Efficacy and tolerability of repeated cycles of a once-weekly regimen of bortezomib in lupus

Sir, Fröhlich et al. [1] described in 2011 the first case of the successful use of twice-weekly bortezomib, a proteasome inhibitor (1.5 mg on days 1, 4, 8 and 11 of each 28-day cycle, for three cycles), in a patient with SLE and concomitant multiple myeloma (MM), supporting the preliminary evidence of the efficacy of bortezomib in mouse models of lupus [2, 3]. The susceptibility of cells to bortezomib is related to the extent of protein production in general, and to the extent of Ig production in myeloma B cells in particular [4]. In SLE, long-lived plasma cells, which are the major source of autoantibody-producing B cells, are generally resistant to immunosuppressive therapies, including the most recent biologic B cell targeting agents. Persistence of the disease or flares may be imputable to survival of such long-lived plasma cells [5], and the efficacy of bortezomib in SLE may be linked to the killing of long-lived and short-lived plasma cells. However, no other reports of bortezomib therapy in SLE have been subsequently published, and a trial in SLE with a standard dose-intensity regimen with bortezomib has been withdrawn (Velcade for proliferative lupus nephritis; www.ClinicalTrials.gov). Polynephropathy, thrombocytopenia and gastrointestinal complaints are frequent side effects that lead to early discontinuation of bortezomib in more than one-third of MM patients. This raises major questions on the feasibility of bortezomib in younger patients with SLE as well as its potential efficacy [6, 7]. One recently proposed option to minimize the toxicity of bortezomib in MM is a longer interval for the administration of the drug—i.e. weekly or longer [8, 9]. Based on these new therapeutic schedules of administration of bortezomib, it is possible to treat MM in patients who are not suitable for a full dose-intensity regimen [8, 9], and the same schedules might be useful in SLE.

We report the case of a 70-year-old woman who suffered from SLE and anti-phospholipid syndrome (APS), with both diseases fulfilling the ACR classification criteria, characterized by photosensitivity, serositis, lymphopenia, venous thrombosis and multiple ischaemic lesions on cerebral MRI, positivity of anti-Sm and anti-RNP autoantibodies, high-titre aCL IgG, and lupus anticoagulant. Renal involvement was absent. The patient also suffered from autoimmune thyroiditis. Treatment with AZA and low doses of glucocorticoids had been used in the past, while other immunosuppressants had been avoided mainly because of recurrent herpetic keratitis (requiring continuous prophylaxis with antiviral drugs) and the low level of disease activity (ECLAM score, 2; SLEDAI score, 2). Platelet anti-aggregants were used for APS.

In 2009 MM (IgA) was diagnosed, in stage I according to Salmon and Durie (bone marrow infiltration 15%), evolving from a monoclonal gammopathy of undetermined significance (MGUS) (IgA. MGUS) known since 2001. Due to the increasing IgA levels (from 1630 to 2600 mg/dl in 3 months), the patient was treated with once-weekly bortezomib infusions [1.3 mg/m² i.v. on days 1, 8, 15 and 22 (for four cycles)] and dexamethasone 40 mg, obtaining a long-term partial response of the MM and negativization of SLE-related autoantibodies (ANA and anti-Sm). Both the ECLAM and SLEDAI scores decreased to zero. At the beginning of 2012, progression of the MM was revealed by a substantial increase in IgA and serum β2-microglobulin, while SLE was in remission and autoantibodies were negative. Bortezomib was repurposed at the same regimen of 1.3 mg/m²/week for 4 weeks (four cycles) plus dexamethasone. From the fifth cycle, CYC 50 mg every other day for 2 months was added. The treatment was interrupted after the sixth cycle, since a new partial remission of the MM was obtained, with SLE remaining in remission.

The overall tolerability of the two cycles of treatment was good, and only a grade 1 peripheral neuropathy occurred, with no reactivation of herpetic keratitis. At the last available follow-up (36 months after the first bortezomib cycle), SLE persisted in remission and the prednisolone dose was 5 mg/day.

The case reported herein highlights the possible usefulness of the once-weekly regimen of bortezomib therapy in SLE. This regimen has already been introduced in MM trials, leading to a decrease in haematological, gastrointestinal and neurological side effects, accompanied by a similar efficacy [8, 10]. Importantly, bortezomib was well tolerated in association with steroids in the present case, and very low doses of oral CYC were subsequently allowed. The evaluation of short-lived and long-lived plasma cells was not performed during bortezomib treatment in this patient. However, the autoantibodies soon became negative after the first cycle of treatment, consistent with a biological activity of the treatment on plasma cells and with the clinical efficacy observed in SLE. On the other hand, since SLE was only mildly active in our patient, the efficacy of the reported regimen of bortezomib remains to be evaluated in more active SLE, which could represent a more common therapeutic target.

The possible use of bortezomib in SLE is described herein when using delayed infusions of the drug. Since bortezomib might represent an important therapeutic option in selected patients with SLE, further investigation would be worthwhile.

Rheumatology key message

- Lower dose regimens of bortezomib might be useful in lupus.

Disclosure statement: The authors have declared no conflicts of interest.
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Accepted 18 July 2013
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