Successful treatment of warm-type haemolytic anaemia with bortezomib in a rituximab-failed systemic lupus erythematosus patient

Sir, Autoimmune haemolytic anaemia (AIHA) is classified as either warm or cold type, based on the characteristics of the autoantibodies involved in the pathogenesis of the disease. Each type of AIHA has a different underlying cause, which has a great impact on the treatment and outcome [1].

Glucocorticoid is the first-line treatment in warm AIHA. In some patients resistant to glucocorticoids, treatment may include immunosuppressive agents, rituximab or even splenectomy. Many immunosuppressive drugs have been used in attempts to treat refractory warm-type AIHA patients, including AZA, CYC, ciclosporin and MMF. Unfortunately the clinical response to these treatments is unpredictable and the response rate is relatively low. Therefore novel therapies for patients with steroid-refractory AIHA are urgently needed [2].

Here we report the case of a 65-year-old woman with SLE and a history of severe anaemia for 21 years. She had a strongly positive direct antiglobulin test with both IgG and C3d deposition on red blood cells (RBCs). She had oral ulcers and polyarthritis intermittently, which responded well to glucocorticoid treatment. The other laboratory findings were as follows: ANA was positive (1:320), anti-dsDNA and anti-ENA were negative, C3 was 0.57 g/l (normal range 0.6–1.5) and C4 was 0.02 g/l (normal range 0.12–0.36). aCL was positive at 32.3 RU/ml (normal <12 RU/ml). Cryoglobulin test was negative. She was diagnosed as SLE according to 1997 ACR classification criteria [3].

The anaemia was so severe that the patient had to receive intensive blood transfusion support (1–3 U of RBCs/day). At first, high-dose prednisone (1 mg/kg) had a good clinical response. However, the anaemia has repeatedly relapsed in the past 5 years when prednisone is tapered. Pulse therapy (1 g/day every 3 days), AZA, CYC and dexamethasone showed poor response. Rituximab (375 mg/m²/week four times) was administered. As shown in Fig. 1, after this treatment the level of haemoglobin rose and reticulocytes fell. The count of plasma cells, identified as k light chain positive and CD138+ among the lymphocyte-gated cells, declined in bone marrow (from 26.7 to 0.01%). Meanwhile, levels of IgM and IgG in serum decreased from 1.14 to 1.05 g/l and 8.39 to 7.04 g/l, respectively. Haemoglobin rose to 150 g/l in December 2012 and stabilized for 2 years, and prednisone was successfully tapered to 10 mg/day.

Bortezomib is an inhibitor of the 26S proteasome, which can directly inhibit myeloma cells from producing immunoglobulin. It has been approved for the treatment of multiple myeloma. Moreover, it has been proved to have some effect in eliminating autoantibody production, ameliorating GN and prolonging the survival of mouse strains with lupus-like disease [4]. The elimination of autoreactive plasma cells by proteasome inhibitors might represent a new treatment strategy for antibody-mediated diseases.

Until now there have been two case reports about successful treatment of bortezomib in patients with rituximab-refractory AIHA. The first report was of a 78-year-old woman with steroid/rituximab-refractory IgM-mediated cold agglutinin disease. Bortezomib targets differentiated plasma cells that typically do not express CD20 but may be responsible for secretion of the abnormal IgM for haemolytic anaemia [5]. The second was an SLE patient with transfusion-dependent and steroid/rituximab-refractory AIHA who responded well to the combination of bortezomib and low-dose CYC [6]. Both reports suggested that bortezomib might be effective in treating AIHA. Our SLE patient also had a good and permanent response to bortezomib in AIHA, without hypergammaglobulinaemia, cryoglobulinaemia or myeloma.

These two reports were both short and there was no detailed information on bone marrow evaluation. The innovation of our study is that we did bone marrow cell flow cytometric analysis before and after the bortezomib treatment. It showed that the plasma cell count in bone marrow cells decreased dramatically after treatment with bortezomib. Nevertheless, serum levels of IgG and IgM decreased only slightly. Bortezomib can only inhibit only active plasma cells, so the plasma cells in bone marrow were more sensitive to proteasome inhibition.
However, bortezomib may also induce haemolytic anaemia. Mehta et al. [7] presented a case of bortezomib-associated thrombotic thrombocytopenic purpura, and Rovira et al. [8] described two patients with acute myeloid leukaemia treated with chemotherapy including bortezomib. Both patients died because of immune haemolysis. Thus the treatment of AIHA with bortezomib still needs to be validated.

Rheumatology key message

- Bortezomib is a well-tolerated treatment and it can be used to treat refractory autoimmune haemolytic anaemia in SLE patients.

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