

3. Verstovsek S, Kantarjian H, Mesa RA, et al: Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. *N Engl J Med* 363(12):1117-1127, 2010

4. Pardanani A, Gotlib JR, Jamieson C, et al: Safety and efficacy of TG101348, a selective JAK2 inhibitor, in myelofibrosis. *J Clin Oncol* 29:789-796, 2011

5. Santos FP, Kantarjian HM, Jain N, et al: Phase 2 study of CEP-701, an orally available JAK2 inhibitor, in patients with primary or post-polycythemia vera/essential thrombocythemia myelofibrosis. *Blood* 115:1131-1136, 2010

6. Verstovsek S: Therapeutic potential of Janus-activated kinase-2 inhibitors for the management of myelofibrosis. *Clin Cancer Res* 16:1988-1996, 2010

7. Barosi G, Bergamaschi G, Marchetti M, et al: JAK2 V617F mutational status predicts progression to large splenomegaly and leukemic transformation in primary myelofibrosis. *Blood* 110:4030-4036, 2007

8. Guglielmelli P, Barosi G, Specchia G, et al: Identification of patients with poorer survival in primary myelofibrosis based on the burden of JAK2V617F mutated allele. *Blood* 114:1477-1483, 2009

9. Tefferi A, Lasho TL, Huang J, et al: Low JAK2V617F allele burden in primary myelofibrosis, compared to either a higher allele burden or unmutated

status, is associated with inferior overall and leukemia-free survival. *Leukemia* 22:756-761, 2008

10. Mesa RA: How I treat symptomatic splenomegaly in patients with myelofibrosis. *Blood* 113:5394-5400, 2009

11. Steensma DP, Mesa RA, Li CY, et al: Etanercept, a soluble tumor necrosis factor receptor, palliates constitutional symptoms in patients with myelofibrosis with myeloid metaplasia: Results of a pilot study. *Blood* 99:2252-2254, 2002

12. Jedidi A, Marty C, Oligo C, et al: Selective reduction of JAK2V617F-dependent cell growth by siRNA/shRNA and its reversal by cytokines. *Blood* 114:1842-1851, 2009

13. Mesa RA, Kantarjian H, Tefferi A, et al: Functional assessment of performance status in patients with myelofibrosis (MF): Utility and feasibility of the 6-minute walk test (6MWT). *J Clin Oncol* 27:376s, 2009 (suppl; abstr 7083)

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Genetic Predisposition for Chemotherapy-Induced Neuropathy in Multiple Myeloma

Pamela S. Becker, *Division of Hematology, University of Washington, Seattle, WA*

See accompanying article on page 797

Peripheral neuropathy is one of the most frequent and debilitating adverse effects encountered by patients with cancer undergoing chemotherapy treatment. For multiple myeloma (MM), every effective regimen includes at least one agent that can cause neuropathy, a major dose-limiting toxicity in clinical trials and in clinical practice. Furthermore, neuropathy occurs even before therapy as a consequence of the disease in approximately 20% of patients with MM, and can even occur in the precursor condition, monoclonal gammopathy of undetermined significance.

In the past, neuropathy was noted as a complication of the vincristine-containing vincristine, doxorubicin, and dexamethasone (VAD) regimen, then occurred with the thalidomide-containing regimens and to a lesser extent with lenalidomide, and is now frequent with bortezomib, one of the most active agents in myeloma. The incidence of thalidomide-associated neuropathy is 27% to 28%,^{2,3} severe (grade \geq 3) in 6%.² The incidence of bortezomib-associated neuropathy is 64% as monotherapy,⁴ and 47% when combined with melphalan and prednisone,⁵ severe (grade \geq 3) in 13% with the latter regimen. The symptoms can vary and include numbness, dysesthesia, paresthesia, hyperalgesia, and severe pain. Both small and large nerve fibers can be affected.

The management of neuropathy in patients receiving chemotherapy has largely been supportive. Antidepressants or antiepileptics such as amitriptyline, gabapentin, and pregabalin have been used to minimize painful neuropathy. In addition, pyridoxine, glutamine, or the antioxidants shown to be effective in diabetic neuropathy, alpha lipoic acid or acetyl L-carnitine, may be protective. Previously, it has not been possible to predict who will develop crippling, irreversible symptoms and who will be able to tolerate the antimyeloma drugs with minimal toxicity. Fortunately, there is some degree of reversibility with discontinuation or dose reduction.

In this issue, Johnson et al¹ describe the single-nucleotide polymorphisms (SNPs) associated with development of neuropathy after treatment with thalidomide or vincristine in MM patients. DNA samples from over 1,500 patients enrolled on Myeloma IX and Stichting Hemato-Oncologie voor Volwassenen Nederland (HOVON 50)/the German-speaking Myeloma Multicenter Group (GMMG) high-dose 3 (HD3) multicenter trials were analyzed for SNPs, and correlations performed for patients who developed neuropathy compared with those who did not. Myeloma IX was a randomized comparison of cyclophosphamide plus VAD (CVAD) versus cyclophosphamide, thalidomide, and dexamethasone (CTD) for younger patients, and CTD versus melphalan and prednisone for older patients. HOVON-50/GMMG-HD3 was a randomized comparison of VAD to thalidomide, doxorubicin, and dexamethasone prior to high-dose melphalan. The study utilized a hypothesis-driven, candidate gene approach to identify SNPs in genes responsible for DNA repair or inflammation of the nervous system. In the two trials, 31.8% of patients receiving thalidomide and 33.6% of those receiving vincristine developed neuropathy at a median time of 8 weeks. The risk of neuropathy was not significantly associated with the clinical features of age, type of immunoglobulin, stage, interphase fluorescent in situ hybridization variant, or response, but was associated with male gender.

The SNPs associated with thalidomide-induced neuropathy included those in the ATP-binding cassette transporter genes *ABCC1* and *ABCC2*, *ADME* (absorption, distribution, metabolism, excretion) genes including *FMO6* (flavin-containing monooxygenase) and ion channel gene *SLC12A6*, *SPRR1A* (promotes axonal outgrowth), and *SERPINB2* (induced in injured neurons). In contrast, those SNPs involved in vincristine-induced neuropathy were in different genes, including *CAMKK1* (expressed in neurons resistant to oxidative stress), *CYP2C8*, and *CYP2C9* (involved in hepatic drug clearance),

Table 1. SNPs With Increased Odds Ratio for Neuropathy

Report	Thalidomide		Vincristine		Bortezomib	
	Gene	Odds Ratio	Gene	Odds Ratio	Gene	Odds Ratio
Johnson et al ¹	ABCC1	2.85	CYP3A7	4.31		
HOVON-50/GMMG-HD3	SPRR1A	1.72	IRF4	4.54		
VAD versus TAD	LIG3	1.94	UGT2A1	3.95		
	CD86	3.03	NQO1	3.81		
	DPYD	2.33	HSD3B1	2.44		
	NQO1	2.04	CYP24A1	3.02		
	TIMM8A	2.90	CYP2C9	2.28		
	TNF	1.84	ATR	2.42		
			ATM	2.65		
			MGST1	2.39		
			EME1	2.24		
			ESR1	2.8		
			SULT1C1	3.38		
Johnson et al ¹	ABCC2	1.51	ADAMTS1	2.31		
Myeloma IX	SFTPC	1.48	SERPINE1	1.90		
CVAD versus CTD	CYP2C9	1.54	ADR2	1.96		
CTD versus MP	VANGL1	1.56	TNXB	2.30		
	PPIA	1.50	SERPINE1	1.88		
	IGF1R	1.40	FRK	1.94		
	CTLA4	1.38	CYP11B1	1.91		
	POLB	1.62	ATM	1.90		
			ID3	2.73		
			PSMA4	1.82		
Johnson et al ¹ common to both Myeloma IX and HOVON-50/GMMG-HD3 (Odds ratios in this order)			SERPINE1	1.88, 2.15		
			ID3	2.73, 2.45		
			CYP2C9	1.90, 2.36		
			CAMKK1	1.70, 1.90		
			CYP2C8	1.74, 2.18		
Broyl et al ⁶			<u>Early (1 cycle)</u>		<u>Early (1 cycle)</u>	
VAD versus PAD			PPARD	13.62	RDM1	3.65
			ALDH1A1	7.62	CASP9	3.59
			HEL308	6.67	ALOX12	3.50
			PPARD	9.67	ALOX12	3.50
			PPARD	9.67	LSM1	4.11
			ABCC4	7.15		
			LTA	4.67		
			PPARD	8.89		
			LTA	4.52		
			SCL10A2	4.30		
			ABCC5	4.64		
			<u>Late (2-3 cycles)</u>		<u>Late (2-3 cycles)</u>	
			CART	4.62	ERCC4	2.74
			SIM1	3.30	ERCC4	2.48
			JUN	5.00	IFNGR2	2.30
			DPYD	3.29	ERCC3	1.26
			SLC22A5	4.80	MRE11A	3.27
			KIA0274	3.89		
			ABCC1	3.36		
			PTGS1	5.40		
			ABCC1	4.22		
			FGFR4	3.47		
			MGMT	3.38		
			BZRP	2.93		
			BZRP	3.14		
			UGT2B7	3.60		

NOTE. Genes in bold are either common to both publications Johnson et al¹ and Broyl et al⁶ or in a gene family common to both. Abbreviations: HOVON-50/GMMG-HD3, Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) -50/German-Speaking Myeloma Multicenter Group (GMMG) -HD3 trial; VAD, vincristine, doxorubicin, and dexamethasone; TAD, thalidomide, doxorubicin, and dexamethasone; CVAD, cyclophosphamide plus VAD; CTD, cyclophosphamide, thalidomide, and dexamethasone; MP, melphalan and prednisone; PAD, bortezomib, doxorubicin, and dexamethasone.

NFATC2 (a transcriptional activator in T lymphocytes), *ID3* (associated with radiation-induced apoptosis), or *SLC10A2* (apical sodium-dependent bile acid transporter). These discrepancies suggest that there may be different pathogenic mechanisms for nerve damage from the two agents.

Since the older regimens that included vincristine and thalidomide have been replaced with regimens including newer agents, it will be critical to determine whether the findings for each drug are applicable to the entire drug class; for example, will the same SNPs that are associated with thalidomide toxicity have relevance to lenalidomide and pomalidomide? Likewise, it will be necessary to learn whether the SNPs that are relevant to the neurotoxicity of the proteasome inhibitor, bortezomib, will extend to carfilzomib and other drugs in this class. Moreover, regimens such as bortezomib, thalidomide, and dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide, combine at least two drugs that each carries a high risk of neuropathy. Furthermore, vincristine use remains widespread in the treatment of acute lymphoblastic leukemia and lymphoma with regimens such as cyclophosphamide, doxorubicin, vincristine, and prednisone; etoposide, doxorubicin, vincristine, prednisone, and cyclophosphamide; and CVAD alternating with methotrexate and cytarabine; so the conclusions of this report may have relevance for current treatment of other diseases. Confirming that the same correlations exist between the SNPs identified in this report and peripheral neuropathy in patients with other conditions such as lymphoma would constitute validation of this approach.

The most difficult aspect of interpreting the results of correlative studies using SNPs is the reproducibility of the same findings in other studies and patient populations. For example, Broyl et al⁶ has independently studied the SNPs associated with the development of neuropathy in patients with multiple myeloma undergoing treatment with vincristine or bortezomib on the HOVON-65/GMMG-HD4 trial, a prospective randomized trial of VAD versus bortezomib, doxorubicin, and dexamethasone. This report identified a nearly completely distinct set of SNPs compared with Johnson et al¹ (Table 1). Broyl et al examined SNPs associated with early (after one cycle) or late (after two to three cycles) development of neuropathy. Because the studies by Johnson et al and Broyl et al were based on different sets of candidate genes derived by different hypotheses, and were applied to patients receiving different drug regimens, it is difficult to reconcile the two data sets. However, the most striking finding is the concordant discovery of the same two genes, *ABCC1* and *DPYD*, having SNPs associated with thalidomide-induced neuropathy in the HOVON trial reported by Johnson et al, and with late vincristine-associated neuropathy in the trial reported by Broyl et al (Table 1). *ABCC1* is a member of the ATP-binding cassette gene family, for which SNPs in other members (*ABCC2*, *ABCC4*, *ABCC5*) were also identified to be associated with neuropathy risk in both studies. The other gene, *DPYD*, which encodes dihydropyrimidine dehydrogenase, is also associated with toxicity in patients treated for GI malignancy with fluorouracil.⁷ A Japanese publication also reports a SNP in *ABCC2* associated with oxaliplatin-associated neuropathy.⁸ Thus, the evidence may be greater for a role for these key genes, the ATP-binding cassette gene family members and *DPYD*, given that they were identified by both reports as having SNPs associated with risk of chemotherapy-associated neuropathy, and independently were shown by others to be associated with toxicity due to other chemotherapy drugs.

Genetic information (ie, cytogenetics/interphase fluorescent in situ hybridization) already guides treatment decisions for multiple myeloma; data from SNP risk profiles for toxicity could be similarly incorporated into treatment algorithms if the data were to be compelling. A priori identification of adverse effect risks in given individuals would not only lead to broader use of protective agents and prophylactic maneuvers including targeting of certain inflammatory pathways, but would also undoubtedly play a role in selection of drug regimens and drug doses, compatible with the evolving era of personalized medicine.

However, caution will need to be exercised in translating genetic risk assessment for toxicity into clinical practice. It will be critical to examine whether the drugs used for prevention of neuropathy or reduced drug dose for selected patients will diminish the efficacy of our best chemotherapy regimens. These decisions may impact survival and even quality of life due to disease progression. For example, the ABC cassette proteins, for which certain SNPs are associated with thalidomide- and vincristine-induced neuropathy, regulate intracellular drug levels, and thus the optimal function of these proteins may be necessary to achieve antitumor effect. It is essential that each of the SNPs deemed to be reliably associated with neuropathy be correlated prospectively with response to treatment to prevent overzealous changes in therapy. It therefore may be difficult to put “primum non nocere” into practice, or “to do no harm” (translated from Hippocrates, *Of the Epidemics*). If not harming nerves becomes paramount, we may jeopardize treatment response. Future studies should be performed to ensure that the benefits of lowering toxicity do not compromise the significant advances made to prolong life.

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REFERENCES

1. Johnson DC, Corthals SL, Walker BA, et al: Genetic factors underlying the risk of thalidomide-related neuropathy in patients with multiple myeloma. *J Clin Oncol* 29:797-804, 2011
2. Glasmacher A, Hahn C, Hoffmann F, et al: A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. *Br J Haematol* 132:584-593, 2006
3. von Lilienfeld-Toal M, Hahn-Ast C, Furkert K, et al: A systematic review of phase II trials of thalidomide/dexamethasone combination therapy in patients with relapsed or refractory multiple myeloma. *Eur J Haematol*. 81:247-252, 2008
4. Richardson PG, Xie W, Mitsiades C, et al: Single-agent bortezomib in previously untreated multiple myeloma: Efficacy, characterization of peripheral neuropathy, and molecular correlations with response and neuropathy. *J Clin Oncol* 27:3518-3525, 2009
5. Dimopoulos MA, Mateos MV, Richardson PG, et al: Risk factors for, and reversibility of, peripheral neuropathy associated with bortezomib-melphalan-prednisone in newly diagnosed patients with multiple myeloma: Subanalysis of the phase 3 VISTA study. *Eur J Haematol* [Epub ahead of print on September 28, 2010]
6. Broyl A, Corthals SL, Jongen JL, et al: Mechanisms of peripheral neuropathy associated with bortezomib and vincristine in patients with newly diagnosed

multiple myeloma: A prospective analysis of data from the HOVON-65/GMMG-HD4 trial. *Lancet Oncol* 11:1057-1065, 2010

7. van Kuilenburg AB, Meijer J, Mul AN, et al: Intragenic deletions and a deep intronic mutation affecting pre-mRNA splicing in the dihydropyrimidine dehydrogenase gene as novel mechanisms causing 5-fluorouracil toxicity. *Hum Genet* 128:529-538, 2010

8. Mori Y, Katsumata K, Tsuchida A, et al: Single nucleotide polymorphism analysis in the GSTP1 and ABCC2 genes about neuropathy by the Oxaliplatin. *Gan To Kagaku Ryoho* 35:2377-2381, 2008

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Treatment of Low-Risk Gestational Trophoblastic Neoplasia

Carol Aghajanian, Memorial Sloan-Kettering Cancer Center, New York, NY

See accompanying article on page 825

Gestational trophoblastic disease (GTD) spans a heterogeneous spectrum of diseases that arise in the fetal chorion during pregnancy. Included in this definition are hydatidiform moles (partial and complete), choriocarcinoma, placental site trophoblastic tumors (PSTTs), and epithelioid trophoblastic tumors (ETTs).

Hydatidiform moles are benign processes with malignant potential. Malignant transformation occurs in 15% to 20% of complete hydatidiform moles (CHMs) and less than 5% of partial hydatidiform moles (PHMs). In fact, malignant transformation is so rare in PHMs that if one is contemplating treatment for this diagnosis, it is prudent to confirm the pathologic diagnosis, to rule out a false-positive human chorionic gonadotropin (hCG) test, and to make sure that the patient has not had an incomplete evacuation before proceeding. In the current era of early detection of pregnancy, it can be difficult to distinguish early CHMs from PHMs histologically. Complete and partial hydatidiform moles can be distinguished by performing a p57 immunostain.¹ Lack of nuclear p57 staining in villous stromal cells and cytotrophoblasts confirms diagnosis of CHMs (as opposed to hydropic abortion or PHMs). CHMs are entirely androgenic, whereas the p57 gene is paternally imprinted and maternally expressed.

According to current International Federation of Gynecology and Obstetrics (FIGO) classification,² hydatidiform moles are considered to have undergone malignant transformation and therefore meet the definition of gestational trophoblastic neoplasm (GTN) if after evacuation there are four values or more indicating an hCG plateau during a period of at least 3 weeks; a rise of hCG of 10% or greater for three values or more during a period of at least 2 weeks; or persistence of hCG 6 months after mole evacuation. Only hydatidiform moles that meet the definition of GTN are subject to staging and risk scoring. GTN is a term used for hydatidiform moles that have undergone malignant transformation; this term is also used for all choriocarcinomas, including PSTTs and ETTs. PSTTs and ETTs are not subject to staging or risk scoring systems and need to be considered separately. Thus, in considering treatment of low-risk GTN, one is referring to hydatidiform moles that have undergone malignant transformation (often referred to as persistence) and choriocarcinomas, which receive a low risk score.

The most recently published FIGO staging and classification systems are detailed in Tables 1 and 2.³ Use of the FIGO staging system is essential for determining initial therapy for patients with GTN to ensure the best possible outcomes with the least morbidity.

Table 1. FIGO Anatomic Staging for GTN

Stage	Description
I	Disease confined to the uterus
II	GTN extends outside the uterus, but is limited to the genital structures (adnexa, vagina, broad ligament)
III	GTN extends to the lungs, with or without known genital tract involvement
IV	All other metastatic sites

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; GTN, gestational trophoblastic neoplasia.

In this issue of *Journal of Clinical Oncology*, Osborne et al⁴ report the results of a randomized phase III trial performed by the Gynecologic Oncology Group of weekly methotrexate versus pulsed dactinomycin for low-risk GTN. The study accrued patients between 1999 and 2007. In 2002, the FIGO definitions for GTN changed, as did the staging and classification system. The investigators chose not to adapt the new definitions for GTN for logistical reasons. They did extend the acceptance of patients with risk scores from 0 to 4 (June 1999 to June 2002) to 0 to 6 (July 2002 to February 2007), and of the 216 evaluable patients, 17 (7.9%) had a risk score 5 to 6. The GTN definitions used in the study (< 10% decrease in hCG in three consecutive weekly values; > 20% sustained rise in hCG over two consecutive weekly values; persistently elevated hCG more than 4 months after initial evacuation; histologically proven nonmetastatic choriocarcinoma; histologically proven metastatic choriocarcinoma if the metastatic site[s] is one [or more] of the following: vagina, parametrium, or lung [if no lung lesion is > 2 cm]) are significantly different than the current FIGO definitions, making application of the study results to current practice difficult.

Several different outpatient chemotherapy regimens have been used to treat low-risk GTN (Table 3). The variability in primary response rates probably, at least in part, represents differences in drug dosages, schedules, routes of administration, and length of therapy delivered after normalization of hCG, as well as patient selection criteria. Chemotherapy is delivered until hCG values have returned to normal and then at least one cycle is given after the first normal hCG value (practice standards and regimens vary with respect to the