34 REFRACTORY SLE PATIENTS RESPOND TO THE PROTEASOME INHIBITOR BORTEZOMIB

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Background and objectives Long-lived memory plasma cells secreting pathogenic autoantibodies are resistant to conventional immunosuppression and B cell targeting therapies. Bortezomib, an approved drug for relapsing multiple myeloma, efficiently depletes short- and long-lived plasma cells and ameliorates nephritis in murine lupus models. Therefore, the authors studied the efficacy of bortezomib in refractory SLE patients in a case series.

Materials and methods At three university centers, 13 SLE patients refractory or intolerant to cyclophosphamide, MMF and/or rituximab were treated with bortezomib intravenously at a dose of 1.3 mg/m^2 body surface area on days 1, 4, and 8 and, in some cases, on day 11. Most patients received 20mg of dexamethasone together with bortezomib. Treatment cycles were repeated up to four times with an interruption of usually 10 to 14 days between cycles. The following clinical and laboratory parameters were monitored: SLEDAI disease activity score, 24 h proteinuria, creatinine clearance, circulating plasma cells, complement C3 and C4, IgG, IgA, IgM, antibodies to dsDNA and ENA, and vaccine titers.

Results SLEDAI and antibody levels significantly decreased under bortezomib while complement levels increased. In seven patients with active nephritis, proteinuria declined within 6 weeks of treatment, and normalised after four months in one case. Anti-dsDNA antibodies decreased by up to 90%, anti-ENA and protective vaccine titers by up to 50%, and immunoglobulin levels by up to 30%. Circulating plasmablasts dropped substantially. Serious side effects were not observed. One patient experienced myalgia, fever and headache 1 day after the first 3 bortezomib doses. Three of five patients treated with four bortezomib injections per cycle developed polyneuropathies, which were reversible upon discontinuation of treatment. One patient developed reversible thrombocytopenia after four treatment cycles.

Conclusions The proteasome inhibitor bortezomib may effectively reduce disease activity in refractory SLE patients by depleting plasma cells. The data encourage initiation of clinical trials with bortezomib in refractory SLE and support the relevance of plasma cells in the pathogenesis of this autoimmune disease.