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# Tumor Lysis Syndrome in Light Chain Multiple Myeloma Treated with Bortezomib Combination Therapy

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## INTRODUCTION

Tumor lysis syndrome (TLS) is a potentially life threatening complication of cancer treatments that typically occurs in highly proliferative malignancies. It is rare in patients with multiple myeloma (MM) given the disease’s indolent nature and is estimated to occur in less than 1% of cases.<sup>1</sup> Increasing reports of TLS have been described in MM, particularly in treatment regimens containing bortezomib, the first available proteasome inhibitor. Here we describe a case of a newly diagnosed light chain multiple myeloma resulting in tumor lysis syndrome following the first dose of combination therapy with bortezomib, cyclophosphamide and dexamethasone.

## CASE REPORT

A 68 year old man presented with 6-8 weeks of gradually worsening lower back pain and fatigue. In addition, he reported symptoms of severe constipation, nausea, night sweats, dysuria, right sided rib pain, and a 30 lb weight loss. On examination, he had tenderness to palpation along the lower thoracic spine, para-spinal muscles and lower anterior ribs bilaterally. He was found to have deranged renal function with a serum creatinine of 2.75 mg/dl, corrected serum calcium of 11.9 mg/dl, macrocytic anemia with hemoglobin of 11.4 g/dl (MCV 102) and urinalysis with trace protein but a urine protein to creatinine ratio of 9.6. The liver function tests were normal. An X-Ray of his thoracic and lumbar spine revealed a T12 compression fracture.

Subsequent labs revealed hypogammaglobulinemia and beta-2 microglobulin elevation of 19.53 mg/L (normal 1.31-2.6 mg/L). Serum protein electrophoresis had a monoclonal lambda light chain spike measuring 14,520 mg/L. 24 hour urine studies showed 11.5g of protein and 12.1g lambda light chains. A skeletal survey showed a questionable lucent lesion in the right 10th posterior rib. He underwent a bone marrow biopsy which showed 45.9% plasma cells. FISH probe was negative for common cytogenetic abnormalities including 13q deletion. The patient was diagnosed with lambda light chain multiple myeloma, International Staging System (ISS) stage III.

For treatment, the day 1 cycle included bortezomib 1.3mg/m<sup>2</sup>, cyclophosphamide 300mg, and dexamethasone 40mg. Prior to starting chemotherapy, his serum creatinine had improved to 2.5 mg/dL with normal serum electrolytes. Calcium remained elevated at 11.2mg/dL despite hydration. His care was transferred to the Veteran’s Hospital’s Community Living Center for the duration of his chemotherapy.

24 hours after his first dose of chemotherapy, he re-presented to the emergency room with hypoxia, hypotension, tachycardia, and tachypnea. No fever was observed. Initial laboratory values were as follows: potassium 5.5 mmol/L, serum uric acid 22.7 mg/dL, serum phosphorous 8.2mg/dL, bicarbonate 20mmol/L with anion gap of 17, serum calcium 8.3mg/dL, lactate 1.7mmol/L, LDH 1147 IU/L, and serum creatinine 3.41 mg/dL. He met clinical and laboratory criteria for tumor lysis syndrome (TLS) based on the Cairo-Bishop definition (Table 1). For TLS treatment the patient was started on IV fluid hydration with bicarbonate supplementation, allopurinol 200 mg daily and given a dose of rasburicase 0.15 mg/kg. The patient was admitted to the ICU and closely monitored.

**TABLE 1: CAIRO-BISHOP DEFINITION OF TUMOR LYSIS SYNDROME (TLS) IN ADULTS**

<b>Laboratory TLS: ≥2 of the following serum abnormalities, developing within 3 days before or 7 days after initiation of chemotherapy</b>
-Uric acid ≥ 8 mg/dL or 25% increase from baseline
-Potassium ≥ 6 meq/L or 25% increase from baseline
-Phosphorous ≥ 4.5 mmol/dL or 25% increase from baseline
-Calcium ≤ 7 mg/dL or 25% decrease from baseline
<b>Clinical TLS: Laboratory TLS AND ≥1 of the following criteria</b>
-Creatinine >1.5x upper limit of normal
-Cardiac arrhythmia or sudden death
-Seizure

## DIFFERENTIAL DIAGNOSIS

Differential diagnosis of new onset lower back pain in this elderly man included multiple myeloma, metastatic prostate cancer, lumbar strain, hyperparathyroidism and severe constipation secondary to an underlying malignancy of the colon.

## OUTCOME AND FOLLOW UP

Over the course of several days, the patient's TLS labs normalized and he was discharged back to the Veteran's Community Living Center for rehabilitation. Per oncology's recommendation, he was treated again with bortezomib, cyclophosphamide and dexamethasone. He was re-admitted to the hospital approximately 2 weeks later with altered mental status and dehydration. Tumor lysis labs at this time were normal. During this hospitalization, the patient and his family made the decision to withhold further treatment and enter home hospice.

## DISCUSSION

Tumor lysis syndrome (TLS) is a complication carrying a high morbidity and mortality most commonly occurring secondary to cell lysis caused by chemotherapy with the subsequent release of intracellular potassium, phosphate, and nucleic acids into the bloodstream. Characteristic laboratory findings include hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia and elevated LDH. Clinically, patients can present with nondescript symptoms such as nausea and vomiting, or life threatening cardiac arrhythmias, renal failure, seizures, or sudden death. TLS is most frequently associated with highly proliferative neoplasms such as non-Hodgkins lymphoma and acute lymphocytic leukemia, while plasma cell dyscrasias such as multiple myeloma are classified as typically having a <1% risk.<sup>1</sup>

Multiple myeloma is characterized by a low proliferative index with less than 1% plasma cells engaging in cellular proliferation.<sup>2</sup> As a result, TLS is a rare complication of chemotherapy in the treatment of multiple myeloma. It is believed to have a higher likelihood of occurrence in patients with a high tumor burden, especially if treated with bortezomib in combination with other agents. The definition of high tumor cell burden is not clear in the literature, but it is believed to be correlated with increased serum lactate dehydrogenase and Beta-2 microglobulin

levels ( $\geq 5.5$  mg/dL) as well as diffuse bone marrow disease, multiple lytic lesions, hypercalcemia ( $>12$  mg/dL) and positive C reactive protein.<sup>8</sup> TLS has also been cited to occur in monotherapy treatment with bortezomib, steroids, or thalidomide.<sup>2</sup> Additional risk factors associated with the development of TLS in multiple myeloma include high proliferative activity, immature plasma cell morphology, and poor cytogenetics.<sup>2,3,4</sup> Case reports by Hung Chang et al associate higher rates of TLS in light chain myeloma with pre-existing renal insufficiency prior to chemotherapy, a presentation similar to our patient. Nonetheless, not enough data exists to have clear understanding of the risk factors and whether certain types of multiple myeloma carry a higher risk.

Since the introduction of bortezomib, there have been several other case reports of patients with multiple myeloma developing tumor lysis syndrome with a reported incidence of 1.4%.<sup>3</sup> As a reversible inhibitor of the 26S proteasome, bortezomib's impact on the transcriptional factor NF-kB is thought to be the mechanism of rapidly induced cancer cell apoptosis.<sup>3</sup> In a case series, Sezer et al. reviewed 496 cases of multiple myeloma treated with bortezomib in three phase II multi-center trials and found that the criteria for tumor lysis syndrome was fulfilled in 7 cases (1.8%). TLS caused renal failure leading to dialysis occurred in three cases, with one patient subsequently dying from renal failure. When a timeline was explicitly described, the earliest TLS case occurred on day 5 following bortezomib administration, making our patient's presentation one day after treatment even more atypical. Additionally, in two of the cases, TLS did not occur on initial exposure to bortezomib, but rather during retreatment with bortezomib in combination with dexamethasone.<sup>6</sup>

Since the majority of reported cases of TLS typically occur very early in the course of treatment with bortezomib, patients are at the highest risk during the first cycle of therapy. Therefore, it is important to closely monitor patients receiving bortezomib, particularly those with higher tumor burden. Concomitant use of thalidomide or dexamethasone, such as in our patient, tends to increase the likelihood of tumor lysis syndrome.<sup>5</sup> Chim in his article suggests TLS prophylaxis with hydration and alkalinization in patients with a high tumor burden who are being started on a treatment with bortezomib.

## CONCLUSION

Although rare, tumor lysis syndrome (TLS) is a potentially severe complication in the treatment of multiple myeloma. After initiation of treatment, patients should be closely monitored, particularly those with a high tumor burden receiving bortezomib. There is a need for further studies and case reports to identify incidence and predicting factors that may lead to TLS in patients treated for multiple myeloma.

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