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Case report

Bortezomib improved the joint manifestations of rheumatoid arthritis in three patients

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ABSTRACT

The proteasome inhibitor bortezomib has been proven effective in the treatment of multiple myeloma. We report on 3 patients with rheumatoid arthritis and multiple myeloma in whom bortezomib therapy was associated with improvements in the joint manifestations. The contribution to this effect of the concomitant glucocorticoid therapy is discussed.

1. Introduction

The proteasome inhibitor bortezomib (Velcade®, Takeda Oncology, Cambridge, MA, USA) is used for the first-line treatment of multiple myeloma. Recent studies in murine models demonstrated that proteasome inhibition avoided the development of severe arthritis, probably via NF-κB inhibition. We describe the cases of 3 patients with rheumatoid arthritis (RA) whose joint manifestations improved after they received bortezomib to treat multiple myeloma.

2. Case-reports

A 78-year-old woman was diagnosed with RA in 1981. She had a limited response to methotrexate (15 mg/week) and was therefore also given leflunomide and prednisolone (15 mg/day). A monoclonal IgA was identified in serum samples, prompting investigations, which showed type 1 multiple myeloma. In January 2010, she was admitted for sepsis after hip arthroplasty. The leflunomide was stopped. A few months later, her rheumatoid joint manifestations worsened and she experienced a decline in general health and back pain due to multiple vertebral fractures. The Disease Activity Score (DAS) was 6.5 (target < 3.5), the erythrocyte sedimentation rate (ESR) 80 mm/h, and the C-reactive protein (CRP) level 21 mg/L. The monoclonal IgA peak was 30 g/L. A bone marrow biopsy showed infiltration by plasma cells. The rheumatoid factor (RF) titer was 264 IU/mL and the anti-citrullinated peptide antibody (ACPA) titer was 87 U/mL ($n < 20$). Her treatment with melphalan, prednisone, and thalidomide was stopped due to severe side effects. She received eight cycles of bortezomib therapy in a dosage of 1.3 mg/m^2. The prednisolone therapy was continued in a dosage of 20 mg/day. Three months after bortezomib initiation, her general health and joint manifestations were improved. Six months later, the IgA peak was 15 g/L, the DAS was 3.0, and the pain and signs of joint inflammation were substantially diminished. The prednisone was stopped at the end of the chemotherapy cycles. One year after bortezomib initiation, she had no evidence of an RA relapse. She died of a stroke 3 years later.

A 72-year-old man diagnosed with RA in 1995 was treated with methotrexate (20 mg/week) and prednisolone (10 mg/day). In February 2011, he was admitted for multiple vertebral fractures after a fall. He had over 10 swollen and tender joints, indicating active RA. The DAS was 6.2. Blood tests showed anemia (8 g/dL) with an ESR of 120 mm/h and a CRP level of 30 mg/L. Serum calcium was 2.75 mg/L and serum creatinine 375 mmol/L. Investigations established a diagnosis of stage III light-chain multiple myeloma. The RF assay was positive in a titer of 120 IU/L and the ACPA titer was 80 IU/L. Bortezomib was started in a dosage of 1.3 mg/m^2 on days 1, 4, 8, and 11 then every 3 weeks, in combination with dexamethasone 20 mg. The methotrexate was stopped. Bortezomib was continued in the same dosage until the 8th cycle. Three months after stopping the bortezomib and dexamethasone, the joint disease was controlled, with a DAS of 2.9. The RF and ACPA assays

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remained positive. The patient died in an accident 3 years later without experiencing any further clinical symptoms of RA.

Finally, the third patient was a 60-year-old man with active RA for the last 5 years. He had successively received hydroxychloroquine, sulfasalazine, and methotrexate. In 2010, due to persistent disease activity and the presence of a monoclonal IgA-κ protein considered to indicate monoclonal gammopathy of undetermined significance, two rituximab cycles were given over a 1-year period. The response was only partial, with persistent arthritis predominating at the extremities. He was admitted 1 year later for severe low back pain refractory to standard treatment. The investigations indicated IgA multiple myeloma with 40% of plasma cells in the bone marrow biopsy. He received three cycles of bortezomib and dexamethasone. The methotrexate was stopped. Autologous stem-cell transplantation was considered but not performed due to the presence of heart failure. Four additional bortezomib cycles were given. Rheumatoid erosions developed and tests for RF and ACPA were positive. During bortezomib therapy, the joint pain and signs of inflammation abated rapidly. Radiation therapy to the lumbar spine lesions was given. Both the multiple myeloma and the RA seemed to be in remission at this point (DAS < 2.5). The subsequent treatment included 10 mg/day of prednisolone.

3. Discussion

RA is a chronic inflammatory joint disease of unknown etiology. The pathogenesis involves cytokines and cell adhesion molecules, which are regulated by the NF-κB family [1]. Bortezomib, the first proteasome inhibitor used to treat multiple myeloma, acts by inhibiting NF-κB and by modulating cytokine expression in the tumor microenvironment [2]. In the murine lupus model, bortezomib modulated plasma cell activity, decreasing the production of double-stranded DNA antibodies and preventing renal involvement [3]. Studies of murine models of experimentally induced arthritis demonstrated that bortezomib was effective in improving the inflammatory joint manifestations [4–7]. In addition, ex vivo incubation with bortezomib of blood samples from patients with RA inhibited the production of TNFα and IL6 and induced T-cell apoptosis [8]. In mice transgenic for human TNFα, which is also a model of arthritis, bortezomib therapy improved the inflammatory joint manifestations, decreased the development of erosions, and increased the osteoclast counts in joint fluid [9]. In our 3 patients with both RA and multiple myeloma, joint disease improvements occurred within 3 months after bortezomib initiation and persisted for several months. In patient #1, the improvements seem entirely ascribable to bortezomib. In the other 2 patients, a beneficial effect of dexamethasone therapy cannot be ruled out. However, glucocorticoid therapy is unlikely to produce a remission or low disease activity sustained in the long term. A synergistic effect with bortezomib is plausible.

Biotherapies including TNFα antagonists, IL6 antagonists, and anti-CD20 antibodies have considerably improved treatment efficacy in inflammatory joint diseases. Rituximab was initially developed for the treatment of B-cell non-Hodgkin's lymphoma. Similarly, bortezomib may find a place within the therapeutic strategies for RA. Clinical trials of bortezomib including risk/benefit ratio and cost evaluations may be warranted in patients with RA refractory to all other treatment options.

Disclosure of interest

The authors declare that they have no competing interest.

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