Management of Tumor Lysis Syndrome in Patients With Multiple Myeloma During Bortezomib Treatment

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Background: Tumor lysis syndrome (TLS) is a severe, life-threatening complication that typically occurs in highly proliferative malignancies. Although TLS is unusual in multiple myeloma (MM), it is still associated with significant morbidity. Bortezomib has been widely used for the treatment of MM with encouraging results, but TLS seems to occur more frequently in patients with MM receiving bortezomib than in patients receiving other conventional agents.

Objectives: The purpose of this article is to present and examine several significant risk factors for the development of TLS, based on the results of a study involving patients with MM who developed TLS during bortezomib treatment.

Methods: Patients with MM were treated with bortezomib-containing regimens.

Findings: The early identification and intervention of high-risk patients with MM is imperative. Timely and efficient management could decrease TLS incidence rates and improve the efficacy of treatment outcomes.

One result of the rapid destruction of malignant cells and the abrupt release of intracellular ions, nucleic acids, and proteins and their metabolites into the extracellular space, tumor lysis syndrome (TLS) encompasses the metabolic changes that occur with tumor breakdown after the initiation of cytotoxic therapy (Cairo & Bishop, 2004). TLS is a collection of metabolic abnormalities, including increased lactate dehydrogenase (LDH), hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and renal failure. These metabolic complications predispose patients with cancer to various clinical toxicities, including renal insufficiency, cardiac arrhythmias, seizures, neurologic complications, and, potentially, sudden death (Cairo & Bishop, 2004; Mathisen, 2011). Multiple myeloma (MM) is a clonal neoplasm affecting terminally differentiated B cells and has been traditionally viewed as a hypoproliferative disease of plasma cells (Kyle & Rajkumar, 2004). Therefore, TLS is thought to only rarely complicate the treatment of patients with MM, usually following high-dose chemotherapy or autologous stem cell transplantation (Fassas et al., 1999). Bortezomib is a potent and reversible proteasome inhibitor that has significant anti-myeloma activity in vitro and in vivo (Sezer et al., 2006). With the widespread use of bortezomib in relapsed and refractory MM, as well as in newly diagnosed MM, the incidence of TLS in patients with MM is increasing (Furtado & Rule, 2008; Sezer et al., 2006; Terpos, Politou, & Rahemtulla, 2004). This article describes five patients with MM who developed TLS during bortezomib treatment.

Case Report

From January to October 2013, 121 patients with MM were treated with bortezomib-containing regimens at Beijing Chao-Yang Hospital, which is affiliated with Capital Medical University in China. Of those patients, five developed TLS; three were women, and two were men. The median age of the five patients...
was 63 years (range = 59–66 years). Three patients had been newly diagnosed with MM, and two had relapsed disease. In addition, three patients had immoglobulin (Ig) G disease, one had IgD disease, and one had light chain disease. At their respective times of diagnosis, all five patients were diagnosed with stage III disease. The patients’ quality of life and performance status were assessed. European Organisation for the Research and Treatment of Cancer (EORTC) Quality of Life Core 30 Questionnaire (QLQ-C30) scores ranged from 78–96; the QLQ-C30 score range is 28–112, with higher scores indicating a lower level of quality of life. Eastern Cooperative Oncology Group (ECOG) scores ranged from 2–4; the range of possible ECOG scores is 0 (normal activity) to 4 (bedridden).

The TLS-inducing chemotherapeutic regimens were cyclophosphamide, bortezomib, and dexamethasone (two patients); bortezomib and dexamethasone (two patients); and bortezomib, dexamethasone, and daunorubicin (one patient) (see Table 1). None of the five patients had been exposed to bortezomib before the TLS-inducing therapy, and they all had extensive tumor burden with bone marrow plasmacytosis ranging from 69%–93%.

Among the five patients, three had elevated serum creatinine (Scr) levels (149, 215, and 344 μmol/l [normal is less than 115 μmol/l]). The patient with the highest Scr levels (Patient 3) had renal insufficiency for about seven months preceding the TLS-inducing chemotherapy. The other two patients had normal Scr levels prior to treatment. In addition, four patients had hyperuricemia before bortezomib treatment, and three of them were prescribed allopurinol before chemotherapy. MM was thought to be the etiology of their renal dysfunction. Most of the concentrations of electrolytes in the five patients were within normal ranges, including potassium, calcium, and phosphorus ions.

Typical TLS symptoms occurred within 12–72 hours after the first subcutaneous injection of bortezomib. All patients developed symptoms of fluid retention, including dyspnea, edema, and oliguria. One patient developed non-ST segment elevation myocardial infarction (NSTEMI), which was accompanied by heart failure. All patients also experienced decline of their renal function during chemotherapy, as evidenced by increased Scr, blood urea nitrogen, and uric acid levels (see Table 2). Other abnormal laboratory findings included elevated LDH levels. In addition, hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia occurred in almost all patients. Following early recognition and management of this life-threatening condition, bortezomib-containing chemotherapies were suspended. Patients were then given xanthine oxidase inhibitors, hydration, loop diuretics, and several supportive care measures to remove excess fluids and metabolites and to protect the functions of vital organs. One patient was given hemodialysis because of oliguria. After 2–10 days of therapy, three patients (Patients 1, 3, and 4) recovered from TLS and continued to receive bortezomib-containing chemotherapies while being closely monitored. Patient 2 presented with severe dyspnea, as well as edema and oliguria, 60 hours after bortezomib administration. Her oxygen saturation and blood pressure dropped rapidly. The administration of diuretics, respiratory stimulants, and noninvasive supportive care measures had limited effect. She had been assigned a do-not-resuscitate order and died of acute respiratory and circulatory failure. Patient 5 presented with signs and symptoms similar to those experienced by Patient 2. He was moved to the hospital’s respiratory intensive care unit and intubated. However, the cardiac insufficiency, complicated by pulmonary infection, contributed to his deterioration, and he died one week after being diagnosed with TLS.

### Risk Factors

Elevated pretreatment serum uric acid level, preexisting renal damage, tumor infiltration of the kidney, obstructive uropathy, and advanced age have been reported as high-risk factors for developing TLS (Cairo & Bishop, 2004). Patients diagnosed with MM have a low risk of developing TLS (less than 1%) (Cairo, Coiffier, Reiter, & Younes, 2010), but the incidence is about 4% (5 of 121 patients) in patients with MM who are treated with bortezomib-containing chemotherapy. Patients with MM who had high tumor burdens and were undergoing their first cycle of bortezomib treatment had an increased risk of developing TLS (Furtado & Rule, 2008; Sezer et al., 2006; Terpos et al., 2004). Of the five patients described in the case report, four patients had hyperuricemia prior to chemotherapy, three patients had

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**TABLE 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Regimen</th>
<th>Ig Isotype</th>
<th>Cancer Stage</th>
<th>QLQ-C30 Score</th>
<th>ECOG Score</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>Male</td>
<td>PCD</td>
<td>Light chain</td>
<td>III</td>
<td>86</td>
<td>3</td>
<td>Recovered</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>Female</td>
<td>PCD</td>
<td>IgG</td>
<td>III</td>
<td>96</td>
<td>4</td>
<td>Deceased</td>
</tr>
<tr>
<td>3</td>
<td>65</td>
<td>Female</td>
<td>PD</td>
<td>IgD</td>
<td>III</td>
<td>78</td>
<td>2</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>Female</td>
<td>PD</td>
<td>IgG</td>
<td>III</td>
<td>80</td>
<td>3</td>
<td>Recovered</td>
</tr>
<tr>
<td>5</td>
<td>59</td>
<td>Male</td>
<td>PAD</td>
<td>IgG</td>
<td>III</td>
<td>92</td>
<td>2</td>
<td>Deceased</td>
</tr>
</tbody>
</table>

* Range = 28–112

ECOG—Eastern Cooperative Oncology Group; Ig—immoglobulin; PAD—bortezomib, dexamethasone, and daunorubicin; PCD—cyclophosphamide, bortezomib, and dexamethasone; PD—bortezomib and dexamethasone; QLQ-C30—Quality of Life Core 30 Questionnaire
renal insufficiency, and four patients were aged 60 years or older. All five patients had high tumor burdens and had been receiving the first cycle of bortezomib treatment; these factors are in accordance with those previously reported. In addition, all five patients had low quality of life and performance scores, suggesting their possibly being risk factors for TLS.

Assessment

The early identification and intervention of high-risk patients is vital for successful treatment outcomes. Several grading systems and predictive models are available for the identification of TLS in some rapidly proliferating hematologic malignancies. However, because myeloma was considered to be a hypoproliferative disease, no effective grading systems for myeloma exist. Prior to bortezomib administration, a comprehensive nursing assessment of patients with MM should be completed. This assessment should include items such as the patient’s past medical history, as well as his or her diagnosis and treatment; a complete metabolic panel; and his or her quality of life and performance status scores. The ECOG scale is a widely used standard functional classification in oncology practice, the verbal descriptors of which refer to physical activity. However, the EORTC QLQ-C30 scale reflects the quality of life for patients with cancer; it incorporates nine multi-item scales: five functional scales (i.e., physical, role, cognitive, emotional, and social), three symptom scales (i.e., fatigue, pain, and nausea and vomiting), and one global health and quality-of-life scale. A number of single items that assess additional symptoms commonly reported by patients with cancer (e.g., dyspnea, loss of appetite, insomnia, constipation, diarrhea) and the patient’s perceived financial impact of the disease also are included (Fayers & Bottomley, 2002). In addition, a complete metabolic panel that includes monitoring of the levels of LDH, calcium, phosphorous, sodium, potassium, uric acid, and creatinine should be performed every 6–8 hours for the first 48–72 hours of treatment, then for every 24 hours thereafter (Tosi et al., 2008). Healthcare providers should pay greater attention to the early signs of TLS, including symptoms of fluid retention (e.g., dyspnea, edema, oliguria) and symptoms of electrolyte imbalances (e.g., nausea, vomiting, diarrhea) in hyperphosphatemia and hyperkalemia, as well as muscular complications in hypocalcemia and abnormal electrocardiograms and cardiac arrhythmias in hyperkalemia.

Management

The successful management of TLS primarily requires the healthcare provider to maintain a high index of suspicion to promptly identify patients at high risk of developing TLS and to aggressively initiate a proactive strategy to prevent or reduce the severity of the disease’s clinical manifestations (Cairo & Bishop, 2004). Among the options for TLS prevention and treatment are hydration and diuresis, control of hyperuricemia with allopurinol prophylaxis and rasburicase treatment, vigilant monitoring of electrolyte abnormalities, and supportive care measures (Cairo & Bishop, 2004). Urinary alkalinization remains controversial (Cairo & Bishop, 2004). Electrolyte imbalances could be fatal and require vigilant monitoring. Oral forms of phosphate binders, such as aluminum hydroxide, can correct hyperphosphatemia and should be administrated when phosphorus levels exceed 2.1 mmol/l. IV calcium gluconate should only be administrated in symptomatic hypocalcemia to relieve muscular, cardiovascular, or neurologic complications. Hyperkalemia in TLS could be life threatening, so infusions of sodium polystyrene sulfonate, as well as insulin and glucose, are required.

All five patients described in the case report were administered allopurinol and diuresis immediately after being diagnosed with TLS. Aggressive hydration was attenuated in one patient who developed NSTEMI and heart failure after chemotherapy. Glucocorticoids were administered in two patients who rapidly developed acute respiratory failure. Continuous renal replacement therapy was administered in a patient whose renal function deteriorated considerably. In addition, the electrolyte imbalances of all five patients were vigilantly monitored and actively managed. Because myeloma is considered to be relatively hypoproliferative, bortezomib-containing chemotherapy was suspended in all five patients following consideration of the risk in delaying therapy versus the risk of exacerbating TLS and its associated complications.

TABLE 2. Values of Certain Serum Characteristics at Various Stages of Treatment

<table>
<thead>
<tr>
<th>Table 2: Values of Certain Serum Characteristics at Various Stages of Treatment</th>
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<tbody>
<tr>
<td><strong>LDH (U/l)</strong> (range = 65–250)</td>
</tr>
<tr>
<td><strong>P</strong></td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
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<td>5</td>
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</tbody>
</table>

Ca²⁺—calcium; K⁺—potassium; LDH—lactate dehydrogenase; P—patient; PO₄—phosphorus; post-Rx—post-treatment; pre-Rx—pretreatment; SCr—serum creatinine
Implications for Practice

- Identify and initiate prevention measures in high-risk patients prior to the first course of bortezomib treatment.
- Be aware of the risk factors for tumor lysis syndrome (TLS).
- Know and monitor patients for the signs and symptoms of TLS.

Implications for Nursing

Identifying and initiating prevention measures prior to the first course of treatment for high-risk patients will help to avoid TLS. Oncology nurses should be familiar with the signs and symptoms of hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia. Nurses should attach importance to any abnormal laboratory results that may be a risk factor for TLS or a sign of the disorder itself; special attention should be paid to abnormal renal function (Held-Warmkessel, 2010). Monitoring and management becomes much more significant for those patients with MM who have an increased risk of developing TLS (e.g., high tumor burdens, intent to receive the first cycle of bortezomib treatment). Oncology nurses should ensure that the most important aspects of the management of TLS are in place, including identifying patients at higher risk for TLS and having preventative measures for hyperuricemia in place prior to the beginning of treatment (Mackiewicz, 2012).

Health education is also an important part of TLS health care. Patients with MM who intend to accept bortezomib administration for the first time, along with their families, should be provided with detailed information regarding appropriate hydration and allopurinol use before treatment begins. Education helps to ensure patient adherence, which plays an important role in the implementation of preventive measures and, ultimately, improves patient safety (Mackiewicz, 2012). In addition, the symptoms associated with TLS should be introduced to high-risk patients for the purpose of self-comprehension and self-monitoring.

Conclusion

With the ready availability of bortezomib for the treatment of newly diagnosed MM, as well as for relapsed and refractory MM, TLS likely will be seen at a clinically significant frequency. The five patients with MM who developed TLS after undergoing bortezomib-containing regimens had elevated pretreatment serum acid levels, preexisting renal damage, advanced age, high tumor burdens, and low quality-of-life and performance status scores; all were also undergoing their first cycle of bortezomib treatment. Subsequently, these characteristics may be high-risk factors for TLS. Timely and efficient management could decrease the incidence of TLS and improve the efficacy of treatment outcomes. The end result will improve patients’ quality of life, allowing for their safe passage into recovery and remission.

References