Linezolid-induced pure red cell aplasia: a case report and literature review

Abstract

Linezolid (LZD) is the first oxazolidinone with excellent safety and efficacy profiles against refractory infections caused by gram-positive organisms. Hematological toxicities such as thrombocytopenia, anemia, and leukocytopenia are common in LZD therapy; however, LZD-induced pure red cell aplasia (PRCA) is rare. An 83-year-old man diagnosed with pleural empyema caused by *Staphylococcus aureus* received LZD after developing resistance to multiple antibiotics. Although his infection-related symptoms were improved by LZD, progressive anemia was noticed after LZD therapy was initiated. Eight weeks after LZD administration began, his hemoglobin level was 5.7 g/dL and reticulocyte proportion was 0.36%, while his white blood cell and platelet counts remained unchanged since admission. Bone marrow examination revealed markedly decreased erythropoiesis with cytoplasmic vacuolation of erythroblasts. Anemia resolved by 14 days after cessation of LZD. It is important to increase the awareness among clinicians about the potential for the hematological effects associated with LZD, particularly for older patients with pre-existing anemia and treatment courses longer than 14 days. To detect bone marrow suppression, including PRCA, we suggest monitoring the complete blood count and reticulocyte count periodically in patients receiving long-term LZD therapy.

Keywords

Pure red cell aplasia, linezolid, *Staphylococcus aureus*, pleural empyema, hematological toxicity, oxazolidinone

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Introduction

Linezolid (LZD) is the first oxazolidinone antibiotic found to be effective against drug-resistant gram-positive organisms, especially vancomycin-resistant enterococci

and *Staphylococcus aureus* (including methicillin-resistant *S. aureus*).[1] The main uses are infections of the skin, infections of the central nervous system, and pneumonia, although it may be used for a variety of other infections including drug-resistant tuberculosis.[2,3] LZD is well tolerated, with the most common adverse reactions being gastrointestinal disturbances, including diarrhea and nausea.[1] Hematologic side effects include pancytopenia, thrombocytopenia, anemia, and neutropenia.[4–6] Thrombocytopenia is observed most often when treatment is continued over 2 weeks, but platelet count usually returns to normal with the termination of LZD.[1,4] Pure red cell aplasia (PRCA) is a rare disorder, induced by gene mutations present at birth; infectious diseases such as parvovirus B19, Epstein-Barr virus, or hepatitis; immunologic disorders such as autoimmune disorders or tumor-associated disorders; or drugs such as chloramphenicol or azathioprine.[7–9] However, PRCA associated with LZD therapy has been reported in only seven patients.[10–14] PRCA can lead to anemia, decreased reticulocytes (to less than 1%), and decreased erythroid lineage cells at various stages, especially erythroid precursor cells.[15]

We report the development of PRCA in a patient who had received linezolid for 8 weeks. Our goal is to share our treatment experience and provide prevention strategies for similar patients.

Case report

An 83-year-old Chinese man was admitted to our hospital with a prolonged fever and cough. His symptoms also included purulent sputum production and left-sided pleuritic chest pain. Physical examination revealed fine crackles, predominantly in the left posterior lower lung. Blood tests showed leukocytosis with white blood cell (WBC) count 11,800/μL, mildly decreased hemoglobin level at 10.2 g/dL, normal platelet count of 177,000/μL, and significantly elevated C-reactive protein concentration at 118.72 mg/L. A chest radiograph revealed left lower lobe pneumonia with a small left-sided pleural effusion. The patient was treated with parenteral antibiotics, but there was minimal clinical response to empiric antimicrobial therapy with ceftriaxone initially. Subsequently, he was treated with gentamicin, piperacillin/tazobactam, and biapenem. A diagnostic thoracentesis was performed. The aspirated pleural fluid was grossly purulent with WBC 93,000/μL, lactate dehydrogenase 2781 U/L, protein 4.47 g/dL, and glucose 0.11 mmol/L). A pigtail catheter was inserted into the left pleural cavity for drainage. Methicillin-resistant *Staphylococcus aureus* (MRSA) was identified in the pleural fluid culture, leading to the diagnosis of pleural empyema. Subsequent treatment with intravenous linezolid (600 mg twice daily) resulted in decreased fever and normalization of inflammatory markers within 5 days. On day 24 of hospitalization, the patient was discharged with normal WBC count (5,700/μL), anemia (hemoglobin level 9.8 g/dL), and normal platelet count (239,000/μL). Therapy was then changed to an oral regimen of LZD (600 mg twice daily).

After discharge from the hospital, as the patient's pulmonary infection was resolving, he presented with general fatigue and repeated attacks of dizziness. Complete blood count monitoring showed a progressive decline in hemoglobin from 10.2 g/dL to 5.7 g/dL over the 8-week course of oral LZD. The reticulocyte proportion was 0.36%, with absolute value 0.008×10^6/μL. The WBC differential count was normal with no dysplastic features. Lymphocytes were 33.6% with absolute value of 1,540/μL. Lymphocyte phenotypes counted by flow cytometry showed CD3+ 71.2%, CD4+ 38.9%, CD8+ 23.5%, CD19+

8.9%, CD44+ 42.6%, and CD25+ 19.8%. There was no decrease in platelets. A peripheral blood smear showed red blood cells (RBCs) with moderate anisocytosis and poikilocytosis. There was no evidence of bleeding, hemolysis, liver dysfunction, or renal dysfunction. Direct Coombs test was negative. Serum haptoglobin concentration by the traditional ELISA method was 2.16 ± 0.34 g/L (reference range 0.50–1.35 g/L). The results of testing for serum parvovirus B19 DNA by PCR and cytomegalovirus antigenemia by immunofluorescence microscopy were negative. Bone marrow aspiration examination confirmed the presence of a hypoproliferative anemia with markedly decreased erythroid cells without evidence of dysplasia or leukemia (Figure 1a). Rare vacuolated pronormoblasts were present (Figure 1b). Chromosomal analysis showed 46, XY in all 20 bone marrow cells examined. The patient was not taking any drugs concurrently that could produce bone marrow suppression.

Linezolid therapy was stopped, and the patient subsequently received a transfusion of packed RBCs (Figure 2). During the 2 weeks after cessation of linezolid therapy, the reticulocyte proportion increased to 4.8% with absolute value 0.436×10^6/μL.

Hemoglobin levels increased to 8.4 g/dL at 2 weeks after cessation of LZD and 9.9 g/dL at 4 weeks. A second bone marrow study with aspiration 2 weeks after stopping LZD treatment showed a normocellular marrow with recovery of erythroid cells, and there was no dysplasia in any of the three lineages (Figure 3). It is noteworthy that all of the patient's other medications remained unchanged. The patient did not receive a transfusion of packed RBCs after the cessation of LZD therapy and there was no recurrence of the pleural empyema.

This study was approved by the Ethical Review Board of Ningbo First Hospital. Written informed consent was obtained from the patient.

Discussion

We describe an older patient with pure red cell precursor toxicity associated with an 8-week course of LZD treatment for pleural empyema. Although anemia was detected before treatment with LZD, likely a consequence of the infection, pure red cell precursor toxicity was attributed to LZD because the anemia worsened after administration of LZD but returned to normal upon termination of LZD therapy.
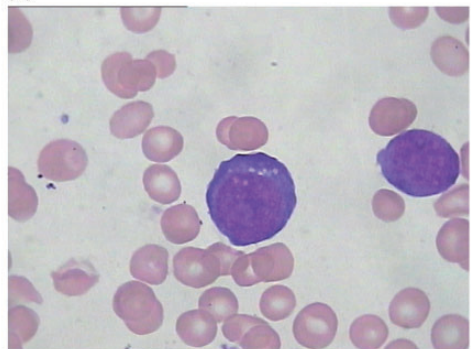
(a)
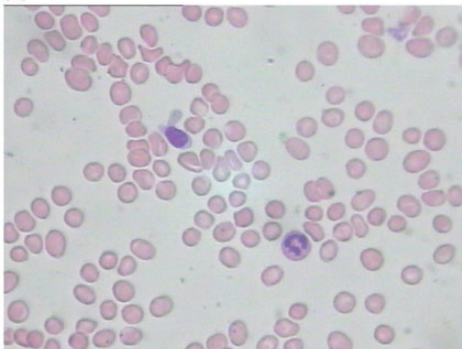
(b)

Figure 1. Bone marrow aspirate. (a) Wright-Giemsa stain demonstrates reduced erythropoiesis, magnification 400×; (b) Wright-Giemsa stain showing vacuolated pronormoblast, magnification 1000×.
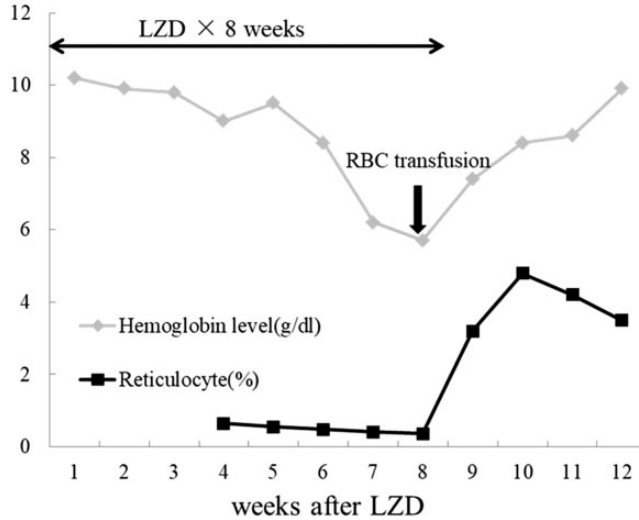
Figure 2. Clinical course of the patient. Trends in hemoglobin level and reticulocyte count after the administration of LZD, and the time to recovery of the two indexes following the termination of linezolid. Bold double-headed arrow represents LZD treatment.
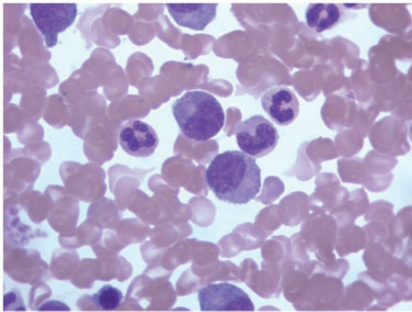LZD, linezolid; RBC, red blood cells.

Figure 3. Bone marrow aspirate. Wright-Giemsa stain showing normocellular marrow with erythropoiesis, magnification 1000×.

The mechanisms underlying LZD-induced anemia are not clear, but the vacuolated pronormoblasts suggested an anemia similar to the mechanism for chloramphenicol-induced myelosuppression. The mechanism is thought to be suppression of mitochondrial respiration via inhibition of mitochondrial protein synthesis,[16] although the ribosomal binding sites for chloramphenicol[16] and linezolid[17] are different.

Hematological toxicities caused by LZD have usually occurred during treatment courses longer than 14 days.[4,18,19] In a review of patients who received LZD therapy in clinical trials, 9%, 4.1%, and 4.7% of patients receiving longer than 2 weeks of LZD therapy developed worsening anemia, thrombocytopenia, and leukopenia, respectively.[4] Senneville et al.[20] reported that the median time of anemia onset and LZD initiation was 7.4 weeks (4–16 weeks) for 45 patients. The time of anemia onset in our patient was 8 weeks, which is consistent with those results. After reviewing the literature, we found LZD-induced PRCA reported in only seven patients (Table 1). Recovery from LZD-induced PRCA is shown in Table 2.

Our patient is the first to be reported with treatment of pleural empyema. With respect to the risk factors for anemia, LZD-induced anemia is time-dependent.

Table 1. Linezolid-induced pure red cell aplasia.

Report	Gender, Age (years)	Underlying Disease	Infecting Organism	Anemia Onset (weeks after initiation of LZD therapy)	Change in Hgb (g/dL) Level During LZD Therapy	Change in Retic Count or Percent During LZD Therapy	Bone Marrow Findings	Other Treatment
Monson et al.	M, 52	Pneumonia	Unclear	8	14.5 to 5.9	N/A to 3,300	RBC aplasia with vacuolated pronormoblasts	None
Taketani et al.	M, 2	Endocarditis	Streptococcus mitis	2	8.9 to 6.5	3.4% to 0.1%	Decreased erythropoiesis (M/E ratio 16:1) with vacuolar degeneration	Single RBC transfusion
Waki et al.	M, 56	Bacteremia after SCT	Staphylococcus epidermidis	2	8.5 to 6.8	6.6% to 0.3%	RBC aplasia (M/E ratio 402:1) with vacuolated pronormoblasts	None
Green et al.	M, 70	Infection of Gore-Tex graft	MRSA	16	14.3 to 7.0	N/A to 0	Erythroid aplasia (M/E ratio 174:1) with vacuolated erythroblasts	N/A
Green et al.	F, 43	Sinusitis	MRSA	6	14.1 to 12.8	N/A to 0	Rare vacuolated erythroblasts	N/A
Green et al.	F, 61	Osteomyelitis	MRSA	4	9.9 to 8.0	4.5% to 0	N/A	N/A
Hu et al.	M, 37	CNS infection after allo-HSCT	Unclear	4	12.8 to 5.5	6.6% to 0.21%	Hypoproliferative anemia with absence of erythroid cells	EPO, two RBC transfusions
Luo et al. (this report)	M, 83	Pleural empyema	MRSA	8	10.2 to 5.7	N/A to 0.36%	Hypoproliferative anemia with markedly decreased erythroid cells	Single RBC transfusion

Allo-HSTC, allogenic hematologic stem cell (transplantation); CNS, central nervous system; EPO, erythropoietin; Hgb, hemoglobin; LZD, linezolid; M/E ratio, myeloid/erythroid ratio; MRSA, methicillin-resistant *Staphylococcus aureus*; N/A, not available; RBC, red blood cells; retic, reticulocyte; SCT, (hematopoietic) stem cell transplantation.

Table 2. Recovery from linezolid-induced pure red cell aplasia.

Report	Recovery (days after cessation of LZD)	Hgb Level (g/dL), Interval After Cessation of LZD Therapy	Retic Count or Percent, Interval After Cessation of LZD Therapy
Monson et al.	10	8.6, 2 weeks; 12.1, 4 weeks	N/A
Taketani et al.	19	9.6, 19 days; 12.1, 3 months	Increased
Waki et al.	12	8.6, 12 days	2.8%, 12 days
Green et al.	10	Normal	5.8%, 10 days
Green et al.	7	Normal	2.4%, 1 week
Green et al.	Unclear	Normal	Normal
Hu et al.	14	11.0, 2 weeks	1.65%, 2 weeks
Luo, et al. (this report)	14	9.9 in 4 weeks	4.8%, 2 weeks

Hgb, hemoglobin; LZD, linezolid; N/A, not available; retic, reticulocyte.

According to the manufacturer's instructions, a complete blood count should be done weekly in patients receiving LZD for longer than 2 weeks. Other risk factors for anemia in patients with prolonged LZD therapy were administration of concurrent medications that can suppress the bone marrow, chronic infections, age above 58 years, alcohol abuse, diabetes mellitus, end-stage renal disease, and pretreatment hemoglobin lower than 10.5 g/dL.[20,21] In addition, Minson et al.[22] indicated that independent risk factors for grade 3–4 anemia induced by LZD included a baseline cardiovascular condition and baseline platelet count of 50–99 × 10^9/L. Our patient was 83 years old and had pre-existing anemia before the LZD therapy with hemoglobin <10.5 g/dL. All of these may be other potential risk factors contributing to the occurrence of PRCA.

Reticulocyte count, as a predictive marker of anemia (including PRCA), is an important index that reflects the erythroid function of the bone marrow. In our patient, when the hemoglobin level dropped slightly after a treatment period of 4 weeks (hemoglobin 9 g/dL), the reticulocyte count was as low as 0.65% and reached 0.36% on week 8. Therefore, the reticulocyte decline might precede the onset of peripheral anemia in patients with PRCA patients, and the reticulocyte count could be used to predict anemia in clinical practice. An early diagnostic bone marrow examination should be considered if the reticulocyte count decreases and/or is inappropriate for the hemoglobin level. Correspondingly, we recommend performing a periodic reticulocyte count to monitor patients on long-term LZD therapy in order to predict the onset of anemia.

Conclusion

In summary, we report a patient with PRCA after LZD treatment; we believe that the long period of LZD treatment was the primary factor resulting in PRCA. Older patients and patients with anemia prior to LZD therapy might also be at risk for PRCA. Therefore, a complete blood count and reticulocyte count are necessary during LZD therapy. A patient with anemia should recover after LZD is withdrawn. However, future studies should be conducted to verify our findings.

Hospital, for analyzing the bone marrow aspirates.

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