Multiple Myeloma

Life-threatening motor neurotoxicity in association with bortezomib

Bortezomib has been licensed to be used in relapsed and refractory multiple myeloma. It is a promising agent for this incurable condition but our effort is to caution hematologists about the life-threatening neurotoxicity (grade 4) which was seen in two of six patients treated with this agent although the complication cannot definitely be attributed to bortezomib

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Bortezomib, a selective proteasome inhibitor with activity in relapsed/refractory myeloma, was given FDA approval for advanced multiple myeloma in the UK in 2004. Toxicity is generally manageable, with grade 2-3 peripheral neuropathy reported in 25-30% of patients.[1-3] Severe sensory neuropathy has been reported[4] but we report here two patients with life-threatening grade 4 motor neuropathy.

Four of the six patients developed peripheral neuropathy. Three had grade 2-3 sensory neuropathy that is resolving and one discontinued the drug after five cycles due to grade 3 peripheral neuropathy and developed impotence at 5 months.

Two patients developed clinical grade 4 motor neuropathy. One 54-year old woman had autoimmune hepatitis for 20 years that was treated with azathioprine and intermittent low dose steroids. Her myeloma was treated with C-VAMP followed by Z-Dex and oral melphalan and associated with grade 2 peripheral neuropathy. On progression she received bortezomib and entered a partial remission after the second dose but developed paraesthesiae in the fingers and toes. After two further doses she complained of numbness across her abdomen, abdominal distension and urinary retention. Clinically, power in her limbs was 3/5, she was unable to carry out any motor activity and was bed-bound. Magnetic resonance imaging of the thoraco-lumbar spine did not reveal cord compression and electrophysiological studies showed severe axonal neuropathy in the lower limbs. Vitamin B12 and folate levels were normal. Heavy doses of opioid analgesics were required to control severe neuropathic pain and subsequently she developed a chest infection and died 4 days later.

The second patient was a 74-year old female with IgG myeloma with cast nephropathy previously treated with CVAMP and thalidomide. She developed grade 2 peripheral sensory neuropathy on thalidomide but subsequently progressed and commenced treatment with bortezomib. After the first course of bortezomib she developed acute diarrhea that precipitated acute on-chronic-renal failure necessitating hemodialysis. Following the second course of bortezomib without dose reduction she experienced grade 4 motor neuropathy with weakness and severe painful paraesthesiae in her upper limbs requiring high doses of opioid analgesia. Electrophysiological studies revealed severe axonal polyneuropathy. No infective cause of her diarrhea was identified and it persisted despite antibiotics and anti-motility therapy. Bortezomib was discontinued. Despite supportive treatment the patient deteriorated and died a few days later.

Both these patients developed motor neuropathy occurring early in the course of bortezomib treatment. Neither patient gave a history of excess alcohol and both declined lumbar puncture so we were unable to rule out Guillian-Barré syndrome. The sudden deterioration and tetraplegia in the first patient was temporally related to bortezomib administration. The development of paralytic ileus, urinary retention and impotence seen in two of our other patients raises the possibility of an autonomic neuropathy although we were unable to prove this. Both these patients had previously been exposed to other neurotoxic agents including vincristine and thalidomide and had co-morbid conditions associated with neurological damage, namely chronic renal failure and autoimmune hepatitis.

Bortezomib is a promising salvage agent for refractory myeloma but its use can be complicated by sensory, motor and autonomic neuropathy. The cause of the nerve damage remains unclear and its development is unpredictable. This is a small series of patients. The severity of neurotoxicity and the motor neuropathy seen in our cases is rare as reported in the APEX trial[4] (1% grade IV toxicity); however, caution is advised especially when using this agent in patients who have received prior neurotoxic therapy or have pre-existing neuropathy.

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References

1. Rajkumar SV, Richardson PG, Hideshima T, Anderson KC. Proteasome inhibition as a novel therapeutic target in human cancer. J Clin Oncol 2005;23:630-9.
2. Goy A, Younes A, McLaughlin P, Pro B, Romaguera JE, Hagemeister F, et al. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma. J Clin Oncol 2005;23:667-75.
3. O'Connor OA, Wright J, Moskowitz C, Muzzy J, MacGregor-Cortelli B, Stubblefield M, et al. Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. J Clin Oncol 2005;23:676-84.
4. Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high dose dexamethasone for relapsed multiple myeloma. Assessment of Proteasome Inhibition for Extending Remissions (APEX) Investigators. N Engl J Med 2005;352:2487-98.