Evidence of long-term disease control with panobinostat maintenance in patients with relapsed multiple myeloma

The introduction of novel agents, especially proteasome inhibitors and immunomodulatory drugs, has resulted in a remarkable improvement in the survival of patients with multiple myeloma (MM).[1,2] However, once patients have been exposed to such agents, resistance is likely to arise, resulting in a very poor prognosis.[3] For this reason, novel agents with distinct mechanisms of action are necessary and are currently being evaluated.[4] Deacetylase inhibitors are a group of novel agents designed to abrogate the pro-oncogenic state induced by the overexpression of deacetylase enzymes in tumors.[4] Panobinostat is a potent, orally administered pan-deacetylase inhibitor with significant anti-myeloma activity in preclinical models[6,7] and with clear synergy in combination with proteasome inhibitors.[8] This preclinical evidence of synergy prompted the phase III Panorama 1 trial, which tested the efficacy of panobinostat combined with bortezomib plus dexamethasone *versus* placebo plus bortezomib plus dexamethasone in patients with relapsed MM, who were not refractory to bortezomib.[9] The addition of panobinostat to bortezomib and dexamethasone resulted in a relevant improvement in progression-free survival (12.0 *versus* 8.1 months), although the toxicity associated with the regimen was an important drawback. The most frequent grade 3-4 adverse events were thrombocytopenia (67%), lymphopenia (53%), diarrhea (26%), asthenia or fatigue (24%), and peripheral neuropathy (18%). Nevertheless, there is no information on the long-term efficacy of panobinostat maintenance.

Here we present two patients with MM at relapse with prolonged follow-up after therapy with panobinostat, bortezomib and dexamethasone. In both cases, the combination was effective as a debulking regimen, and, most importantly, maintenance with panobinostat (with or without dexamethasone) was able to keep the disease under control for a long period. In fact, the two patients are currently still receiving treatment and have been relapse-free for more than 5 years since the salvage therapy was initiated.

The first case is a 52-year old male, diagnosed in June 2008 with IgA kappa MM, ISS-2, with t(11;14) and *RB* deletion. He presented with anemia and neutropenia at diagnosis and received first-line therapy with bortezomib, thalidomide and dexamethasone (VTD), achieving a partial response after six cycles. Disease progression was observed before autologous stem cell transplantation (ASCT) could be performed, and the patient was then included in the phase 1b open label clinical trial CLBH589B220710 and received induction with eight cycles of bortezomib 1.3 mg/m^2 iv + panobinostat 25 mg po (Figure 1). After two cycles, he achieved a partial response, with a 75% decrease in M-protein levels. However, due to the lack of any further decrease in M-protein and following the protocol guidelines, dexamethasone was added to the treatment after the sixth cycle, giving rise to a very good partial response. After the eighth cycle, bortezomib was discontinued, and panobinostat 15 mg three times per week and dexamethasone 40 mg weekly were continued until disease progression. During induction with bortezomib plus panobinostat, the patient developed grade 4 neutropenia and thrombocytopenia, which required administration of granulocyte colony-stimulating factor and transfusion of platelets, and a reduction in the dose of both agents (bortezomib to 1 mg/m^2 and panobinostat to 20 mg initially, and thereafter to 15 mg). Other treatment-related side effects during induction were diarrhea, asthenia, anorexia, nausea and dysgeusia, all of which were of grade 1 or 2, as well as worsening of a previous peripheral neuropathy to a maximum of grade 2. These symptoms improved after dose reduction, although during maintenance therapy with panobinostat plus dexamethasone asthenia worsened to grade 3 and the panobinostat dose was further reduced to 10 mg. Later on, in cycle 49, the dexamethasone dose was reduced to 20 mg weekly due to insomnia. At present, 65 months after inclusion in the trial, the patient continues to receive therapy, exhibiting excellent tolerability and maintaining the very good partial response, with a residual and stable M-protein level between 0.2-0.3 g/dL.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Panobinostat	P		P		P			P		P		P			P		P		P		
Bortezomib	B			B				B			B										
Dexamethasone	D	D		D	D			D	D		D	D									

Panobinostat po at escalating doses (10, 20, 25 & 30 mg)

Bortezomib iv at escalating doses (1.0 & 1.3 mg/m^2)

Dexamethasone po at a fixed dose of 20 mg added from cycle 2 in suboptimal responders

Induction: eight 21-day cycles with the triple combination

Maintenance: Panobinostat (± dexamethasone) until progression

Figure 1. Schema of therapy with panobinostat + bortezomib (+/- dexamethasone) in the CLBH589B2207 trial.

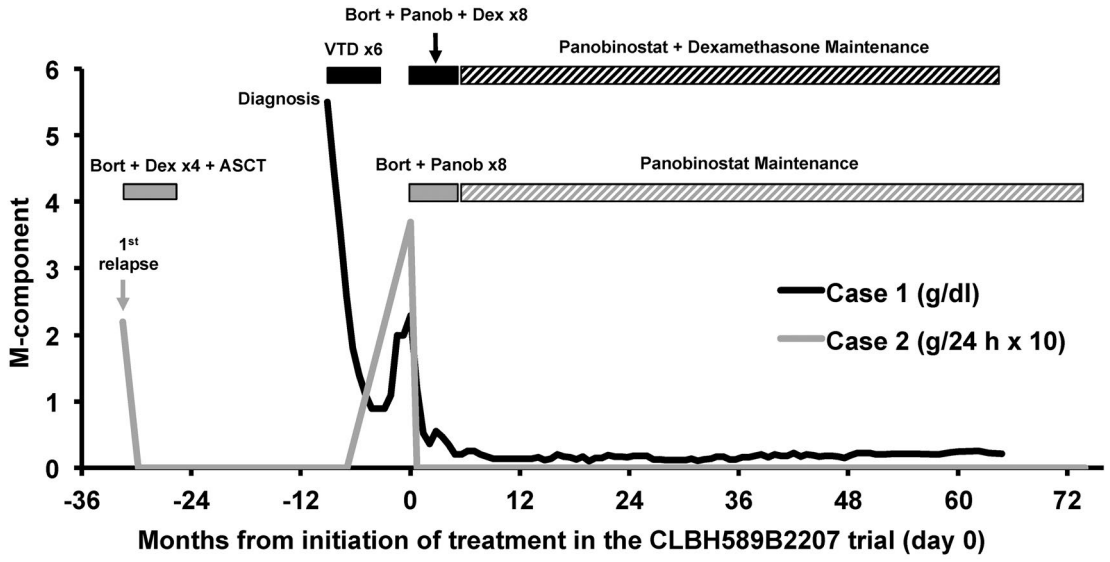

Figure 2. Evolution of the M-component in both reported cases during the course of the disease; from diagnosis in case 1 and from first relapse in case 2.

The second case is that of a 52-year old female who was diagnosed in December 2001 with Bence-Jones kappa MM, harboring t(4;14) and *RB* deletion, and a cranial plasmacytoma. No other myeloma-related symptoms were present at that point. She initially received six cycles of polychemotherapy (VBAD/VBCMP) and radiotherapy for the plasmacytoma. She achieved complete remission, which was consolidated with high-dose therapy (melphalan 200 mg/m^2) followed by ASCT. Maintenance therapy with interferon-prednisone was subsequently started. Three years after ASCT, the patient relapsed, presenting a plasmacytoma in the left eye-socket. Bortezomib plus dexamethasone was given, which yielded a second complete remission, followed by a second ASCT. No maintenance treatment was given at that time, and 23 months later she had a second relapse. The patient was then included in the clinical trial CLBH589B2207 (Figure 1), receiving panobinostat 20 mg and bortezomib 1.3 mg/m^2. After six cycles of panobinostat plus bortezomib she achieved stringent and immunophenotypic complete remission without requiring the addition of dexamethasone. With respect to tolerability, she devloped grade 2 neutropenia and grade 4 thrombocytopenia, which required platelet support, and also asthenia, dizziness, diarrhea and neuropathy, all of which attained grade 1 or 2. The panobinostat dose was reduced from 20 to 15 mg in cycle 5 due to an acute respiratory infection, and further reduced to 10 mg in cycle 7 due to a second severe pulmonary infection, and persistent asthenia. All adverse events improved with dose reduction. Bortezomib was stopped after eight cycles, in accordance with the protocol. Panobinostat as a single agent at a dose of 10 mg was continued as maintenance therapy. No significant panobinostat-related side effects have been reported so far during this phase and the patient is still maintaining her complete remission more than 6 years (75 months) after inclusion in the trial.

The hypothesis of the efficacy of deacetylase inhibition in MM has been validated in several trials in which panobinostat, a pan-deacetylase inhibitor, has been found to be safe and effective in combination with bortezomib in relapsed or relapsed and refractory MM patients.[10,11] These results inspired the phase 3 Panorama 1 trial, in which the three-drug combination (panobinostat + bortezomib + dexamethasone) gave a better progression-free survival than that achieved with bortezomib and dexamethasone alone.[9]

The clinical cases presented here confirm the activity of this combination in patients with relapsed MM. It is important to point out that the first patient relapsed very early after VTD, a similar situation to the one reported in the Panorama 2 trial in which 35% of patients refractory to bortezomib responded to the combination of panobinostat plus bortezomib.[11]

Most importantly, the long-term duration of the response in these two patients compared with the duration of previous responses suggests that panobinostat alone or in combination with dexamethasone may help to keep the disease under control and to prolong progression-free survival. In fact, in both cases, the response has lasted longer than 5 years so far, with disease control being maintained. These responses are longer than the previous ones in the respective patients, which were shorter than 5 months after VTD for the first patient, and 23 months for the second patient after bortezomib plus dexamethasone followed by a second ASCT (Figure 2). It is also worth noting that one patient achieved complete remission following induction but the other exhibited a small residual serum M-component that has been completely stable for 65 months at the time of writing.

This effectiveness might appear to contradict previous findings in which panobinostat as a single agent was not effective in a phase II trial in relapsed patients.[12] However, this discrepancy may arise from the different settings for the patients. In the trial in relapsed/refractory MM, patients had uncontrolled disease in the bulky stage, a condition that may be challenging for a drug that, due to its mechanism of action, may require time to exert its

effects; by contrast, the patients presented in this report initially received panobinostat in combination with bortezomib, which has a much more rapid mechanism of action and is able to control active disease. Subsequently, a maintenance phase with panobinostat monotherapy (or in combination with dexamethasone) was started, and in this situation of residual disease, an epigenetic agent might have a more important role.

In the Panorama 1 trial, the addition of panobinostat to bortezomib plus dexamethasone resulted in an increase in toxicity.[9] Our patients experienced some of these toxic effects, but tolerability significantly improved after prompt dose adjustment. This early dose reduction during induction was crucial to enabling the patients to remain on the treatment, and to proceed to the maintenance phase with panobinostat monotherapy (with or without dexamethasone). Long-term tolerability of this regimen was very satisfactory, with only one of the patients requiring a further reduction of the doses of panobinostat and dexamethasone.

In summary, these two cases provide further evidence of the efficacy of the combination of panobinostat plus bortezomib in relapsed or relapsed and refractory MM patients, and more importantly, suggest that panobinostat maintenance has been able to control the disease for remarkably long periods in both patients. This activity, combined with the convenience of an oral agent and a reasonable tolerability as a result of promptly reducing the doses as soon as toxicity appeared, should encourage further research into the use of panobinostat for maintenance therapy in MM.

Enrique M. Ocio,[1] Julio Dávila,[1] Juan-Carlos Caballero,[1] Sara Alonso,[1] Verónica González de la Calle,[1] Ramón García-Sanz,[1] Lucien Gazi,[3] Socrates Opio,[3] Mónica Jiménez,[3] Jesús F. San-Miguel,[2] and María-Victoria Mateos[1]

[1]Hospital Universitario de Salamanca y Centro de Investigación del Cáncer-IBSAL, IBMCC (USAL-CSIC), Salamanca, Spain; [2]Clínica Universidad de Navarra, Centro de Investigaciones Médicas Aplicadas (CIMA-IDISNA), Pamplona, Spain; and [3]Novartis Pharmaceuticals, Basel, Switzerland

Correspondence: emocio@usal.es
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References

1. Kumar SK, Dispenzieri A, Lacy MQ, et al. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. Leukemia. 2014;28(5):1122-1128.
2. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008;111(5):2516-2520.
3. Kumar SK, Lee JH, Lahuerta JJ, et al. Risk of progression and survival in multiple myeloma relapsing after therapy with IMiDs and bortezomib: a multicenter International Myeloma Working Group Study. Leukemia. 2012;26(1):149-157.
4. Ocio EM, Richardson PG, Rajkumar SV, et al. New drugs and novel mechanisms of action in multiple myeloma in 2013: a report from the International Myeloma Working Group (IMWG). Leukemia. 2014;28(3):525-542.
5. Ocio EM, San Miguel JF. The DAC system and associations with multiple myeloma. Invest New Drugs. 2010;28 (Suppl 1):S28-35.
6. Maiso P, Carvajal-Vergara X, Ocio EM, et al. The histone deacetylase inhibitor LBH589 is a potent antimyeloma agent that overcomes drug resistance. Cancer Res. 2006;66(11):5781-5789.
7. Catley L, Weisberg E, Kiziltepe T, et al. Aggresome induction by proteasome inhibitor bortezomib and alpha-tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. Blood. 2006;108(10):3441-3449.
8. Ocio EM, Vilanova D, Atadja P, et al. In vitro and in vivo rationale for the triple combination of panobinostat (LBH589) and dexamethasone with either bortezomib or lenalidomide in multiple myeloma. Haematologica. 2010;95(5):794-803.
9. San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol. 2014;15(11):1195-1206.
10. San-Miguel JF, Richardson PG, Gunther A, et al. Phase Ib study of panobinostat and bortezomib in relapsed or relapsed and refractory multiple myeloma. J Clin Oncol. 2013;31(29):3696-3703.
11. Richardson PG, Schlossman RL, Alsina M, et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. Blood. 2013;122(14):2331-2337
12. Wolf JL, Siegel D, Goldschmidt H, et al. Phase II trial of the pan-deacetylase inhibitor panobinostat as a single agent in advanced relapsed/refractory multiple myeloma. Leuk Lymphoma. 2012; 53(9):1820-1823.