·001	27·73
	LDH ≥190 U/l	189/616 (31%)	1·54 (1·19,1·99)	0·001	30·60
	IgA myeloma	153/616 (25%)	1·40 (1·06,1·85)	0·016	31·33
	IgD myeloma	8/616 (1%)	2·23 (0·98,5·11)	0·057	31·67

P-value from Wald chi-square test in Cox regression.

Multivariate model uses stepwise selection with entry level 0·1 and variable remains if meets the 0·05 level. A multivariate *P*-value greater than 0·05 indicates variable forced into model with significant variables chosen using stepwise selection.

Variables considered for OS (all patients) multivariate analysis included: IgA myeloma, IgD myeloma, kappa versus lambda light chain, TT protocol, age ≥65 years, CA, albumin <35 g/l, B2M >5·5 mg/l, creatinine ≥176 μmol/l, CRP ≥8 mg/l, Hb <100 g/l and LDH ≥190 U/l.

Variables considered for OS (patients with GEP data) multivariate analysis included: IgA myeloma, IgD myeloma, kappa versus lambda light chain, TT protocol, age ≥65 years, CA, B2M >5·5 mg/l, creatinine ≥176 μmol/l, CRP ≥8 mg/l, Hb <100 g/l, LDH ≥190 U/l, 70-gene-derived high-risk MM as well as molecular subgroups: CD-1 and CD-2, hyperdiploid, low bone disease, *WHSC1*/*FGFR3*, *MAF*/*MAFB* and proliferation.

Variables considered for EFS (all patients) multivariate analysis included: IgA myeloma, IgD myeloma, kappa versus lambda light chain, TT protocol, age ≥65 years, CA, albumin <3·5 g/dL, B2M >5·5 mg/l, creatinine ≥176 μmol/l, CRP ≥8 mg/l, Hb <100 g/l and LDH ≥190 U/l.

Variables considered for EFS (patients with GEP data) multivariate analysis included: IgA myeloma, IgD myeloma, kappa v lambda light chain, TT protocol, age ≥65 years, CA, albumin <3·5 g/dl, B2M >5·5 mg/l, creatinine ≥176 μmol/l, CRP ≥8 mg/l, Hb <100 g/l, LDH ≥190 U/l, 70-gene-derived high-risk MM as well as molecular subgroups: CD-1 and CD-2, hyperdiploid, low bone disease, *WHSC1*/*FGFR3*, *MAF*/*MAFB* and proliferation.

HR, hazard ratio; 95% CI, 95% confidence interval; B2M, beta-2-microglobulin; EFS, event-free survival; CRP, C-reactive protein; LDH, lactate dehydrogenase; CA, cytogenetic abnormalities; OS, overall survival; MM, multiple myeloma; GEP, gene expression profiling; TT, total therapy.