Lenalidomide efficacy in bortezomib-resistant myeloma

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We read with great interest the Case Study by Ludwig and Zojer in which they describe a case of a 51-year-old man with IgG λ stage III B multiple myeloma who presented with renal impairment associated with urinary secretion of free λ chains (Renal recovery with lenalidomide in a patient with bortezomib-resistant multiple myeloma. Nat. Rev. Clin. Oncol. 7, 289–294; 2010).[1] The authors reported lenalidomide efficacy after failure to two cycles of PAD regimen (bortezomib, doxorubicin, dexamethasone).

The authors did not report if cytogenetic and/or fluorescence *in situ* hybridization (FISH) analysis was performed to detect chromosomal and/or genomic abnormalities. We believe this test could be important because we recently treated two similar patients with severe renal failure, with both patients having distinct outcomes.

The first patient, an 82-year-old man, presented with IgG λ stage III B myeloma with free λ chains at diagnosis (IgG 67.8 g/l) and acute renal failure requiring temporary dialysis (proteinuria 10.2 g per 24 h, glomerular filtration rate 10 ml/min/1.73 m^2 and creatinine levels of 780 μmol/l). FISH analysis at diagnosis on $CD138^+$ positively-selected bone marrow plasma cells showed a deletion of 13q in 58% of cells. Our patient achieved a very good partial response (VGPR) after six cycles of PAD lasting 7 months. Following a relapse, he responded again (VGPR) to three cycles of PAD lasting this time for 5 months. At second relapse bortezomib did not work and lenalidomide was started at 10 mg on alternate days for cycles of 21 days. After two cycles, the patient achieved a VGPR with 0.4 g per 24 h, creatinine levels at 142 μmol/l, IgG 19.7 g/l and lenalidomide was given as maintenance therapy at 10 mg per day for cycles of 21 days. This response lasted for 12 months.

We also observed a 54-year-old patient with IgG λ myeloma and severe renal failure with free λ chains (proteinuria 8.7 g per 24 h, glomerular filtration rate 16 ml/min/1.73 m^2 and creatinine levels of 480 μmol/l) who was primary refractory to bortezomib (PAD) and also did not respond to lenalidomide. FISH analysis on bone marrow selected plasma cells at diagnosis showed a translocation (4;14) in 70% of the cells and a deletion of 17p in 55% of the cells.

A study by Reece *et al.*[2] showed that patients with relapsed myeloma carrying a deletion of 17p13 were refractory to lenalidomide and had an inferior outcome compared with patients not carrying this abnormality. Patients with either a deletion of 13q or a t(4;14) translocation experienced a median time to progression and overall survival comparable with those without these cytogenetic abnormalities, whereas patients with a deletion of 17p13 had a significantly worse outcome, with a median time to progression of 2.22 months (hazard ratio 2.82; $P<0.001$) and median overall survival of 4.67 months (hazard ratio 3.23; $P<0.001$). The mechanisms of resistance to lenalidomide are unknown. Indeed, the second of our two cases seems to confirm that.

In conclusion, these cases suggest that patients with myeloma who have a deletion of 17p are likely to be refractory to treatment with lenalidomide, whereas patients without this deletion seem to respond to lenalidomide. We believe this information needs to be confirmed in larger studies, but could be useful for more targeted treatment strategies.

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Competing interests
The authors declare no competing interests.

1. Ludwig, H. & Zojer, N. Renal recovery with lenalidomide in a patient with bortezomib-resistant multiple myeloma. *Nat. Rev. Clin. Oncol.* **7**, 289–294 (2010).
2. Reece, D. *et al.* Influence of cytogenetics in patients with relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone: adverse effect of deletion 17p13. *Blood* **114**, 522–525 (2009).