Guillain-Barre Syndrome in newly diagnosed multiple myeloma patients treated with bortezomib: Two case reports

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Abstract
Bortezomib is one of the mainstay treatments for patients with multiple myeloma (MM) in front line, relapsed, refractory and maintenance phases. Peripheral neuropathy is one of the most common adverse effect associated with its use. Herein we report two cases of Guillain–Barre syndrome in newly diagnosed MM patients treated with Bortezomib. The patients were treated with high-dose intravenous immunoglobulins and plasmapheresis with improvement in their symptoms. Guillain–Barre syndrome is a rare but serious adverse effect in newly diagnosed MM patients treated with Bortezomib. Immediate discontinuation of therapy and appropriate neurological work up should be initiated to confirm the diagnosis. It is prudent to recognize the association and avoid further Bortezomib therapy in these patients.

Introduction
Guillain–Barre syndrome (GBS) is a rare acute immune-mediated polyneuropathy. The key to management of this disease is early diagnosis to prevent progression into respiratory failure which can otherwise occur in 30% of cases [1-3]. Identification of the inciting event and prompt discontinuation is crucial. Herein we report two cases of Bortezomib-induced GBS in newly diagnosed MM.

Case presentations
Patient # 1 was a 76-year-old patient who presented with generalized weakness and anemia. Work up lead to a diagnosis of IgA kappa Myeloma ISS stage II. The patient was started on Bortezomib 1.3 mg/m2 on days 1, 4, 8, 11 and dexamethasone 20 mg (VD) days 1, 2, 4, 5, 8 after completion of work up. After the first cycle the patient was admitted with worsening renal failure with creatinine of 3mg/dl, BUN of above 40 mg/dl, and calcium level of 13.1mg/dl. At this point he was placed on prednisone 60 mg that was tapered and stopped over 4 weeks. He also received Zometa 2 mg IV once during the 1st cycle of Velcade and dexamethasone. Almost a month later the treatment was switched from VD to VRD (Lenalidomide 25 mg PO once per day on days 1 to 14 with Bortezomib 1.3 mg/m2 SC once per day on days 1, 4, 8, 11 and Dexamethasone 20 mg PO once per day on days 1, 2, 4, 5, 8, 9, 11, 12). The patient was taken off treatment about 5 days after starting the second cycle due to progressive generalized weakness.

The patient tolerated the first cycle of VD without any major complication except for some constipation that was treated symptomatically. During the second cycle the patient noticed that he has some numbness and tingling in the upper and lower extremities which was self-limiting. The patient developed progressively weakness with an abnormal gait. He noticed difficulty in standing up from a sitting position later difficult in ambulating. The weakness progressed to involve the upper limbs. He denies any urinary or bowel symptoms. The chemotherapy was held but the patient clinical condition worsened to the point that he now become bedridden. The patient was subsequently transferred to the Myeloma institute for further work up and management. The patient was in complete response according to the IWMG response criteria at the time of presentation to our hospital. Lumbar puncture was performed, and cerebrospinal fluid showed protein of 49 CSF glucose 52, Cell count- WBC 100%, RBC 423/cumm. Vascular Endothelial Growth Factor- 112 (9-86 pg/ml). Fat Pad biopsy showed no evidence of amyloidosis by Congo red staining. Nerve conduction study showed demyelination pattern of nerve injury. The patient was started on IVIG 400 mg /kg /day for a total of 5 days followed by plasma exchange (PLEX) for 5 days. He was later discharged to an acute rehabilitation unit with good recovery of motor function. He was later lost to follow up.

Patient # 2 was a 70 year old African American male presented anemia and worsening renal failure leading to a diagnosis of IgA Kappa myeloma ISS stage II. The patient was started on Bortezomib, Lenalidomide and Dexamethasone (Lenalidomide 25 mg PO once per day on days 1 to 14 with Bortezomib 1.3 mg/m2 SC once per day on days 1, 4, 8, 11 and Dexamethasone 20 mg PO once per day on days 1, 2, 4, 5, 8, 9, 11, 12). He received 4 cycles of treatment with very good response criteria at the time of presentation to our hospital.

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partial response according to the IWMG criteria. The patient presented to the emergency room with 2 weeks of progressively weakness of the bilateral lower limbs with right sided weakness more than left sided. Physical examination showed proximal motor strength of 3/5 on the left side with 4/5 weakness on the right side. Sensory examination was unremarkable. Reflexes were absent except for a right knee jerk. MRI with contrast of the lumbar, thoracic spine showed no pathological enhancement of the conus medullaris or cauda equina. EMG showed findings of acute denervation. CSF studies showed protein of 148 mg/dl, glucose 92 mg/dl, and cell count-WBC 1/ummm lymphocyte 100%, RBC 1/ummm. PCR for West nile, CMV, EBV were negative. Patient was treated with IVIG 400 mg/kg/day for 5 days and was discharged to acute rehabilitation facility. He was seen in follow up in the clinic and had good recovery of motor function.

Discussion and conclusion

Bortezomib was the first proteasome inhibitor shown to have anti-myeloma effects. It was approved by the FDA fast track route in 2003 following promising results in the relapsed and/or refractory setting [4]. Bortezomib is the backbone therapy for patients both in the upfront and relapsed setting [5,6]. Historically bortezomib was given intravenously but can be administered subcutaneous with same efficacy. Peripheral neuropathy is the most common side effect of bortezomib therapy [2,7]. Peripheral neuropathy is sensory and is usually reversible with dose adjustment [8]. About 16% of the patient in the reported peripheral neuropathy when used in the upfront setting [9]. The incidence of peripheral neuropathy increases with cumulative dose generally occurring after the five 3 week cycles with a cumulative dose of 45mg/m2 as shown in APEX trial of relapsed refractory myeloma and reaches a plateau after about 8 cycles at a dose of 42 mg/m2 as shown in APEX trial of relapsed refractory myeloma and reaches a plateau after four 6 cycles (cumulative dose of 45mg/m2) in VISTA trial [10,11].

Both of our patients presented with severe motor fiber dysfunction with very minimal sensory involvement which is in sharp contrast to the sensory neuropathy [12] described in associated with bortezomib. EMG examination showed subacute axonal or mixed axonal aspects superimposed to a demyelinating pattern. The second patient had albumin-cytological dissociation demonstrated in the cerebrospinal fluid. Of note both the patients had a very good response to treatment. Bortezomib was stopped at the time of initial presentation and the patients were later placed on carfilzomib-based therapy.

Pathogenesis of GBS is an immune mediated response against a neuronal cell that is triggered by an antecedent infection or drugs and is usually a diagnosis of exclusion. Paraneoplastic GBS is another entity described and usually occur within five years of diagnosis of a cancer and usually gets better with the treatment of the cancer [13,14]. In both our patients the MM had clearly responded to the upfront treatment and they were in complete response (CR) and very good partial response (VGPR) respectively as per IWMG criteria respectively when they presented with progressive weakness. There were no clinical signs or symptoms of nerve infiltration and no other identifiable risk factors in our patients. Bortezomib induced GBS has been described previously early during treatment like in our patients. The exact mechanism or risk factors for development of GBS is not known.

References