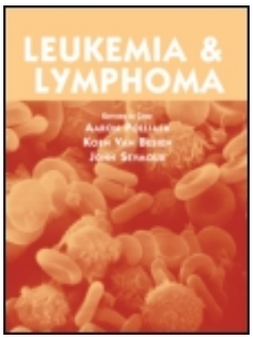

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: informahealthcare.com/journals/ilal20

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To cite this article: Morie A. Gertz (2011) Reducing neurotoxicity in the management of multiple myeloma, Leukemia & Lymphoma, 52:11, 2043-2044, DOI: 10.3109/10428194.2011.602773

To link to this article: https://doi.org/10.3109/10428194.2011.602773

Leukemia & Lymphoma, November 2011; 52(11): 2043–2044

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2011.602773

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COMMENTARY

Reducing neurotoxicity in the management of multiple myeloma

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In this issue of ***Leukemia and Lymphoma***, Mangiacavalli and colleagues attempted to reduce the neurotoxicity of thalidomide-based therapy by giving a 1-week drug holiday out of every 4 weeks of therapy. Unfortunately, the intermittent thalidomide schedule did not reduce neurological toxicity [1].

Response rates, depth of response, progression-free survival and overall survival have improved in multiple myeloma with the introduction of novel agents. However, there has been a price paid in terms of toxicity, particularly neurotoxicity, which is not consistently reversible and can significantly impact the quality of life of patients. In the phase 3, Dutch Belgian Hemato-Oncology Cooperative Group (HOVON)-50 trial, the incidence of neuropathy was 64% [2]. Grade 2–4 peripheral neuropathy was seen in 47% of patients in the HOVON-49 myeloma trial [3]. Combining bortezomib with thalidomide produces a higher rate of peripheral neuropathy ($p = 0.0004$) than with thalidomide alone [4]. In a study that used bortezomib, melphalan, prednisone and thalidomide [5] the protocol was amended because of the high incidence of peripheral neuropathy. After the first 139 patients enrolled, the induction schedules were changed. Grade 3–4 sensory neuropathy was reported in 8% of patients receiving the four-drug combination followed by bortezomib–thalidomide maintenance. Twenty-three percent discontinued treatment for adverse events, the major reason being peripheral neuropathy. The modification chosen was reduction in the bortezomib frequency from twice weekly to once weekly, with a significant reduction in the development of peripheral neuropathy. As the survival in multiple myeloma increases, the long-term consequences of symptomatic neurotoxicity become less acceptable.

What are the options available to reduce the long-term risks of neurotoxicity? Four opportunities for managing this have been reported: modification of dose, schedule and route of administration, and identification of host factors that uniquely predispose patients to this toxicity. Reduction in bortezomib and thalidomide doses, so-called VTD-lite, has recently been incorporated into protocols, with the thalidomide dose at 50 mg/day and the bortezomib dose at 1.0 mg/m^2. Successful treatment of multiple myeloma using thalidomide in a dose of 100 mg every other day has been reported [6], maintaining efficacy of myeloma control. Reducing the frequency of bortezomib scheduling from twice weekly to once weekly appears to sustain response without compromising long-term outcomes, including 3-year progression-free survival [7], and reduces the incidence of grade 3–4 peripheral neuropathy from 28% using a twice-weekly bortezomib schedule to 8% in the once-weekly usage group. The combination of bortezomib, given once weekly, with cyclophosphamide has been reported to maintain high response rates [8].

An important modification in the route of administration of bortezomib has resulted in a significant reduction in neurotoxicity. By administering bortezomib subcutaneously days 1, 4, 8 and 11 of a 21-day schedule, peak levels of bortezomib were reduced, and peripheral neuropathy of any grade was reduced from 53% to 38%. Grade 3 or greater neuropathy was reduced from 16% to 6% using the subcutaneous administration route. Efficacy was similar and the safety profile was improved [9].

Recently, with the use of single-chain nucleotide polymorphisms (SNPs), an individual's risk of developing a peripheral neuropathy after thalidomide treatment can be predicted. These genes primarily govern repair mechanisms and inflammation in the peripheral nervous system [10]. This could allow the development of neuroprotective strategies in patients who are predisposed to develop this complication. Similar studies have been undertaken to predict the risk of peripheral neuropathy associated with bortezomib. Gene expression profiles of myeloma plasma cells and SNPs in DNA samples identified genetic factors that increase the risk of bortezomib-induced peripheral neuropathy and included enzyme-coding genes involved in drug-induced apoptosis and mitochondrial dysfunction [11]. In a second study, genes associated with immune function, drug binding and neuron function were found to be associated with bortezomib-induced peripheral neuropathy, and may be used in the future to develop a predictive genetic signature for those at increased risk of peripheral neuropathy [12].

Practicing oncologists should be delighted with the new options available to their patients, with the hope of substantially improved survival. However, they need to be aware of the significant neurotoxicity that these patients are at risk of developing. Prompt dose reduction in patients who begin to

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This commentary accompanies an article which is due to be published in a coming issue of *Leukemia & Lymphoma*.

develop early paresthesias is mandatory to avoid long-term morbidity. Reduction in frequency of administration, subcutaneous administration of bortezomib, and alternate-day or reduced dose administration of thalidomide are all options to help improve the toxicity profile associated with these highly effective agents.

Potential conflict of interest: The author has received honoraria from Celgene & Millenium pharmacuticals. A disclosure form provided by the author is available with the full text of this article at www.informahealthcare.com/lal.

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