Author reply: Lenalidomide for bortezomib-resistant multiple myeloma

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We thank Briani *et al.*[1] and Gozzetti *et al.*[2] for their additional comments to the topics discussed in our Case Study.[3] Briani and colleagues report on their experience with lenalidomide treatment in patients with relapsed or refractory disease after previous bortezomib and/or thalidomide therapy and chemotherapy-induced peripheral neuropathy.[1] They observed a significant improvement in neurological symptoms and Total Neuropathy Score clinical version (TNSc). The improvement was most pronounced in patients with a high baseline TNSc. Bortezomib induces sensory neuropathy, which usually resolves in about two-thirds of patients within a median time of 2–3 months after discontinuation of therapy.[4] The likelihood of sensory neuropathy normalization is improved when guidelines for treatment modifications are followed and dose reductions implemented or treatment discontinued at early grades of neurotoxicity. By contrast, thalidomide induces a sensory neuropathy in most patients and in 30–40% of affected patients a mixed sensory-motor neuropathy with low potential for complete resolution. Improvements or resolutions are seen in about one-quarter of patients, mostly after long follow-up, ranging between 4 and 6 years.[4] In the future, other drugs such as carfilzomib with no or very limited neurological adverse effects may provide additional treatment alternatives for patients with pre-existing neuropathy.

Gozzetti and colleagues report on two patients with light-chain induced renal failure.[2] Both patients were started with a bortezomib-based regimen. One patient, with a deletion of 13q identified by fluorescence *in situ* hybridization analysis, responded to this treatment and was re-exposed to bortezomib therapy after relapse. At a subsequent second relapse the same regimen was applied but was found to be ineffective, while rescue therapy with lenalidomide (dose adapted to the glomerular filtration rate) induced a very good partial response. This finding motivated the authors to continue therapy with lenalidomide maintenance treatment. Three trials presented at cancer meetings support this concept; all three reported a significant increase in progression-free survival with lenalidomide maintenance therapy.[5–7] A substantial survival benefit, however, has not been demonstrated as yet.

We fully agree with Gozzetti and colleagues regarding the importance of cytogenetic testing for prognostication in myeloma. Approximately 15–20% of all myeloma patients present with high-risk disease[8] and these patients are clear candidates for treatment with potent multidrug combinations upfront. In addition to cytogenetic data, gene arrays and molecular markers (such as interferon regulatory factor 4)[9] could be helpful in designing rational treatment strategies for individual myeloma patients.

Gozzetti and colleagues report on another patient with renal failure, with a deletion of 17p and a t(4;14) detectable by cytogenetic analysis.[2] This patient was refractory to bortezomib and did not respond to lenalidomide rescue treatment. Recent data show that both bortezomib and—to a lesser extent—lenalidomide can overcome the negative prognostic impact of poor cytogenetics such as loss of 13q or a t(4;14). Loss of *p53*, which occurs with a deletion of 17p, seems to be associated with a poor response to all drugs presently approved for treatment of myeloma and is linked to a very short survival. Hopefully, new drugs in clinical development will overcome this therapeutic dilemma.

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Competing interests
H. Ludwig declares associations with the following companies: Celgene and Ortho-Biotech. See the article online for full details of the relationships. N. Zojer declares no competing interests.

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