

# The Addition of Low-dose Thalidomide to Bortezomib and Dexamethasone for Refractory Multiple Myeloma

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## Abstract

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Five cases were treated by adding daily low-dose thalidomide (50 mg) to bortezomib and dexamethasone therapy for refractory multiple myeloma. This therapy was effective in four cases, with an improvement of bone pain and regression of M-protein. One case was treated with cyclophosphamide, thalidomide, and dexamethasone, adding bortezomib after starting the three-drug combination therapy. This patient has remained in a stable disease state since the beginning of this therapy. Regarding the other four cases, a partial response and a prolonged survival for approximately one year were noted. Peripheral neuropathy did not increase after thalidomide addition. Adding low-dose thalidomide may safely improve the responses for multiple myeloma refractory to bortezomib and dexamethasone.

**Key words:** multiple myeloma, bortezomib, dexamethasone, thalidomide

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## Introduction

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Combination therapy using bortezomib and dexamethasone (BD) is now widely considered to be the standard induction chemotherapy for newly-diagnosed or relapsed symptomatic multiple myeloma (1-5). Although the effect of this therapy is better than that of previous conventional therapies such as melphalan with prednisolone (MP), many patients may develop refractory disease or may only demonstrate a brief remission after BD therapy. We herein report five cases with multiple myeloma that were treated with BD therapy and subsequently experienced disease progression during BD therapy. In four of five cases, the addition of low-dose thalidomide (50 mg per day) to BD therapy [bortezomib, thalidomide, dexamethasone (VTD) 50] made refractory disease respond to therapy. One case was treated with the combination of four drugs (bortezomib, cyclophosphamide, dexamethasone and thalidomide) after the disease had become refractory to the three drug combination. After adding bortezomib to thalidomide, 50 mg/day, cyclophosphamide and dexamethasone, back pain was relieved quickly and the laboratory findings, including anemia and elevation of  $\beta_2$  microglobulin, showed continuous improvement since

this four-drug combination was started. Several reports showed the effects of bortezomib, dexamethasone and thalidomide therapy for multiple myeloma as induction chemotherapy, consolidation chemotherapy after autologous stem cell transplantation and salvage chemotherapy (6, 7). However, most of these reports used thalidomide at a dose of 100 mg to 200 mg per day. There are few reports of low-dose thalidomide in combination with BD therapy, and adding only 50 mg daily thalidomide (VTD 50) may be effective against multiple myeloma refractory to BD therapy. We herein report the results of VTD 50 therapy.

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## Case Reports

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### Case 1

A 68-year-old man was referred to our hospital after the detection of an IgG  $\lambda$  elevation. The serum IgG level was 3,861 mg/mL, with all other globulins markedly suppressed. He had been diagnosed with stage I multiple myeloma according to the International Staging System (ISS) in January 2009. He had been treated with MP therapy first with a minimal response, and was subsequently treated with 100 mg of daily dose thalidomide with dexamethasone and MP

plus thalidomide. The effect of that therapy with thalidomide was a minimal response. Computed tomography revealed the development of an interstitial shadow in both lung fields; therefore, BD therapy was not considered for primary therapy. In early 2011, weekly BD therapy (2.1 mg of bortezomib and 20 mg intravenous dexamethasone) was safely started, and IgG decreased markedly. The serum levels of IgG decreased from 3,806 mg/mL to 1,684 mg/mL within two months. He was considered to have attained a partial remission by February 2011. After weekly outpatient injections of bortezomib, the patient was later switched to two injections every three weeks, and he had neither any lung side effects nor severe sensory disturbances for over a half year. In October 2011, a rapid increase in the IgG levels was observed (3,066 mg/mL). He was given VTD 50 therapy, adding 50 mg of thalidomide daily, even though thalidomide previously had been ineffective when combined with dexamethasone or MP. We administered VTD 50 therapy with bortezomib due to concerns of potential sensory disturbance from the administration of both drugs. The combination of VTD 50 caused a decrease in the levels of IgG (down to 2,163 mg/mL in May 2013) and  $\beta$ 2 microglobulin, which was considered to be a partial response, again with the disappearance of back pain and no sensory disturbance, and this partial response was maintained for eleven months. After a repeated deterioration of the laboratory findings, he refused further therapies using bortezomib or other combination chemotherapies. He has been treated with conventional therapy using melphalan, cyclophosphamide, and prednisolone and has since remained stable since that time.

### Case 2

A 75-year-old woman was referred to our hospital in June 2010 after the detection of anemia and renal dysfunction. Her serum IgA level was 2,845 mg/mL. She was diagnosed with IgA  $\lambda$  myeloma, ISS stage III. She initially refused BD therapy, as she was concerned about potential side effects such as interstitial pneumonia. She had agreed to use weekly BD therapy (1.7 mg of bortezomib and 20 mg intravenous dexamethasone) when her IgA was elevated after several conventional therapies, including MP and dexamethasone monotherapy (serum level of IgA was up to 946 mg/mL in April 2011 from the normal range). Pancytopenia was observed after weekly bortezomib and dexamethasone injection with a marked decrease in the IgA levels (down to 73 mg/mL after one month), suggesting a very good partial response. Bortezomib therapy was changed to weekly, then monthly, and the patient was free of granulocytopenia and did not require transfusions. After continuing BD therapy for approximately one year, IgA and  $\beta$ 2 microglobulin again became elevated. Biweekly injection of bortezomib became ineffective by early 2012. The patient's serum IgA level was 1,515 mg/mL in March 2012. She agreed to add thalidomide, 50 mg daily, to BD, according to our previous treatment experience (as in case 1). After VTD 50 was initiated, a rapid decrease in the IgA and  $\beta$ 2 microglobulin levels was

observed and the patient again attained a partial response (IgA level was reduced to 290 mg/mL in October 2012). These effects continued for eleven months without any sensory disturbance. After repeated deterioration of the laboratory data despite VTD 50 therapy, a rapid progressive disease status was observed, and other drugs such as lenalidomide had a minimal effect. She died from plasma cell leukemia in December 2013.

### Case 3

A 62-year-old man was diagnosed with ISS stage III IgG  $\kappa$  myeloma in September 2007. He was treated with tandem autologous stem cell transplantation followed by several courses of vincristine, doxorubicin, and dexamethasone induction therapy from July through November 2008. No further treatment after transplantation was performed due to the development of a viral infection and pneumonia shortly after transplantation. After transplantation, he remained in a complete remission for several years. In February 2011, a routine examination revealed re-elevation of IgG (2,215 mg/mL), elevation of the atypical plasma cell ratio in the bone marrow, and positive monoclonal immunoelectrophoresis, leading to a diagnosis of relapsed myeloma. BD therapy (2.2 mg of bortezomib and 20 mg intravenous dexamethasone) was started in March 2011. Outpatient bortezomib was given on a weekly to biweekly basis. The IgG level increased again from the normal range to over 2,000 mg/mL in May 2012, suggesting a partial response after relapse. The patient began VTD 50 therapy in combination with BD therapy in July 2012. VTD 50 therapy decreased the IgG levels to 1,077 mg/mL by August 2011, again achieving a partial response with the disappearance of bone pain, and this response was maintained until June 2013, when the patient again developed progressive bone pain and IgG elevation. Lenalidomide plus dexamethasone or bortezomib, cyclophosphamide and dexamethasone combination therapy had no effect after progression. He eventually died from plasma cell leukemia in November 2013.

### Case 4

A 58-year-old woman was transferred from another hospital with severe back pain in January 2012. She was diagnosed with ISS stage II IgG  $\kappa$  multiple myeloma. Her serum IgG level was 5,440 mg/mL at the initial visit. She initially refused up-front autologous stem cell transplantation at the diagnosis, and thus began biweekly BD therapy (2 mg of bortezomib and 20 mg intravenous dexamethasone) from April 2012 to January 2013, achieving a partial response. Progressive back pain and re-elevation of IgG were observed after ten months of BD therapy. The serum IgG level had increased to 2,364 mg/mL at that time. She agreed to take VTD 50 therapy with BD therapy. She had a rapid decrease of IgG and disappearance of back pain within two to three weeks after starting VTD 50 therapy. The IgG level was decreased to 1,208 mg/mL in May 2013, again achieving a partial response. This response was sustained for 10 months

before progressive bone pain again developed in December 2013. The IgG level had increased to 1,825 mg/mL at that time. She was treated with 20 mg of lenalidomide for several months after VTD 50 therapy. Although lenalidomide controlled the IgG elevation, symptomatic bone pain had not disappeared completely. She then decided to undergo autologous stem cell transplantation after achieving a response after multiple salvage chemotherapies.

### Case 5

A 63-year-old man was referred to our hospital following the detection of anemia in October 2011. He was diagnosed with ISS stage III Bence Jones  $\lambda$  multiple myeloma. Since all peripheral blood gamma-globulins were heavily suppressed, his disease status was followed according to symptoms of back pain, anemia, and elevation of  $\beta$ 2 microglobulin (7.864 mg/L at the initial visit). He was not considered to be a candidate for up-front autologous stem cell transplantation due to a past history of cardiac bypass. Weekly to biweekly BD therapy (2 mg of bortezomib and 20 mg intravenous dexamethasone) was started in December 2011, which resulted in a rapid improvement in back pain, improvement in anemia, and a decrease in the  $\beta$ 2 microglobulin levels within two weeks. In March 2013, his back pain returned, and in October 2013,  $\beta$ 2 microglobulin increased rapidly (4.146 mg/L) accompanied by uncontrollable back pain. Increased cycles of BD with VTD 50 or treatment with lenalidomide plus dexamethasone had no effect. Morphine was required to reduce his severe pain, and within a short time, he could not walk. In December 2013, he developed worsening anemia and hypogammaglobulinemia, and further elevation of the  $\beta$ 2 microglobulin levels (up to 5.685 mg/L) was observed, and he had to be admitted to our hospital. Treatment with cyclophosphamide (500 mg biweekly), thalidomide (50 mg daily), and dexamethasone (20 mg weekly) combination therapy briefly stabilized the  $\beta$ 2 microglobulin levels, but his severe back pain persisted. Adding bortezomib (2 mg weekly) to the three-drug combination rapidly improved the back pain and decreased the  $\beta$ 2 microglobulin levels. He has been treated with this four-drug combination (100 mg oral cyclophosphamide for four continuous days/ every two weeks, 50 mg thalidomide daily, 20 mg oral dexamethasone weekly, and 2 mg bortezomib injected subcutaneously weekly) for over one and a half years maintaining stable disease without back pain, elevated  $\beta$ 2 microglobulin levels (2 to 3 mg/mL by a biweekly routine examination), or further sensory disturbance beyond those present at the time of BD therapy.

### Discussion

BD therapy is considered a standard chemotherapy for multiple myeloma for autologous transplantation eligible patients (1-3), transplantation ineligible patients (4) and even patients with relapsed or refractory disease following previous therapy (5). In transplantation-eligible patients and re-

fractory or relapsed patients, cyclophosphamide (VCD) or thalidomide (VTD) may be added to BD therapy to achieve optimal results (6). With VTD, peripheral neuropathy is one of the adverse effects, which is observed more often than with thalidomide and dexamethasone therapy (7). Both bortezomib and thalidomide have peripheral neurotoxicity. In particular, when these two drugs are used in combination, the thalidomide daily dose can range from 50 to 200 mg (6). A dose reduction of thalidomide (50 mg) may reduce this toxicity considerably (8, 9). Among transplantation-ineligible patients, there are decision criteria according to the patients' clinical status or frailty (10). For induction, patients can be treated with monotherapy up to a three-drug combination. After induction, therapeutic options include bortezomib-based, lenalidomide-based or bortezomib and thalidomide-based combinations [such as bortezomib-melphalan-prednisone-thalidomide (VMPT)-bortezomib-thalidomide (VT) therapy (11)]. In frail patients, bortezomib, lenalidomide, dexamethasone and cyclophosphamide should be considered for dose reduction, however, dose reduction of thalidomide is excluded (6). Another report showed that the daily dose of thalidomide could be reduced 50 mg in two days to 100 mg per day for frail patients (12). According to the findings of our study, combination therapy with thalidomide and other drugs may be used for both transplantation-eligible and -ineligible patients with a wider range to reduce the daily dose of thalidomide than for other drugs while still achieving optimal effects. Our five cases were treated with a 50 mg daily dose of thalidomide together with BD therapy for refractory disease. Four of five cases showed improvement, including reduction of M protein and symptoms. One case showed improvement with combination therapy of bortezomib, thalidomide, cyclophosphamide, and dexamethasone. All five cases were treated with thalidomide, 50 mg daily, without excess peripheral neuropathy. Two of five cases were over 65 years of age. VTD 50 therapy safely induced a partial response of refractory disease and a rapid improvement of bone pain, together with simultaneous regression of M protein and  $\beta$ 2 microglobulin. These findings were maintained for nearly one year in four of five cases. In two of five cases, the diseases eventually transformed into plasma cell leukemia after VTD 50 therapy. Further studies are required to find new strategies for further extending the response duration or maintaining stable disease using this drug combination.

**The authors state that they have no Conflict of Interest (COI).**

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