Genetic factors underlying the risk of bortezomib induced peripheral neuropathy in multiple myeloma patients

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ABSTRACT

Bortezomib induced peripheral neuropathy is a dose-limiting side effect and a major concern in the treatment of multiple myeloma. To identify genetic risk factors associated with the development of this side effect in bortezomib treated multiple myeloma patients, a pharmacogenetic association study was performed using a discovery set (IFM 2005-01; n=238) and a validation set (HOVON65/GMMG-HD4 and a Czech dataset; n=231). After multiplicity correction, none of the 2,149 single nucleotide polymorphisms tested revealed any significant association with bortezomib induced peripheral neuropathy. However, 56 single nucleotide polymorphisms demonstrated an association with bortezomib induced peripheral neuropathy with pointwise, uncorrected significance. Pathway analysis of these polymorphisms demonstrated involvement of neurological disease (FDR <20%). Also a clear enrichment of major bortezomib metabolizing genes was found. Univariate evaluation of these 56 polymorphisms in the validation set demonstrated one single nucleotide polymorphism with pointwise significance: rs619824 in *CYP17A1*. *(IFM 2005-01 clinicaltrials.gov identifier: NCT00200681; HOVON-65/GMMG-HD4 isrctn.org identifier: ISRCTN64455289)*

Key words: bortezomib, peripheral neuropathy, risk, single nucleotide polymorphism.

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Introduction

The introduction of bortezomib (Millennium Pharmaceuticals, Cambridge, MA, USA), an inhibitor of the 26S proteasome, has greatly improved the management of multiple myeloma (MM).[1] The dose-limiting toxicity of bortezomib is peripheral neuropathy, which frequently requires a dose reduction or treatment discontinuation.[2-4] Bortezomib induced peripheral neuropathy (BiPN) differs from pre-existing peripheral neuropathy associated with 10% of untreated MM patients. BiPN, described in detail by Delforge *et al.*,[4] is predominantly sensory, reversible in most cases, and characterized by distal paresthesias, numbness and neuropathic pain.

A multifactorial pathogenesis for BiPN seems likely, with suggested mechanisms including blockade of nerve-growth-factor-mediated neuronal survival through inhibition of the activation of nuclear factor κB (NFκB),[5] damage to mitochondria and the endoplasmic reticulum through activation of apoptosis,[6] dysregulation of mitochondrial calcium homoeostasis,[7] autoimmune factors, interference with mRNA processing, and translation[8] and inflammation.[9-10] A number of studies, including a report by our own group, have looked at the pharmacogenetic characterization of BiPN.[11-12] In the study carried out by our group, the comparison between early onset (within one treatment cycle) BiPN and late onset (after two or three treatment cycles) BiPN revealed that genes for apoptosis contribute to early onset BiPN, whereas genes that have a role in inflammatory pathways and DNA repair contribute to the development of late onset BiPN, indicating that distinct genetic factors are involved in the development of early onset and late onset forms of this side effect.[11] Recently, Favis *et al.* reported on the association between SNPs and the time to bortezomib induced peripheral neuropathy within the VISTA trial with associated SNPs including a SNP in the gene *CTLA4*.[12]

In this study, we further explore the genetic risk factors associated with the development of BiPN in patients with MM who had not been previously treated with bortezomib. A large dataset from the IFM 2005-01 trial was used as discovery set.

The online version of this article has a Supplementary Appendix.

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In addition, a dataset based on the patients from the HOVON-65/GMMG-HD4 trial were used as a validation set.[11]

Design and Methods

Patients

The study was performed on patients who had been included in two randomized clinical trials, i.e. the Institutional Review Board-approved HOVON-65/GMMG-HD4 (ISRCTN64455289) trial for newly diagnosed patients with MM (n=833), and the IFM 2005-01 trial (NCT00200681; n=493) approved by the Ethics Committee of the University of Nantes, both of which compared standard induction treatment (VAD) with a bortezomib combination prior to high-dose therapy (HDT) and stem cell transplantation (*Online Supplementary Figure S1A*). In addition, as part of the cooperative program of the International Myeloma Foundation and International Myeloma Working Group, a set of 56 patients (i.e. 56 unique DNA samples), uniformly treated with bortezomib and dexamethasone at relapse, were obtained. In addition, a prospectively collected set of samples (n=56) from the Babak Research Institute (Czech Republic) was included as part of the cooperative program of the International Myeloma Foundation and International Myeloma Working Group. All patients gave written informed consent for this genetic study. Patients with amyloidosis (AL-) or monoclonal gammopathy of undetermined significance (MGUS) were excluded. Adverse events (AEs) were prospectively assessed using standard National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0 (CTCAE 3.0). To ensure homogeneity of allelic frequencies, 15 patients of non-European descent were excluded from the study. In total, 238 of 246 patients from IFM 2005-01, 183 of 412 patients from HOVON-65/GMMG-HD4 and 48 of 56 from the Czech Republic who were randomized for treatment with bortezomib were included in the analysis. Samples were divided into a discovery and validation set (*Online Supplementary Figure S1B*, *Online Supplementary Table S1*).

Genotyping

DNA was extracted from peripheral blood nucleated cells or CD138 negative bone marrow cells. Genotyping was performed using an Affymetrix® Targeted genotyping custom built panel, comprising 3404 SNPs, selected using a hypothesis-driven strategy, targeting genes and SNPs with previously described associations or putative functional effects.[13]

Statistical analysis

After imputation and applying SNP exclusion criteria (minor allele frequency (MAF) <0.05, Hardy Weinberg equilibrium $<1\times10^{-5}$), a panel containing 2,149 SNPs was analyzed by univariate association analysis using the software package PLINK.[14] Categorical comparisons with respect to frequencies were performed with the χ^2 or Fisher's exact test, and continuous variables were analyzed using the Mann-Whitney U test (*Online Supplementary Table S1*).

SNP association analysis comparing grade 1-4 BiPN with no BiPN patients in the discovery set (IFM 2005-01) was performed as previously described.[11]

The associated gene sets were subjected to Ingenuity Pathway Analysis (Ingenuity System Inc., USA) using 2,149 SNPs as a reference set. Only the top three associated pathways with a FDR≤20% are reported.

As validation, a Cochran Mantel-Haenszel stratified association test was performed in an independent dataset comprised of patients from the HOVON-65/GMMG-HD4 trial and patients from the Czech Republic to evaluate cross validating SNP associations and Odds Ratios (ORs). Specifically, ORs from significant SNPs (pointwise $P<0.05$) in the discovery set were selected for validation. A one-sided test for OR was performed to test whether the observed effects in the validation set were associated with the same effect direction as observed in the discovery set.

Based on the numbers of the discovery and validation set, a conservative power calculation for both sets was performed. According to this calculation, ORs need to be higher than 2.28 or lower than 0.44 to be found at a significance level of 0.05 for SNPs with a minor allele frequency (MAF) of 0.5. These ORs diverge as the MAF decreases (*Online Supplementary Figures S2 and S3*, *Table S1 and S2*). Please note this is a conservative analysis in which multiplicity correction is performed by Bonferroni correction and no linkage is taken into account.

Results and Discussion

The BiPN rates and clinical characteristics of both the discovery set (n=238) and the validation set (n=231) are shown in the *Online Supplementary Table S1*. In the discovery set, 27 patients developed BiPN grade 1, 57 grade 2, 11 grade 3, and 4 grade 4. *Online Supplementary Figure S4* shows the time to BiPN for each grade separately in patients from the HOVON-65/GMMG-HD4 trial,who are included in the validation set. The median time to BiPN grade 1 was six weeks, and seven weeks to grade 2, 3 or 4. The peripheral neuropathy rates in the VAD treatment arm (i.e. not bortezomib) of the HOVON-65/GMMG-HD4 trial, will not be discussed further here (*Online Supplementary Table S3*).

After imputation and applying PLINK exclusion filters, a panel containing 2,149 SNPs was analyzed for association by conducting a χ^2 association analysis. None of the SNPs were found to be significantly associated with BiPN using the permutated *P* value correction for multiple testing in the discovery set (IFM2005-01; Table 1). The highest ranking SNP, with corrected *P* value of 0.3, is in the locus of the cell cycle gene *CDKN1B*. This SNP, rs3759217, has been evaluated in a number of cancer studies, but was not reported to be significantly associated with any cancer type.[15] Using the pointwise, uncorrected *P* value, 56 SNPs were found to be associated with BiPN in this set (Table 1).

The results of the analysis performed in the discovery set (IFM 2005-01 trial) were validated using an independent dataset from the Czech Republic combined with the dataset from the HOVON-65/GMMG-HD4 trial (*Online Supplementary Figure S1*). A Cochran Mantel-Haenszel stratified association test was performed. Associated SNPs (pointwise $P<0.05$) in this validation set are shown in *Online Supplementary Table S5*. To investigate whether associated SNPs (pointwise $P<0.05$) in the discovery set and available in the validation set (n=51) had the same direction of effect, a one-sided test for ORs was performed in the validation set. This resulted in one pointwise significantly cross validating SNP; rs619824 in CYP17A1 (*Online Supplementary Table S6*).

CYP17A1, cytochrome P-450c17α, is involved in steroid hormone biosynthesis, and has both steroid 17α-hydroxylase activity and 17,20-lyase activity.[16] Steroids have been shown to affect nerve cells, and have even been suggested for use as a therapeutic option to prevent the development of neuropathy.[17] Treatment with progesterone has been

Table 1. SNPs associated with BiPN (pointwise $P<0.05$) using an χ^2 association analysis. The genomic inflation factor λ is 1.0201.

SNP	Chr	Alleles			OR	95% CI			Pointwise P for χ^2	Permutated P for χ^2	Gene	SNP Type	In LD with
rs3759217	12	C	>	T	2.76	1.58	-	4.84	< 0.001	0.3291	*CDKN1B*	Locus	
rs11466155	17	C	>	T	1.87	1.25	-	2.80	0.004	0.9744	*NGFR*	Coding-synonymous	
rs6033	1	A	>	G	2.53	1.30	-	4.94	0.006	0.9993	*F5*	Coding-nonsynonymous	rs6018, rs6027
rs2228088	6	G	>	T	0.56	0.36	-	0.87	0.006	1	*TNF*	Coding-synonymousymous, TagSNP:TNF	
rs2686184	8	G	>	A	1.72	1.19	-	2.49	0.006	0.9966	*FDFT1*	3' UTR	
rs12721516	1	C	>	T	0.55	0.34	-	0.90	0.007	1	*CSF1*	Coding-nonsynonymous	
rs6945306	7	G	>	C	1.71	1.17	-	2.52	0.007	0.9999	*STK31*	Coding-nonsynonymous	
rs228851	20	G	>	T	0.59	0.41	-	0.86	0.008	0.9998	*NFATC2*	Intron	
rs3136516	11	A	>	G	0.61	0.42	-	0.88	0.008	1	*F2*	Intron	
rs584589	17	A	>	G	2.01	1.16	-	3.47	0.009	1	*NGFR*	Promoter	
rs4148949	10	C	>	T	0.60	0.41	-	0.88	0.010	1	*CHST3*	Untranslated	rs4148946
rs619824	10	G	>	T	0.64	0.44	-	0.93	0.010	1	*CYP17A1*	3' UTR	
rs338599	19	G	>	C	2.97	1.24	-	7.08	0.011	1	*CYP2S1*	Coding-synonymous	
rs121	7	A	>	G	1.61	1.11	-	2.32	0.011	1	*OSBPL3*	Intron	
rs7169	1	T	>	C	1.65	1.14	-	2.39	0.012	1	*SLC16A1*	Untranslated	rs1049434
rs2239330	16	C	>	T	0.59	0.39	-	0.90	0.012	1	*ABCC1*	Coding-synonymous	rs212090, rs212087
rs2295155	22	C	>	A	0.43	0.23	-	0.81	0.012	1	*CARD10*	Intron	
rs2976437	8	A	>	G	1.63	1.13	-	2.37	0.013	1	*NEFL*	Promoter	rs2976436
rs2033178	12	C	>	T	2.42	1.23	-	4.74	0.014	1	*IGF1*	Intron	
rs878201	1	G	>	A	1.54	1.04	-	2.29	0.015	1	*Admixture*	Admixture	
rs1149901	10	C	>	T	1.62	1.07	-	2.45	0.015	1	*GATA3*	Locus,untranslated	
rs2973015	5	A	>	G	0.63	0.44	-	0.91	0.017	1	*GHR*	Intron	
rs2227956	6	T	>	C	0.52	0.30	-	0.88	0.018	1	*HSPA1L*	Coding-nonsynonymous	
rs504122	13	C	>	T	0.63	0.43	-	0.93	0.018	1	*SPRY2*	Coding-nonsynonymous	
rs1641536	17	G	>	A	0.43	0.22	-	0.86	0.021	1	*SHBG*	3' UTR	
rs2472299	15	G	>	A	0.62	0.42	-	0.92	0.022	1	*CYP1A1*	Promoter	
rs9885672	6	T	>	C	1.86	1.08	-	3.21	0.024	1	*KIAA0274*	Coding-nonsynonymous	
rs163078	2	C	>	T	0.63	0.43	-	0.92	0.026	1	*CYP1B1*	Intron,TagSNP:CYP1B1	rs163077
rs20432	1	T	>	G	0.59	0.35	-	0.97	0.027	1	*PTGS2*	Intron	
rs762551	15	A	>	C	0.63	0.42	-	0.93	0.027	1	*CYP1A2*	Intron,TagSNP:CYP1A_cluster	
rs3776432	5	G	>	A	1.52	1.04	-	2.24	0.028	1	*NSUN2*	Intron	
rs3817074	19	C	>	T	1.95	1.06	-	3.60	0.029	1	*BAX*	Intron	
rs1126526	1	C	>	T	1.41	0.96	-	2.08	0.029	1	*ATF3*	5'UTR	
rs1805405	1	C	>	A	0.56	0.33	-	0.95	0.030	1	*PARP1*	Intron	rs1805407, rs2280712
rs1002153	1	T	>	C	0.56	0.33	-	0.95	0.030	1	*PARP1*	Intron	rs1805408
rs4799055	18	G	>	T	1.61	1.10	-	2.35	0.030	1	*NFATC1*	Intron	
rs854556	7	C	>	T	0.64	0.44	-	0.95	0.031	1	*PON1*	Intron,TagSNP:PON1	
rs1052637	2	G	>	C	0.66	0.45	-	0.97	0.031	1	*DDX18*	Coding-nonsynonymous	
rs440454	6	C	>	T	0.62	0.39	-	0.97	0.032	1	*RDBP*	Locus,intron	
rs854555	7	C	>	A	1.53	1.05	-	2.24	0.032	1	*PON1*	Intron,TagSNP:PON1	
rs2857605	6	A	>	G	0.57	0.36	-	0.92	0.034	1	*TNF*	Intron,TagSNP:TNF	
rs6768093	3	T	>	A	0.66	0.45	-	0.96	0.036	1	*ATR*	Locus	rs2227930, rs2227928
rs1405655	19	T	>	C	1.56	1.05	-	2.32	0.036	1	*NR1H2*	Intron	
rs3733890	5	G	>	A	0.66	0.45	-	0.98	0.037	1	*BHMT*	Coding-nonsynonymous	
rs1801105	2	C	>	T	1.95	1.06	-	3.60	0.041	1	*HNMT*	Coding-nonsynonymous	
rs2231142	4	C	>	A	2.12	1.04	-	4.31	0.042	1	*ABCG2*	Coding-nonsynonymous	
rs3212254	14	C	>	A	2.12	1.04	-	4.31	0.042	1	*RIPK3*	Coding-nonsynonymous	

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rs9640663	7	A	>	G	0.67	0.46	-	0.98	0.042	1	*PTPN12*	Coding-nonsynonymous	
rs1050152	5	C	>	T	0.68	0.47	-	0.99	0.044	1	*SLC22A4*	Coding-nonsynonymous	
rs2007231	1	T	>	C	0.66	0.44	-	0.97	0.044	1	*NRAS*	Intron	
rs1296028	8	A	>	G	0.64	0.42	-	0.99	0.045	1	*FDFT1*	3' UTR	
rs3758581	10	G	>	A	2.35	1.12	-	4.97	0.047	1	*CYP2C19*	Coding-nonsynonymous	
rs2124459	21	T	>	C	0.66	0.45	-	0.96	0.047	1	*CBS*	Intron	
rs2228233	14	C	>	T	0.65	0.43	-	0.98	0.048	1	*NFATC4*	Coding-synonymous	
rs10759326	9	T	>	G	1.57	0.99	-	2.48	0.048	1	*IKBKAP*	Coding-nonsynonymous	rs10979601
rs2074351	7	G	>	A	1.51	1.01	-	2.26	0.050	1	*PON1*	Intron,TagSNP:PON1	

SNP indicates single nucleotide polymorphism; Chr: chromosome; OR: Odds Ratio; CI: confidence interval.

reported to increase the expression of myelin protein zero in both rat sciatic nerve and Schwann cells.[17] Due to the paucity of cross validated SNPs, we have examined the SNPs with a significant pointwise *P* value in the discovery set (Table 1). Foremost, we have performed a pathway analysis based on this set of SNPs. This analysis showed enrichment of genes involved in cardiovascular disease (11 genes), genetic disorder (22 genes) and neurological disease (21 genes). The latter include the genes *NEFL*, *PON1*, *PTGS2* and *ABCG2*, which have been reported frequently in relation to neurological disease such as Alzheimer's.

Previous studies showed that bortezomib is primarily metabolized by cytochrome P450 isoforms *CYP3A4*, *CYP2C19*, *CYP1A2*, with a minor contribution of *CYP2D6* and *CYP2C9*.[18] The results show an enrichment of the major bortezomib metabolizing genes within the top 56 SNPs (*P*=0.0013).

Previously, genes involved in inflammation were found to be associated with late onset BiPN.[11] Indeed, one of the most associated SNPs, rs3136516 (pointwise *P*=0.008) was an intronic SNP located in prothrombin (coagulation factor II; F2), which has been reported in relation to the neurotoxic cascade leading to neurodegenerative diseases.[19] Two SNPs that lie within or in close proximity to the *TNFα* gene (rs2857605 and rs2228088; *Online Supplementary Figure S5*) were associated with BiPN. TNFα has been implicated in the pathogenesis of several neurodegenerative diseases, including multiple sclerosis, Alzheimer's disease, and human immunodeficiency virus-related encephalopathy.[20] Additionally, the TNFα system is activated in diabetic polyneuropathy, which leads to increased microvascular permeability, hypercoagulability and even direct nerve damage. Improvement of diabetic polyneuropathy following suppression of TNFα has been shown in several animal models.[21] Furthermore, neuropathic pain, one of the determinants of the CTCAE-neuropathy score, and thus of BiPN severity, is mediated through TNF-mediated induction of stress-activated kinases like p38 MAPK.[22]

The NFκB pathway is central to the immune response and two associated SNPs are located in the *IKBKAP* gene; rs10979601 and rs10759326. This is a particularly relevant association because hereditary sensory and autonomic neuropathy type III, or familial dysautonomia (FD), can be caused by mutations in the *IKBKAP* gene, leading to poor development, reduced survival, and progressive degeneration of the sensory and autonomic nervous system.[23]

Mutations in *neurofilament light polypeptide* (*NEFL*) cause Charcot-Marie-Tooth Neuropathy Type 2E/1F, the most common inherited peripheral neuropathy.[24] Two promoter SNPs (rs2976437 and rs2976436) in NEFL were associated with BiPN. Two SNPs were located in the *nerve growth factor receptor* (*NGFR*; rs11466155 and rs584589), a gene particularly important with respect to neurological functions. The NFGR signals via NFκB activation and binds neutrophin precursors that stimulate neuronal cell survival and differentiation. These results support the finding in our previous study that late onset BiPN is associated with genes involved in the development and function of the nervous system.[11] In a recent paper, the time to BiPN was found to be associated with the occurrence of the SNP rs4553808 in the gene *CTLA4*.[12] Comparison with that study is not feasible, due to the fact that the SNP set tested had only minimal overlap with our SNP set (2% overlap).

We evaluated genetic risk factors associated with BiPN in MM patients who had not been previously treated with bortezomib in the largest study to date using a hypothesis-driven approach. This method is limited by the possibility of population heterogeneity. However, a limited set of patients with different genetic backgrounds were selected out, as described in *Design and Methods* and reported previously.[11] Further limitations are: i) the inability of assessing SNPs outside the candidate panel; and ii) the possibility of finding false-positive associations as a result of multiple testing. To address both issues, we are currently performing a genome-wide scan that will clarify and possibly confirm the associations reported in this study. The power analysis indicated in this study has sufficient power to detect associations with an OR of less than 0.44 or an OR of more than 2.28 and diverging with MAF. It is unlikely that smaller effects can be found. Using the custom BOAC SNP array in a discovery set of 238 patients, no SNP was found to be significantly associated to BiPN at the corrected $P<0.05$ significance level. However, based on the highest-ranking SNPs found using the uncorrected *P* value in the discovery set, pathway analysis did demonstrate clear enrichment of neurological disease SNPs.

Authorship and Disclosures

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