The combination of cyclophosphamide, velcade and dexamethasone (CVD) induces high response rates with comparable toxicity to velcade alone (V) and velcade plus dexamethasone (VD)

The combination of bortezomib (velcade), pulsed dexamethasone and weekly cyclophosphamide (CVD) in relapsed/refractory myeloma patients induces high overall (75%) and complete (31%) response rates compared to velcade/dexamethasone (overall 47%, CR 5%) and velcade alone (overall 27%, CR 0%). The toxicity profiles including thrombocytopenia, neutropenia, and neuropathy were comparable between the groups.

Haematologica 2007; 92:1149-1150

Bortezomib (Velcade™), as the first-in-class proteasome inhibitor, has been shown to be effective for the treatment of relapsed refractory myeloma.[1,2] Clinical studies showed improved activity when this agent was combined with dexamethasone, and *in vitro* laboratory data suggest synergistic effects when Velcade is combined with a number of conventional chemotherapeutic agents.[3,4,5] We, therefore, conducted a retrospective analysis of relapsed/refractory myeloma patients to assess the efficacy and toxicity profile of velcade alone, in combination with dexamethasone, and in combination with both cyclophosphamide and dexamethasone. Between October 2003 and April 2006, 47 consecutive patients were included in the study. The patients were characterised by heavy pre-treatment (median number of therapies 3, range 1-6), and the majority would be expected to be resistant to conventional chemotherapy.

Velcade 1.3 mg/m^2 was given to 11 patients as a single intravenous bolus injection on days 1, 4, 8 and 11 of a 21 day cycle, for a maximum of 9 cycles. Oral dexamethasone 40 mg was added to Velcade 1.3 mg/m^2 (VD) on the day of injection and the day after in 20 patients, and a regimen comprising oral cyclophosphamide, 500 mg once a day on days 1, 8, 15 in combination with Velcade and dexamethasone (CVD) was used to treat 16 patients. Toxicity profiles and response were assessed every 3 weeks. Response was assessed using EBMT criteria[6] and toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0).

There was no statistical difference in baseline characteristics (age, ISS, number of previous lines of treatment) between the three treatment groups (p>0.05) (Table 1). The overall response rates (CR+PR) within the three groups were 27% for Velcade alone, 47% for velcade/dexamethasone, and 75% for the combination of cyclophosphamide, velcade and dexamethasone respectively. Patients who initially achieved a PR but who progressed while on treatment were counted as non-responders; this occurred in 1 patient with CVD, 4 patients with VD and 1 with V. The achievement of a complete response has become the *gold standard* against which to compare treatment, and the CR rate of CVD group is impressive at 31% compared to 5% with velcade/dexamethasone and 0% with velcade alone.

The side effect profiles between the three groups were similar (Table 2). Although grade 3/4 thrombocytopenia occurred in 44% of the CVD group, this was similar frequency to the velcade/dexamethsone group (50%) and the velcade alone group (64%). Grade 3/4 neutropenia also occurred in all three groups with an incidence of 19% in the CVD group, 15% in the VD group and 45% in the V group. Although neutropenia did not differ between the three groups it did lead to a cyclophosphamide dose reduction in 19% of patients treated with CVD. Grade 3 infection rates were also similar at 18%, 30% and 13% in all three groups (V vs VD vs CVD). Peripheral neuropathy is well recognised to be a troublesome side effect, and was the main reason for Velcade dose reduction and/or discontinuation in each group (27% V, 45% VD, 38% CVD), similar to previously published reports.[1,2] Neutropenia, neuropathy or infection resulted in a delay in treatment in 31% of CVD group, 35% of VD and 9% of V. These results suggest that the addition of weekly oral cyclophosphamide does not exacerbate the three known side effects of thrombocytopenia,

Table 1. Baseline characteristics of patients.

	CVD (n=16)	*VD (n=20)*	*V (n=11)*
Median age (years), range	59 (38-70)	63 (34-75)	60 (4-87)
Previous lines of TX, range	3 (1-5)	4 (2-5)	3 (2-6)
HDM	14	20	7
Thalidomide	16	20	7
Revlimid	0	1	0
ISS staging			
I	4	2	1
II	8	7	6
III	4	11	4
Median duration of treatment (days), range	87 (10-171)	98 (10-171)	115 (11-157)
Median number of cycles, range	4.5 (1-9)	4.5 (1-8)	6 (1-8)

**p>0.05 for all the baseline characteristics between three groups.*

Table 2. Major hematologic and non-hematologic toxicities.

	CVD (n=16)	*VD (n=20)*	*V (n=11)*
New grade 3/4 thrombocytopenia	7 (44%)	10 (50%)	7 (64%)
Grade 3 baseline thrombocytopenia	3	4	2
Thrombocytopenia (grade 3/4)	10	14	9
New grade 3/4 neutropenia	3 (19%)	3 (15%)	5 (45%)
Grade 3/4 baseline neutropenia	0	1	3
Neutropenia (grade 3/4)	3	4	8
Grade 3 infection	2 (13%)	6 (30%)	2 (18%)
Peripheral neuropathy (new/worse)	6 (5/1) (37%)	12 (6/6) (60%)	1 (1/0) (9%)
New neuropathy (grade 1-2/3-4)	4/1 (25%/6%)	6/0 (30%/0)	1/1 (9%/9%)
Worsening neuropathy (grade 3 above)	1 (6%)	6 (30%)	0
Postural hypotension	1	3	0
Shingles/chickenpox/herpes simplex	1 (6%)	7 (35%)	1 (9%)

neutropenia and peripheral neuropathy. Among patients with a minimum 6-month follow-up, 3 out of the 8 patients who achieved at least PR have relapsed in the CVD group, while in the VD group 6 out of 9 patients who achieved PR have relapsed. The median progression free survival (PFS) of Velcade alone and velcade/dexamethasone agree with previously published results at 5 months.[2] The PFS for the combination of CVD is 7 months suggesting that the improved complete response rate with CVD may translate into an improved progression free survival. However, a longer follow up is needed to confirm this.

In conclusion, CVD is a well-tolerated regimen producing high overall and complete response rates, with little increase in toxicity compared to VD or V alone. Importantly, the toxicity associated with Velcade melphalan combinations is avoided and it produces similar responses to those reported using this regimen.[7-10] The effects of this combination need to be evaluated further in randomised studies in both the relapsed and presentation settings.

Faith E. Davies, Ping Wu, Matthew Jenner, Muralikrishan Srikanth, Radovan Saso, Gareth J. Morgan
The Royal Marsden Hospital, London, UK

Key words: cyclophosphamide, velcade and dexamethasone (CVD), comparable toxicity, high response rates.

Correspondence: Faith Davies, Haemato-oncology Unit, Royal Marsden Hospital, Downs Road, Sutton, Surrey, UK. Phone: international +44.208.6613670. Fax: international +44.208.6429634. E-mail: faith.davies@icr.ac.uk

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: 2609-17.
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;352:2487-98.
3. Hideshima T, Richardson P, Chauhan D, Palombella VJ, Elliott PJ, Adams J, et al. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. Cancer Res 2001;61:3071-6.
4. Ma MH, Yang HH, Parker K, Manyak S, Friedman JM, Altamirano C, et al. The proteasome inhibitor PS-341 markedly enhances sensitivity of multiple myeloma tumor cells to chemotherapeutic agents. Clin Cancer Res 2003;9: 1136-44.
5. Mitsiades N, Mitsiades CS, Richardson PG, Poulaki V, Tai YT, Chauhan D, et al. The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: therapeutic applications. Blood 2003;101:2377-80.
6. Blade J, Samson D, Reece D, Apperley J, Bjorkstrand B, Gahrton G, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Br J Haematol 1998;102:1115-23.
7. Mateos MV, Hernandez JM, Hernandez MT, Gutierrez NC, Palomera L, Fuertes M, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study. Blood 2006;108:2165-72.
8. Berenson JR, Yang HH, Sadler K, Jarutirasarn SG, Vescio RA, Mapes R, et al. Phase I/II trial assessing bortezomib and melphalan combination therapy for the treatment of patients with relapsed or refractory multiple myeloma. J Clin Oncol 2006;24:937-44.
9. Popat R, Williams C, Cook M, Craddock C, Basu S, Singer C, et al. A Phase I/II Trial of Bortezomib, Low Dose Intravenous Melphalan and Dexamethasone for Patients with Relapsed Multiple Myeloma. ASH Annual Meeting Abstracts 2006:[Abstract 3542].