Case Reports in Oncology
Case Rep Oncol 2009;2:140–143
DOI: 10.1159/000228161
Published online: July 29, 2009

ISSN 1662–6575
www.karger.com/cro

Fatal Cytomegalovirus Pneumonia and Associated Herpes Virus Infection in a Relapsed/Refractory Multiple Myeloma Patient Treated with Bortezomib plus Dexamethasone

Daisuke Taniguchi[a] Osamu Takahara[b] Yumi Takasaki[a]
Masayuki Tawara[a] Tatsuro Joh[a] Masao Tomonaga[c]

[a]Department of Internal Medicine, [b]Department of Pathology, The Japanese Red Cross Society Nagasaki Genbaku Hospital, and [c]Department of Hematology, Molecular Medicine Unit, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki, Japan

Key Words
Bortezomib · Cytomegalovirus pneumonia · Death · Dexamethasone · Multiple myeloma

Abstract
Multiple myeloma (MM) remains a largely incurable disease in the long term despite positive responses to first-line chemotherapy. Herein we report the case of a 68-year-old woman who died following treatment with bortezomib plus dexamethasone for refractory MM. The combination was associated with significant antitumor activity, but bacterial pneumonia/sepsis was followed by bilateral cytomegalovirus pneumonia with herpes simplex co-infection, and this was almost certainly the cause of death. Physicians need to pay careful attention when treating patients with refractory MM with bortezomib plus dexamethasone, and to be mindful that antiviral therapy may be needed in some cases.

Multiple myeloma (MM) is still largely incurable despite continued intensive efforts. Following recent advances in terms of treatment options, patients generally respond to first-line chemotherapy; however, the majority will experience relapse or become refractory to therapy. Bortezomib, the first-in-class proteasome inhibitor, has been shown to have significant antitumor activity in the treatment of relapsed/refractory patients with MM [1, 2]. The most common adverse events with bortezomib reported to date include

Tatsuro Joh
Department of Internal Medicine
The Japanese Red Cross Society Nagasaki Genbaku Hospital
3–15 Mori-machi, Nagasaki (Japan)
Tel. +81 847 1511, Fax +81 841 9613, E-Mail firetj@nagasaki-med.jrc.or.jp

gastrointestinal symptoms, fatigue, thrombocytopenia, and peripheral neuropathy [1, 2]. The main dose-limiting toxicity associated with bortezomib therapy is peripheral neuropathy [3]. Here we report a relapsed/refractory MM case with severe cytomegalovirus (CMV) and herpes virus (HSV) coinfection after bortezomib therapy. In this patient, bortezomib produced a significant antimyeloma effect, but CMV was detected in multiple organs and HSV-induced esophagitis was also observed. CMV pneumonia and bilateral diffuse alveolar damage led to death.

The female patient was diagnosed with MM (IgG, λ light-chain isotype, stage IIIA) in August 2006 at the age of 68. Multiple compression fractures of the lumbar spine and extensive destruction of the iliac bones were observed. Due to these bone lesions, the patient was unable to stand on her own. Two courses of VAD therapy (dexamethasone 40 mg/day on days 1–4, 9–12, and 17–20, doxorubicin 9 mg/m^2/day on days 1–4, vincristine 0.4 mg/day on day 1–4) were administered. The chemotherapy was effective and the patient was discharged in December 2006. After rehabilitation to help with her walking, the patient was treated with MP therapy (melphalan 8 mg/m^2/day on days 1–4, prednisolone 60 mg/m^2/day on days 1–4) as an outpatient, from May 2007 to December 2007. However, the left mandibular bone and its surrounding tissues became increasingly swollen with myeloma from late December 2007. When the patient visited our hospital in January 2008, a bulky mass had formed in her jaw and its surroundings. A total of 40 Gy of radiation therapy plus dexamethasone therapy (40 mg/day on days 1–4, 9–12, 17–20) was administered, but only a partial response was achieved, and the patient's general condition gradually worsened.

Both the patient and her family refused treatment with thalidomide. In March 2008, bortezomib 1 mg/m^2 was injected intravenously on days 1 and 8 and this was administered in combination with dexamethasone therapy. However, an aggressive increase of M protein was observed and it was thought possible that clonal evolution was occurring. We considered the patient to have progressive disease, and selected an EPOCH-like regimen (etoposide 50 mg/m^2/day on days 1–4, vincristine 0.4 mg/m^2/day on days 1–4, doxorubicin 10 mg/m^2/day on days 1–4, prednisolone 60 mg/m^2/day on days 1–6) as salvage chemotherapy in April 2008. This proved to be ineffective and computed tomography and magnetic resonance imaging revealed the formation of a huge mass from the upper abdomen to the pelvic cavity (**fig. 1**a), together with multiple bone lesions and multiple intra-muscular lesions.

In May 2008, a second course of bortezomib therapy (1 mg/m^2, by intravenous injection on days 1, 4, and 8) was administered together with dexamethasone therapy, and a reduction in M protein was observed. However, high fever and bilateral pneumonia occurred late in May 2008, after the chemotherapy. Coagulase-negative staphylococci were detected in a pharyngeal culture specimen and *Staphylococcus epidermidis* was detected in a venous blood culture specimen. Serum β-D glucan was 5.62 pg/ml. Examination for viral infection was not performed. Adequate antibiotics and antifungal agents were used to treat the pneumonia and sepsis, but antiviral agents were not used. The patient's general condition worsened rapidly and she died as a result of respiratory failure early in June 2008.

Post-mortem examination revealed that the two courses of therapy with bortezomib plus dexamethasone had been quite effective at reducing MM tumor burden. No trace of bacterial pneumonia was found, but CMV was detected in both lungs in conjunction with severe diffuse alveolar damage (fig. 1b, c). CMV was also detected in the spleen and both adrenal glands (data not shown). In addition to CMV infection, HSV was found to have

Case Rep Oncol 2009;2:140–143
DOI: 10.1159/000228161
Published online: July 29, 2009

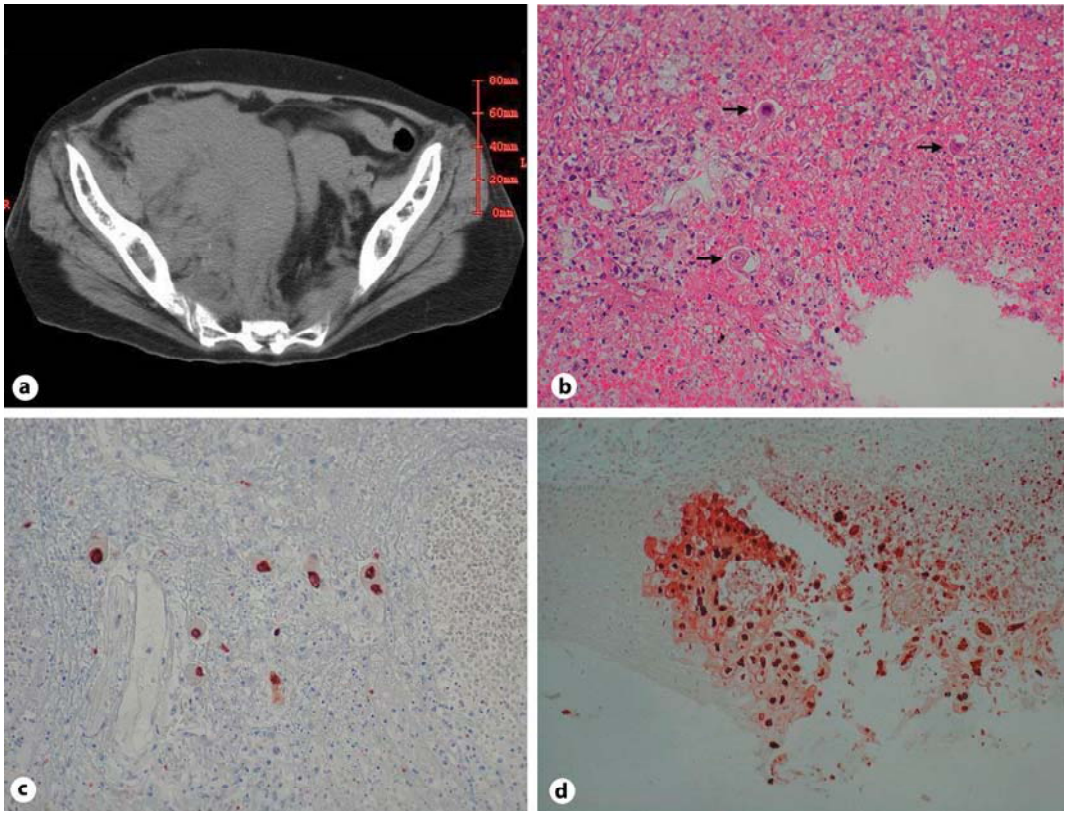
ISSN 1662–6575
www.karger.com/cro

caused esophagitis (fig. 1d). Pathologically, the cause of death was diagnosed as bilateral CMV pneumonia with severe diffuse alveolar damage.

To our knowledge, there has been no report of CMV and HSV coinfection in patients treated with bortezomib. It has been reported that bortezomib inhibits T-cell function in a dose-dependent manner and can reduce the ability to react to both viruses and bacteria, resulting in an increased risk of infection during the drug administration period [4]. In this patient, severe lymphopenia occurred after the first session of bortezomib plus dexamethasone therapy and continued until the end. Both reduced T-cell function and severe lymphopenia caused by bortezomib plus dexamethasone therapy might have enabled severe CMV and HSV coinfection to develop in this patient.

In conclusion, bortezomib in combination with dexamethasone demonstrated significant antitumor activity in this relapsed and refractory myeloma patient. However, bacterial pneumonia, sepsis, and fatal viral infections occurred. Bilateral CMV pneumonia probably triggered death. Careful attention and countermeasures against viral infections might be needed during therapy with bortezomib plus dexamethasone.

Fig. 1. **a** Computed tomography image of huge intra-pelvic tumor composed of myeloma cells. **b** CMV infection in the lung. Arrows indicate inclusion bodies (hematoxylin and eosin; ×200). **c** CMV infection in the lung. CMV antigens are positively stained (immunohistochemical staining; ×200). **d** HSV-induced esophagitis. HSV antigens are positively stained (immunohistochemical staining; ×200).



Case Rep Oncol 2009;2:140–143
DOI: 10.1159/000228161
Published online: July 29, 2009

ISSN 1662–6575
www.karger.com/cro

References

1 Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, et al: A phase 2 study of bortezomib in relapsed, refractory myeloma. N Engl J Med 2003;348:2609–2617.

2 Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al: Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352:2487–2498.

3 Badros A, Goloubeva O, Dalal JS, Can I, Thompson J, Rapoport AP, et al: Neurotoxicity of bortezomib therapy in multiple myeloma: a single-center experience and review of the literature. Cancer 2007;110:1042–1049.

4 Orciuolo E, Galimberti S, Petrini M: Bortezomib inhibits T-cell function versus infective antigenic stimuli in a dose-dependent manner in vitro. Leuk Res 2007;31:1026–1027.