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Sustained remission and reversal of end-organ dysfunction in a patient with anaplastic myeloma

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Dear Editor,

Anaplastic myeloma (AM) is a rare, aggressive, and poor risk form of myeloma characterized by dedifferentiated plasma cells and extensive extramedullary disease [1]. Since myeloma presenting with severe end-organ damage and poor performance status are excluded from clinical trials, treatment paradigms for these patients are not usually guided by clinical trial data. Combinations of cyclophosphamide (Cy) and bortezomib have been

successfully used in the treatment of myeloma [2–4]. Since hepatic dysfunction secondary to myeloma is rare, there is paucity of data regarding the use of bortezomib and Cy in this setting. In this paper, we describe the efficacy of a Cy- and bortezomib-based induction in a patient with anaplastic myeloma who presented with fulminant hepatic and renal failure.

A 59-year-old woman presented with 3–4 weeks of easy bruising, abdominal pain, 20-lb weight loss, and jaundice. She was admitted for acute liver failure (MELD score 42), anemia (Hb 7.6 g/dL), thrombocytopenia (Plt $44 \times 10^9/L$), abnormal coagulation markers (INR 3.2, aPTT 47.3 s), metabolic acidosis (lactate acid 16.1 mmol/L), hyperbilirubinemia (TBil 11.4 mg/dL, peaked at 61 mg/dL), transaminitis (AST 242 U/L, ALT 78 U/L), elevated LDH (1,527 U/L), gross hepatosplenomegaly, and acute kidney injury (Cr 4.2 mg/dL) requiring continuous venovenous hemodialysis (CVVHD).

A bone marrow biopsy showed infiltration with atypical kappa-restricted plasma cells. Serum protein electrophoresis (SPEP) demonstrated three spikes in the gamma region adding to 0.44 g/dL. The serum-free kappa light chain was elevated (7,220 mg/L), lambda light chain (0.5 mg/L). Liver biopsy showed infiltrating CD138+, kappa-restricted, atypical plasmacytoid cells (Fig. 1).

Initial treatment consisted of Cy (1,500 mg/m² IV) on day 1 and dexamethasone 20 mg on days 1–4, followed by bortezomib at 1 mg/m² IV (dose reduced for hepatic dysfunction) and dexamethasone 40 mg on days 9, 12, 15, 18 post Cy. This was followed by two cycles of Cy 300 mg/m², bortezomib 1 mg/m² IV (dose reduced for hepatic dysfunction), and dexamethasone 40 mg (CyBorD) on a weekly schedule days 1, 8, 15, and 22 of a 28-day cycle as reported previously [4]. Renal function normalized (Cr 1.0 mg/dL) during the second cycle of CyBorD. Her liver function normalized in 7 months after initiation of therapy.

For the last 30 months, she has been in a near-complete remission (nCR) with normal free light chains and her bone marrow biopsy shows no evidence of myeloma. Due to convenience of an oral regimen, she was switched to lenalidomide and dexamethasone. Her ECOG performance score is 0, and she has maintained normal renal and hepatic function.

Although Cy does not appear to be hepatotoxic, it is activated by the hepatic cytochrome P-450 enzyme system [5]. In severe hepatic failure, there is uncertainty regarding the clinical efficacy of Cy. Bortezomib undergoes hepatic clearance and is metabolized by CYP3A4 and CYP2C19 [6]. Although there are case reports of bortezomib-induced hepatic dysfunction [7], the majority of patients with normal liver function do not experience hepatic dysfunction with bortezomib [8, 9]. In an organ dysfunction study in solid tumors, the systemic exposure to bortezomib was found to be increased in patients with moderate to severe hepatic dysfunction [10] but the frequency of adverse events was not increased with increasing degree of hepatic impairment or with increasing dose of bortezomib. The efficacy and long-term follow-up in patients with myeloma and hepatic dysfunction are lacking.

We report the long-term outcome in a patient with aggressive anaplastic myeloma presenting with extensive extramedullary disease leading to multiorgan failure. Induction with Cy, bortezomib, and dexamethasone led to a rapid remission and reversal of hepatic

and renal dysfunction. The remission has been sustained with lenalidomide and dexamethasone. This case demonstrates that myeloma can rarely present with fulminant hepatic failure, and rapid initiation of treatment may lead to reversal of organ dysfunction.

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Fig. 1.

The atypical plasmacytoid cells were confirmed as plasma cells with strong CD138 immunoreactivity (a CD138, $\times 200$). Moreover, these lesional cells displayed kappa restriction, demonstrating hepatic involvement by the neoplastic plasma cells (b kappa light chain, $\times 400$ versus c lambda light chain, $\times 400$)