Myelosuppression and Serotonin Syndrome Associated with Concurrent Use of Linezolid and Selective Serotonin Reuptake Inhibitors in Bone Marrow Transplant Recipients

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We report 2 cases of serotonin syndrome and myelosuppression in bone marrow transplant recipients who received linezolid in combination with a selective serotonin reuptake inhibitor (SSRI). Given the risks to patients in this high-risk group, we recommend that this combination of medications be avoided if alternative antibiotic therapy is possible. If no alternative therapy is possible, prescribers should discontinue SSRI therapy and monitor these patients closely for evidence of serotonin syndrome or the development of hematological toxicity.

Linezolid is an oxazolidinone antibiotic that was recently approved by the US Food and Drug Administration for treatment of vancomycin-resistant Enterococcus (VRE) infection, skin infection due to Staphylococcus aureus, and pneumonia due to Streptococcus pneumoniae [1]. Although linezolid appeared to be effective in clinical trials and in numerous case reports for the treatment of various infections with gram-positive organisms [2–6], recent letters from prescribers and the manufacturer report that prolonged use of linezolid can lead to myelosuppression, including neutropenia, thrombocytopenia, and anemia [7]. According to a review by Kuter and Tillotson [7], many patients who developed severe myelosuppression in postmarketing surveillance were at increased risk for preexisting cytopenia or had decreased bone marrow reserve. Because of the potential risks involved, bone marrow transplant recipients were largely excluded from linezolid clinical trials. Therefore, information regarding adverse effects and tolerability of linezolid within this patient population is lacking.

In addition to its antimicrobial action, linezolid has been shown in vitro to be a weak reversible inhibitor of the enzyme monoamine oxidase. However, this unique property may lead some to expect adverse drug interactions to occur if and when linezolid is used concurrently with sympathomimetic agents or with selective serotonin reuptake inhibitors (SSRIs) [8]. In clinical trials of linezolid, no clinically significant effects attributed to this interaction were reported [9]. Nevertheless, a recent study [8] reported statistically significant elevations in blood pressure when linezolid was combined with over-the-counter sympathomimetic medications. An additional report documented a case of serotonin syndrome in a patient treated with linezolid shortly after the discontinuation of therapy with paroxetine [10]. Here, we present 2 cases of serotonin syndrome coupled with leukopenia and thrombocytopenia in allogeneic bone marrow transplant patients who received both linezolid and SSRI therapy.

Case report. Patient 1 was a 56-year-old woman with acute lymphocytic leukemia in first remission who underwent matched-sibling allogeneic peripheral blood stem cell transplantation after she received a preparative regimen of fludarabine and melphalan. Her medical history included depression (treated with 20 mg of citalopram per day), congestive heart failure, and modest renal impairment. Her early posttransplantation course was complicated by the development of compartment syndrome of left lower extremity, deep vein thrombosis, and cutaneous graft-versus-host disease. At day 40 after the transplantation, she developed bilateral pulmonary infiltrates, and she subsequently developed respiratory failure, which required mechanical ventilation for a total of 7 days. She also received broad-spectrum intravenous antibiotics for presumed pneumonia. During that period of time, she had multiple episodes of asymptomatic cytomegalovirus viremia, which were treated with intravenous ganciclovir for 2 weeks, and skin lesions consistent with Fusarium infection, which was confirmed by culture of a skin biopsy specimen.

Linezolid therapy (600 mg iv q12h) was started on day 58 after transplantation for treatment of fever that persisted despite administration of broad-spectrum antibiotics. Blood cultures became positive for vancomycin-resistant E. faecalis a day later. After 2 days of linezolid therapy, her WBC count decreased dramatically, from $5.2 \times 10^9$ to $2.5 \times 10^8$ cells/UL, re-
underwent matched unrelated donor allogeneic transplantation with alemtuzumab, cyclophosphamide, and rituximab. The patient was diagnosed with lymphocytic leukemia that had failed to respond to multiple treatments, including sertraline, thalidomide, benzodiazepines, and opioids. Vital signs revealed new-onset hypertension and postural hypotension, with systolic blood pressure ranging from 160 to 190 mm Hg and diastolic blood pressure ranging from 90 to 110 mm Hg (baseline blood pressure, 120/60 mm Hg), which could only be controlled by triple antihypertensive therapies. Subsequently, therapy with cyproheptadine and propranolol was started, and linezolid and citalopram were both suspended on day 71 after transplantation. Of note, her platelet count never recovered completely, even after discontinuation of linezolid therapy and dialysis. Twelve days after linezolid therapy was discontinued, the patient demonstrated an increasing need for platelet support, from every other day up to every 8 h. The results of an examination of a bone marrow biopsy specimen obtained at this time were negative for relapse and for the presence of cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6.

In addition to the hematological changes, the patient also began to experience extreme fatigue, weakness, decreased concentration, tremors, periods of confusion, an inability to get out of bed, and nonspecific cardiac symptoms, such as palpitations, after 2 days of receiving linezolid therapy. Vital signs revealed both new-onset hypertension and postural hypotension, with systolic blood pressure ranging from 160 to 190 mm Hg and diastolic blood pressure ranging from 90 to 110 mm Hg (baseline blood pressure, 120/60 mm Hg), which could only be controlled by triple antihypertensive therapies. Subsequently, therapy with cyproheptadine for 3 days and improved neurologically, with normalization of the blood pressure 9 days after linezolid and citalopram therapy was discontinued. Unfortunately, she died of a cerebral hemorrhage on day 90 after transplantation. Of note, her platelet count never recovered completely, even after discontinuation of linezolid therapy 19 days earlier. The platelet count at the time of death was 24,000 platelets/UL. On the basis of her last bone marrow studies, leukemia was determined to be in complete remission at the time of death.

Patient 2 was a 36-year-old man with refractory chronic lymphocytic leukemia that had failed to respond to multiple chemotherapy agents, including fludarabine, chlorambucil, alemtuzumab, cyclophosphamide, and rituximab. The patient underwent matched unrelated donor allogeneic transplantation in April 2000 after receiving conditioning with high-dose cyclophosphamide, total body irradiation, and antithymocyte globulin. His posttransplantation course was complicated by severe hemorrhagic cystitis, steroid-refractory graft-versus-host disease, thrombotic thrombocytopenic purpura, renal failure requiring dialysis, and multiple polymicrobial pulmonary infections, including infections with Candida glabrata, Xanthomonas maltophilia, and Pseudomonas aeruginosa. VRE was also cultured from several additional specimens, including stool, urine, and blood. On day 137 after transplantation, he began receiving linezolid (600 mg iv q12h). Medications at the time of initiation of linezolid therapy also included tacrolimus, corticosteroids, thalidomide (100 mg q.d.), sertraline (50 mg q.d.), sustained-release morphine, and alprazolam (for anxiety). On day 5 of linezolid therapy, the patient had episodes of confusion, excessive somnolence with increased restlessness, delirium, and agitation. Vital signs also became more erratic, with development of labile hypertension requiring triple antihypertensive therapy and high fevers (i.e., temperatures up to 40°C). CT of the brain and electroencephalography were performed, and no abnormalities were found.

Twelve days after the initiation of linezolid therapy, the patient’s WBC and platelet counts began to decrease significantly. His WBC count decreased from $12.8 \times 10^3$ to $2.6 \times 10^3$ cells/UL within 17 days after initiation of linezolid therapy, and G-CSF support was required, even after linezolid was discontinued (table 2). He also required more-frequent platelet transfusions (up to twice daily). Other possible causes of cytopenia, such as relapse or viral infection, were investigated and ruled out. On day 6 of therapy, administration of linezolid and all other concomitant medications with neurologic effects was halted, including sertraline, thalidomide, benzodiazepines, and opioids. The patient’s symptoms resolved within 1 day after discontinuation of the medications and did not recur, even after therapy with thalidomide, alprazolam, and morphine was reinitiated. Ten days later, the patient was transferred to home hospice because of refractory thrombotic thrombocytopenic purpura with associated multiorgan failure.

### Discussion

Patients with hematologic malignancy, especially those who undergo bone marrow transplantation and require administration of granulocyte colony-stimulating factor (G-CSF) at doses that increased to up to 960 µg daily to maintain absolute neutrophil counts $>1.0 \times 10^5$ neutrophils/UL (table 1). The patient remained dependent on G-CSF support until 12 days after linezolid therapy was discontinued. Simultaneously, the patient demonstrated an increasing need for platelet support, from every other day up to every 8 h. The results of an examination of a bone marrow biopsy specimen obtained at this time were negative for relapse and for the presence of cytomegalovirus, Epstein-Barr virus, and human herpesvirus 6.

### Table 1. Laboratory data and medication flowsheet for patient 1.

<table>
<thead>
<tr>
<th>Treatment or laboratory data</th>
<th>44</th>
<th>51</th>
<th>58</th>
<th>60</th>
<th>64</th>
<th>72</th>
<th>86</th>
</tr>
</thead>
<tbody>
<tr>
<td>Point in relation to linezolid therapy</td>
<td>2 w before</td>
<td>1 w before</td>
<td>Day 1</td>
<td>Day 3</td>
<td>Day 7</td>
<td>D/C</td>
<td>2 w after D/C</td>
</tr>
<tr>
<td>G-CSF dose, µg/day</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>150</td>
<td>300</td>
<td>960</td>
<td>—</td>
</tr>
<tr>
<td>WBC count, cells $\times 10^3$/UL</td>
<td>6.4</td>
<td>3.5</td>
<td>5.2</td>
<td>2.5</td>
<td>3.4</td>
<td>1.5</td>
<td>5.6</td>
</tr>
<tr>
<td>ANC, neutrophils $\times 10^3$/UL</td>
<td>5.5</td>
<td>3.2</td>
<td>5.0</td>
<td>2.25</td>
<td>3.0</td>
<td>0.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Platelet count, platelets $\times 10^3$/UL</td>
<td>45</td>
<td>15</td>
<td>10</td>
<td>25</td>
<td>16</td>
<td>9</td>
<td>9</td>
</tr>
</tbody>
</table>

**NOTE.** ANC, absolute neutrophil count; D/C, therapy discontinued; G-CSF, granulocyte colony-stimulating factor; w, week(s).
receive myelosuppressive therapy, are at an increased risk of developing severe sepsis due to viral, bacterial, or fungal infection. Antimicrobial agents associated with myelosuppression should be used cautiously.

Recently, several reports have documented the development of profound myelosuppression (pancytopenia, leukopenia, anemia, and thrombocytopenia) in patients receiving linezolid therapy, especially in patients receiving prolonged treatment (i.e., >2 weeks) [6, 7]. Both patients described in our report developed severe leukenia and thrombocytopenia while receiving treatment with both linezolid and SSRIs. The neutropenia was reversible in both cases on discontinuation of linezolid and the SSRIs and the initiation of G-CSF. Leukopenia lasted ~10 days, with WBC counts returning to baseline values 14 days after discontinuation of the offending agents. In contrast, the platelet count did not return to normal in either patient, and both patients remained transfusion dependent until the time of death or loss to follow-up. The onset of decreased blood cell counts correlated with the start of linezolid therapy. One patient developed myelosuppression very early during the treatment regimen. These observations suggest that certain high-risk patient populations (such as allogeneic transplant recipients) may be more susceptible to the hematological adverse effects of linezolid than are other patient groups.

In addition, both of our patients also developed serotonin syndrome, which was diagnosed on the basis of symptoms of serotonergic hyperstimulation. Our patients exhibited fever, mental status changes, agitation, delirium, and tremors, which correlate well with Sternbach’s criteria [11]. Often, the effects of serotonin excess can be mild and difficult to detect [12]. In contrast, our patients exhibited a more obvious and extreme constellation of symptoms, indicating a possible predisposition for the development of the syndrome. In a recent review, Brown et al. [13] categorized patients as high risk for the development of serotonin syndrome if they also had an underlying disease related to the metabolism of serotonin (e.g., preexisting hepatic, pulmonary, or cardiovascular disease). Both patients in our case report had underlying pulmonary-related disease. The first patient also had a history of congestive heart failure. These factors may have placed our patients in the high-risk category, compared with the patient population studied in previous trials. In the review by Brown et al. [13], thrombocytopenia was also reported as a potential adverse effect of serotonin syndrome. Therefore, it is possible that the myelosuppressive effects of linezolid may be potentiated by the development of serotonin syndrome, leading to more-prolonged and more-severe thrombocytopenia.

In conclusion, linezolid is a relatively new antibiotic used to treat unusually complicated and resistant infections that are predominantly seen in bone marrow transplant recipients with prolonged hospitalizations. Because this patient population was excluded from many clinical trials of linezolid, information regarding drug interactions and adverse effects in these high-risk patients is still lacking. Our 2 cases suggest that one should be cautious and monitor patients closely when linezolid therapy is given to high-risk patients, such as those who have received a bone marrow transplant. Complete blood cell counts should be performed frequently to detect any evidence of myelosuppression. In these patients, treatment with SSRIs should be discontinued before linezolid therapy is commenced and delayed for 2 weeks (“washout” period) after linezolid treatment has been completed. Additional studies are needed to better define and manage toxicities related to linezolid use in a critically ill, high-risk patient population.

References


