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Multiple Myeloma

Efficacy of bortezomib therapy for extramedullary relapse of myeloma after autologous and non-myeloablative allogeneic transplantation

We report the successful use of bortezomib to treat a patient with multiple myeloma (MM) who had extramedullary relapse (paraspinal and thoracic masses and multiple cranial nerve palsy) after autologous and non-myeloablative allogeneic hematopoietic stem cell transplantation (HSCT).

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A 50-year woman was diagnosed with stage III IgG lambda MM in October 2001; she was treated with 4 VAD cycles, radiotherapy to the lumbar spine and autologous HSCT after 200 mg/m² melphalan in October 2002, followed by a non-myeloablative allogeneic HSCT from her HLA identical brother 3 months later. Conditioning was 2 Gy total body irradiation and graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine A and mycophenolate mofetil. In February 2003, a complete remission was obtained (negative serum immunofixation and no marrow plasma cell infiltration), which lasted 9 months. No significant GVHD developed and GVHD prophylaxis was withdrawn on day +195. In November 2003, the patient complained of spine and right hemithorax pain. Magnetic resonance imaging (MRI) of the spine detected a T9 paraspinal mass, with partial compression of the spinal medulla; the mass proved to be a plasmacytoma at biopsy. Computed tomography (CT) of the thorax showed 3 masses (maximum diameter, 7 cm) involving the second, third, fourth and fifth right ribs. No serum or urine paraprotein was detected and marrow biopsy was normal, with 100% of cells being of donor origin. The patient underwent urgent radiotherapy to T9 and complained of paresthesia of the right cheek, difficulty in speaking, dysphagia, and inability to move her tongue to the right. Palsy of the IX, X and XII cranial nerves was diagnosed. Cerebral MRI with post-contrast T1-weighted images showed abnormal enhancement of the meninges of the right cerebellar hemisphere and of the interhemispheric sylvian fissure. Cerebrospinal fluid (CSF) showed a protein and cell content within the normal limits. CSF polymerase chain reaction for cytomegalovirus, herpesvirus and neurotropic

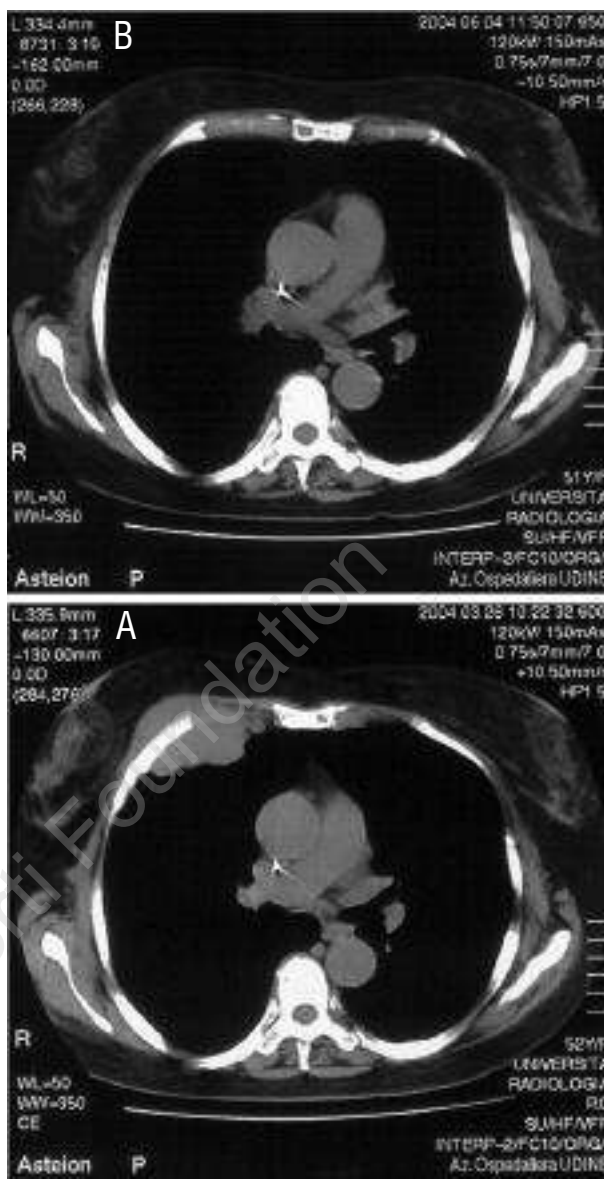


Figure 1. A. The thorax computer tomography (CT) showed a plasmacytoma of the fifth right rib. B. After 3 cycles of bortezomib the mass had disappeared.

viruses was negative. High-dose dexamethasone therapy and one intrathecal administration of corticosteroids and cytosine-arabioside did not modify any neurological sign. In January 2004, the patient started treatment with bortezomib (VELCADE) at the dose of 1.3 mg/m² on days 1, 4, 8, 11, every 21 days. WHO grade III thrombocytopenia and WHO grade I intestinal toxicity were reported. At the end of the first cycle, all the neurological symptoms and signs had disappeared and after 3 cycles cerebral MRI and thoracic CT had returned to normal (Figure 1). CSF examination was again normal. This response has persisted up to now, without any clinical sign of GVHD. Our patient had an extramedullary MM relapse after autologous and non-myeloablative allogeneic transplantation, involving a vertebra and 4 ribs. Moreover, she developed multiple cranial nerve palsies. We did not detect plasma cells in the CSF or masses in MRI. However, the MRI showing thick-

ening and enhancement of meninges, the biopsy-proven MM recurrence in extramedullary sites, and the absence of viruses in CSF suggested that myeloma cells had involved the central nervous system (CNS).

Extramedullary manifestations such as multiple plasmacytomas with minimal or no monoclonal component were reported in 14% of patients after autologous HSCT from the Spanish Registry¹ and in a few cases after allogeneic transplantation.² Localizations of MM in CNS are even rarer; they usually appear as a terminal event of a progressive systemic disease, although a few cases of CNS relapse without overt medullary plasmacytosis have been reported.^{3,4} Recently, the Arkansas group⁵ reported on 18 MM patients who relapsed with CNS involvement after HSCT, for an overall incidence of approximately 1%. The prognosis of these patients is very poor,^{5,6} despite the use of aggressive local and systemic treatment, including autologous stem cell transplantation. Extramedullary recurrences in sites other than the CNS were reported to respond successfully to thalidomide treatment by Biagi;⁶ however, the group of Bladé⁷ described progression of soft-tissue masses in 11 patients treated with thalidomide.

In our case, the patient received radiotherapy to the 9th thoracic vertebra and then bortezomib, with disappearance of the cranial nerve palsies and the masses involving the ribs. Bortezomib is a proteasome inhibitor⁸ that has been reported to induce responses in about one-third of patients with refractory or relapsed MM.⁹ Bortezomib has an extensive tissue penetration; however, data from studies conducted in non-human primates have indicated that bortezomib does not penetrate into the CNS or into various regions of the eye.¹⁰

This is the first report on the activity of this promising agent on extramedullary plasmacytomas. The resolution of all neurological symptoms and signs and the normalization of cerebral MR images could also be due to an immunological graft-versus-myeloma (GVM) effect; however, since the patient did not develop clinical GVHD, a GVM effect is unlikely and bortezomib's activity in the rare CNS localizations of MM should be confirmed by further pharmacokinetic and clinical studies.

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Monoclonal Gammopathies

Advanced Waldenström's macroglobulinemia: usefulness of Morel's scoring system in establishing prognosis

New treatments for patients with Waldenström's macroglobulinemia (WM) have necessitated the development of prognostic indices. Using a sample of 92 patients with refractory or relapsing WM treated in a randomized trial, we show that Morel's prognostic scoring system for patients at diagnosis is also effective in patients with advanced disease.

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In Waldenström's macroglobulinemia (WM), alkylating agents, alone or combined with corticosteroids, used to be the first line treatment for patients with symptomatic disease.¹ However, preliminary results suggest that fludarabine is effective in 30 to 40% of previously treated patients.² Therefore, we conducted a randomized multicenter clinical trial comparing the efficacy of fludarabine to that of the cyclophosphamide-doxorubicin-prednisone combination in 92 patients with WM in first relapse or with primary refractory disease.³ Two prognostic studies, concerning only newly diagnosed patients, have been recently proposed by Dhodapkar⁴ and our group.⁵ In order to test the external validity of these staging systems for patients with relapsing WM or primary refractory disease, we applied them to our cohort of 92 patients. The clinical characteristics of the 92 patients have been reported elsewhere. In brief, 46 patients were randomized in each arm and assigned to receive 6 courses of either CAP (cyclophosphamide, doxorubicin, prednisone) or fludarabine. Fifty patients were in first relapse and 42 patients had primary resistant disease. There was no difference in overall survival between the two arms.³ With actualized data at the reference date of the 1st June 2004, the conclusions of the comparison were not modified. Survival was measured from randomization to death or last follow-up, using 01/06/2004 as the reference date. Survival curves were plotted using the Kaplan-Meier method⁶ and compared by log-rank tests. The following predictors were tested: age \leq 65 years, male gender, general status (WHO) of 2 or more, presence of peripheral