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CASE REPORT

Plasma Concentrations of Contezolid and Its Efficacy and Safety in Elderly Patients with Multidrug-Resistant Tuberculosis and Renal Insufficiency

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Abstract: As a new generation of oxazolidinone antibacterial drugs, contezolid has been shown to have comparable or even stronger activity than linezolid and has a low risk of adverse reactions such as bone marrow suppression toxicity. However, there are currently very few clinical reports and pharmacokinetic data of contezolid on the anti-tuberculosis therapy. Therefore, we report a case study of the pharmacokinetic study of contezolid in elderly patients with renal insufficiency and tuberculosis. The patient's condition improved after receiving an anti-tuberculosis regimen containing contezolid, with significant absorption of pleural effusion and lung plaques and nodules reduced. During the treatment, the patients' platelet and white blood cell levels fluctuated within normal ranges, but hemoglobin levels significantly decreased and did not recover after discontinuation of contezolid. The trough concentration of contezolid and the concentration at 2, 4, 6, and 10 h after administration were 1.27μg/mL, 3.88μg/mL, 6.32μg/mL, 8.99μg/mL, and 3.14μg/mL, respectively. The plasma concentrations of bedaquiline and cycloserine during the treatment were also monitored. This study demonstrated the efficacy and safety of contezolid in the treatment of multidrug-resistant tuberculosis and analyzed its pharmacokinetic changes in elderly patients with renal insufficiency, providing a reference for the clinical use of contezolid.

Keywords: contezolid, tuberculosis, plasma concentration, efficacy, safety

Introduction

Tuberculosis (TB) is the second deadliest infectious disease after COVID-19 and the 13th leading cause of death worldwide and China remaining one of the countries with a high TB burden.[1] Recently, as a representative oxazolidinone, linezolid has been increasingly used in the treatment of drug-resistant and severe TB. Given the outstanding antibacterial performance, linezolid has been listed as a class A drug for drug-resistant tuberculosis in the latest WHO and Chinese guidelines for multidrug-resistant TB (MDR-TB) treatment. Therefore, linezolid is currently one of the main therapeutic drugs for MDR/rifampicin-resistant (RR) TB.[2,3] However, due to the occurrence of myelosuppression, neurotoxicity, lactic acidosis and other adverse reactions, and potential drug interactions, narrow therapeutic window, the use of linezolid in long-term anti-TB treatment has been increasingly unfavored.[4–6] Moreover, Linezolid-associated peripheral neuropathy is an agonizing experience for the patient at times, with no established definite treatment. Consequently, linezolid has to be withdrawn occasionally, leading to its replacement with a drug that is often less effective and more toxic. Due to these linezolid-associated adverse drug reactions (ADRs), alternative oxazolidinones like sutezolid, delpazolid, and sutezolid need to be reviewed for possible increased efficacy with reduced toxicity in people with drug resistant TB.[7]

Contezolid (CZD), a new generation of oxazolidinone antibiotics, has comparable or more potent antibacterial activity than linezolid and a lower risk of myelosuppression, neurotoxicity, and lactic acidosis.[8,9] CZD is the first new

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generation of oxazolidinone antibacterial drug and was approved by Chinese Food and Drug Administration and successfully marketed in 2021. With structural modification, CZD possesses stronger antibacterial activity, fewer adverse reactions and drug–drug interactions.[10]

Pharmacokinetic (PK) studies in animals showed that CZD can be rapidly absorbed and dispensed to most organs, including the skin and skeletal muscles. The apparent volume of distribution of CZD was approximately 0.61 L/kg in healthy subjects after oral administration, which is comparable to that of 0.65 L/kg for linezolid, suggesting a wide distribution of CZD in human body. In vitro tests showed that the antibacterial activity of CZD against both drug-sensitive and drug-resistant *Mycobacterium tuberculosis* (Mtb) was comparable to that of linezolid.[11] CZD also showed strong antibacterial activity against different species of Mtb and has significantly better intracellular bactericidal activity than linezolid against drug-resistant Mtb.[12]

However, clinical reports of the use of CZD for anti-tuberculosis treatment are very few currently, especially the pharmacokinetic changes in clinical patients. Therefore, this study demonstrated the efficacy and safety of CZD in the treatment of multidrug-resistant tuberculosis and analyzed its pharmacokinetic changes in elderly patients with renal insufficiency, providing a reference for the clinical use of CZD.

Case Presentation

A 90-year-old male (56 kg) was admitted to the hospital with fever and pulmonary lesions discovered for 5 days. Six days ago, the patient was treated in local hospital for "an elevated creatinine level for 20 years and bilateral lower limb edema for 1 week". During hospitalization, he developed a nocturnal fever, with the body temperature fluctuating between 38 and 39 °C. The patient experienced chest tightness, shortness of breath, and limb weakness, without cough or expectoration. The CT scan of lung showed diffuse miliary nodules, multiple fibrosis, and scattered pulmonary cysts in both lungs, bilateral pleural effusion and incomplete expansion of the lower lobes of both lungs. A sputum smear testing for Mtb was positive. Therefore, the patient was considered may have pulmonary TB and was admitted to our hospital for further diagnosis and treatment. The patient had a history of hypertension, coronary artery disease (CAD), chronic kidney disease (CKD) 3 period, and prostate cancer and had undergone cardiac pacemaker implantation two years prior.

Given the patient has hypertension, CAD, and CKD 3 period, with pulmonary infection and a lower blood potassium level, moxifloxacin injection (0.4 g, once a day), 10% potassium chloride (10 mL, three times a day, oral administration), spironolactone tablets (20 mg, once a day, oral administration), valsartan capsules (80 mg, once a day, oral administration), atorvastatin tablets (20 mg, once a day, oral administration) and furosemide injection (20 mg, once a day) were given as corresponding treatment, and the relevant examinations were conducted.

On the second day after admission (May 9th), the patient coughed and expectorated occasionally and felt chest tightness and discomfort after activity, with no chills, fever, chest pain, hemoptysis, abdominal pain, or diarrhea. The sputum smear testing for Mtb was positive. Computed tomography (CT) results of lung suggested diffuse miliary nodules, multiple fibrous foci and air sacs in both lungs, and pleural effusion on both sides. Laboratory tests showed that the white blood cell (WBC) level was $6.1*10^9$/L, with 80.7% neutrophils and 10.2% lymphocytes; the hemoglobin (Hgb) level was 115 g/L, the platelet count (PLT) was $66*10^9$/L, the blood urea nitrogen (BUN) level was 6.11 mmol/L. The blood creatinine level was 128.1 μmol/L. The creatinine clearance (CrCL) was 27.04 mL/min. The total bilirubin (TB) and direct bilirubin (DB) levels were 31.8 μmol/L and 15.3 μmol/L, respectively. Moreover, the C-reactive protein (CRP) level was 102.7 mg/L. Considering the patient's elevated CRP level, cefoperazone/sulbactam injection (2.0 g, twice a day) was given as antimicrobial treatment.

On the third day after admission (May 10th), the next-generation sequencing (NGS) of sputum samples indicated that the Mtb was resistant to isoniazid, rifampicin, and streptomycin, therefore, the patient was diagnosed with MDR-TB. Given he has an older age, and Hgb and PLT levels were lower than normal, the patient was treated with an individualized anti-TB regimen including bedaquiline tablets (400 mg, once a day, for 2 weeks; 200 mg, three times a week, for the following 22 weeks), CZD tablets (400 mg, twice a day), cycloserine capsules (0.25 g, twice a day, once every other day), and moxifloxacin tablets (400 mg, once a day). Cefoperazone/sulbactam injections were discontinued. Moreover, the patient refused bone marrow puncture examination to rule out hematopoietic function damage.

On the ninth day after admission (May 16th), the patient had no chills or fever but had paroxysmal cough and expectoration, as well as tightness in the chest after activity. Detection of Mycobacterium tuberculosis and rifampicin resistance (Xpert MTB/RIF) in sputum samples revealed that the Mtb complex group was positive and Mtb was resistant to rifampicin. Laboratory tests

showed that the WBC count was 9.5*10^9/L, with 70.3% neutrophils and 18.4% lymphocytes. The Hgb level was 107 g/L. The PLT count was 133*10^9/L. The BUN level was 11.87 mmol/L. The creatinine level was 218.4 μmol/L, and the CrCL was 15.0 mL/min. The TB and DB levels were 21.7 μmol/L and 11.7 μmol/L, respectively. The CRP level was 37.59 mg/L. Compared to the previous testing results, the blood potassium level of this patient recovered to normal, creatinine level was elevated after the treatment. Therefore, the use of spironolactone was suspended, and the changes in the patient's renal function were closely monitored.

On the eleventh day of admission (May 18th), the patient had a normal body temperature, with no chills, fever, nausea, or vomiting. The anti-MDR-TB regimen was continued. Blood samples were collected from the patient 2h after drug administration for monitoring plasma drug concentrations. It was shown that the plasma concentration of bedaquiline was 1.50 μg/mL (the reference range of bedaquiline after 2 weeks of use: 2.8–3.3 ug/mL) and the plasma concentration of cycloserine was 31.26 ug/mL (reference range: 20–35 ug/mL).

On the seventeenth day of admission (May 24th), the patient had a normal body temperature and the consciousness was clear, with no dizziness, headache, or swelling in either leg. The results of the laboratory tests showed that the WBC count was 5.3*10^9/L, and the Hgb level was 82 g/L. The BUN level was 12.39 mmol/L, the blood creatinine level was 196.9 μmol/L, the CrCL was 17.4 mL/min. The TB and DB levels were 29.2 μmol/L and 17.1 μmol/L, respectively. The total protein level was 56.5 g/L, and the albumin level was 32.3 g/L. The aspartate aminotransferase (AST) level was 56 U/L, and the CRP level was 25.71 mg/L. The anti-TB regimen was continued. Moreover, blood samples were collected and the results showed that the plasma concentration of bedaquiline 2-hour post-administration was 2.7 μg/mL (reference range: 2.8–3.3 ug/mL). On the eighteenth day of admission, the plasma concentration (trough concentration) of contezolid was 1.82 μg/mL.

On the twenty-second day of admission (May 29th), the patient had paroxysmal cough and expectoration, normal body temperature, and clear consciousness, with no dizziness or headache. The results of the regular blood tests were as follows: the WBC count was 4.1*10^9/L, Hgb level was 77 g/L, PLT count was 125*10^9. The BUN level was 11.44 mmol/L. The creatinine level was 159.5 umol/L. The CrCL was 21.5 mL/min. The total protein level was 53.9 g/L, and the albumin level was 30.4 g/L. The AST level was 49 U/L. The alanine transaminase (ALT) level was 11 U/L, and the CRP level was 20.75 mg/L. Given the decreased Hgb level after anti-TB treatment, the administration of CZD was discontinued. The patient was stabilized condition and discharged after 23 days of admission, with instructions to continue anti-MDR-TB treatment and receive weekly tests of the blood, liver and kidney functions, and urine.

Follow-up after discharge indicated that the patient's condition was stable, and the results of regular blood tests were as follows: on June 7th (1 week after discharge), the patient had a Hgb level of 78 g/L, and a PLT count of 100*10^9/L; On June 14th (2 weeks after discharge), the Hgb level was 73 g/L, and the PLT count was 78*10^9/L. On June 19th (3 weeks after discharge), he had a Hgb level of 83 g/L, and a PLT count of 92*10^9/L.

The patient was admitted to the hospital for the second time on June 20th due to "sinus arrhythmia and a QT/QTc of 424/519 ms". After admission, pulmonary CT showed bilateral pulmonary tuberculosis accompanied by intrapulmonary spread and was more serious than the previous test results; pleural effusion increased on both sides. The laboratory tests showed the WBC count was 5.9*10^9/L, Hgb level was 79 g/L, PLT count was 101*10^9. The BUN level was 8.7 mmol/L. The creatinine level was 145.7 umol/L. The CrCL was 23.5 mL/min. The AST level was 42 U/L, and the alanine transaminase (ALT) level was 15 U/L. The CRP level was 51.26 mg/L. Considering that the patient was admitted to hospital for adverse reactions caused by anti-tuberculosis drugs, anti-tuberculosis treatment was suspended. Symptomatic treatment such as diuretic potassium supplementation, blood pressure control by valsartan, CAD treatment by atorvastatin were given. In addition, since the patient's hemoglobin and red blood cells have been below the normal range, folic acid (5mg, once a day, oral administration) and enteral nutrition emulsion (200mL, twice a day, oral administration) were administered from July 10th.

The patient's condition was subsequently stabilized, and the anti-TB treatment was continued on July 26th with CZD tablets (400 mg, twice a day), moxifloxacin tablets (400mg, once a day), and cycloserine capsules (0.25g, twice a day). Moreover, iron protein succinate oral solution (40mg, twice a day, oral administration) was added to improve the anemia of the patient. On August 3rd, after 8 days of continuous administration of contezolid, the plasma concentrations of contezolid pre-dose (trough concentration level) and 2, 4, 6, and 10 hours post-dose were monitored, and the results are shown in Figure 1. The patient was subsequently continued anti-TB regimen treatment, and his condition was stable after that. The pleural fluid and nodules in his lungs were obviously absorbed than before. He was discharged from the hospital on August 23th, the chest imaging scan at

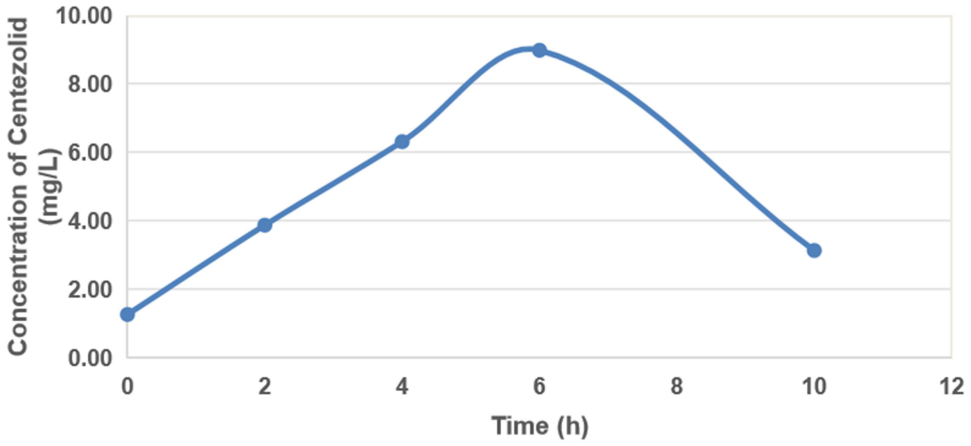

Figure 1 Changes of plasma concentration of contezolid after one week of continuous administration (400 mg, twice a day).

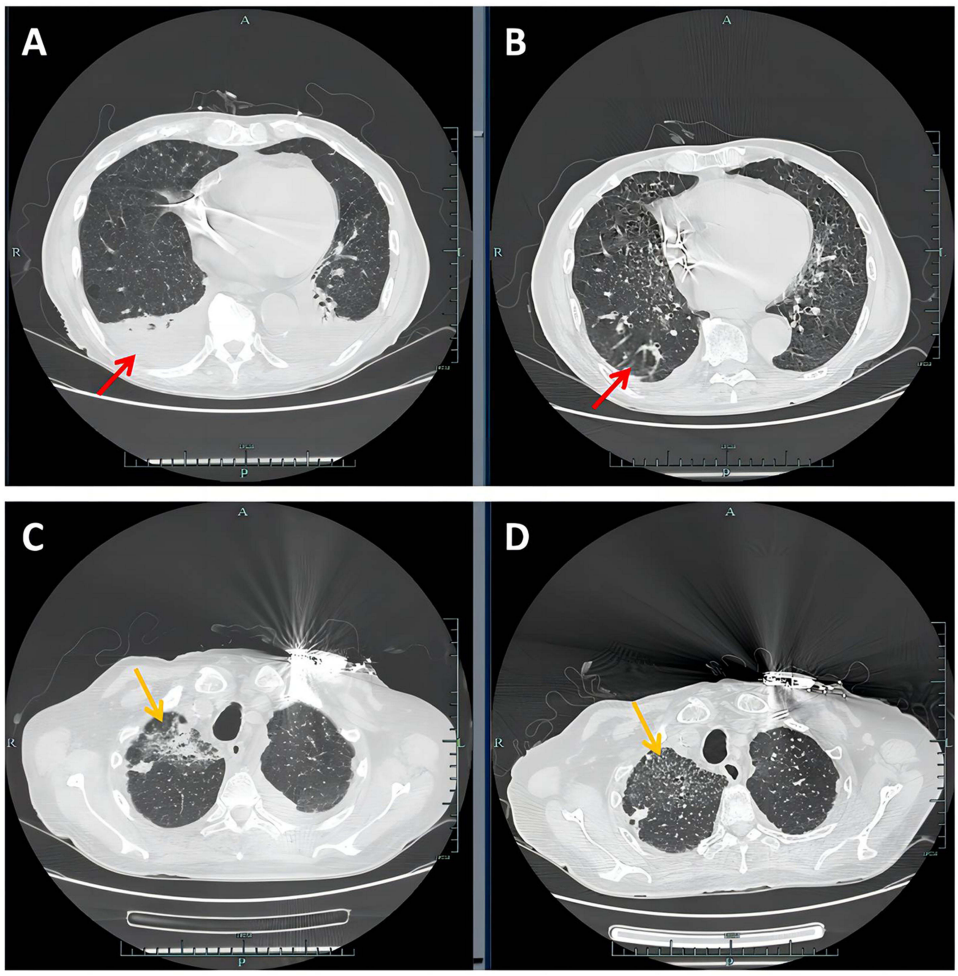

Figure 2 Chest imaging scan at admission (**A** and **C**) and after treatment (**B** and **D**). (**A**) A moderate amount of liquid density shadow in the chest cavity bilaterally. (**B**) Pleural effusion was almost completely absorbed. The red arrow indicates the site of pleural fluid. (**C**) There were obvious plaques and nodules in the upper lobe of the right lung. (**D**) Plaques and nodules of the upper right lung were obviously absorbed. The yellow arrow indicates the site of plaques and nodules.

admission and before discharge is showed in Figure 2. Moreover, the changes of the PLT, Hgb, and WBC count levels in the patient throughout the course of treatment are shown in Figure 3. The CT results of follow-up at 2 months, 4 months and 6 months showed that the patient's condition gradually improved, the pleural effusion absorbed completely, and bilateral tuberculosis did

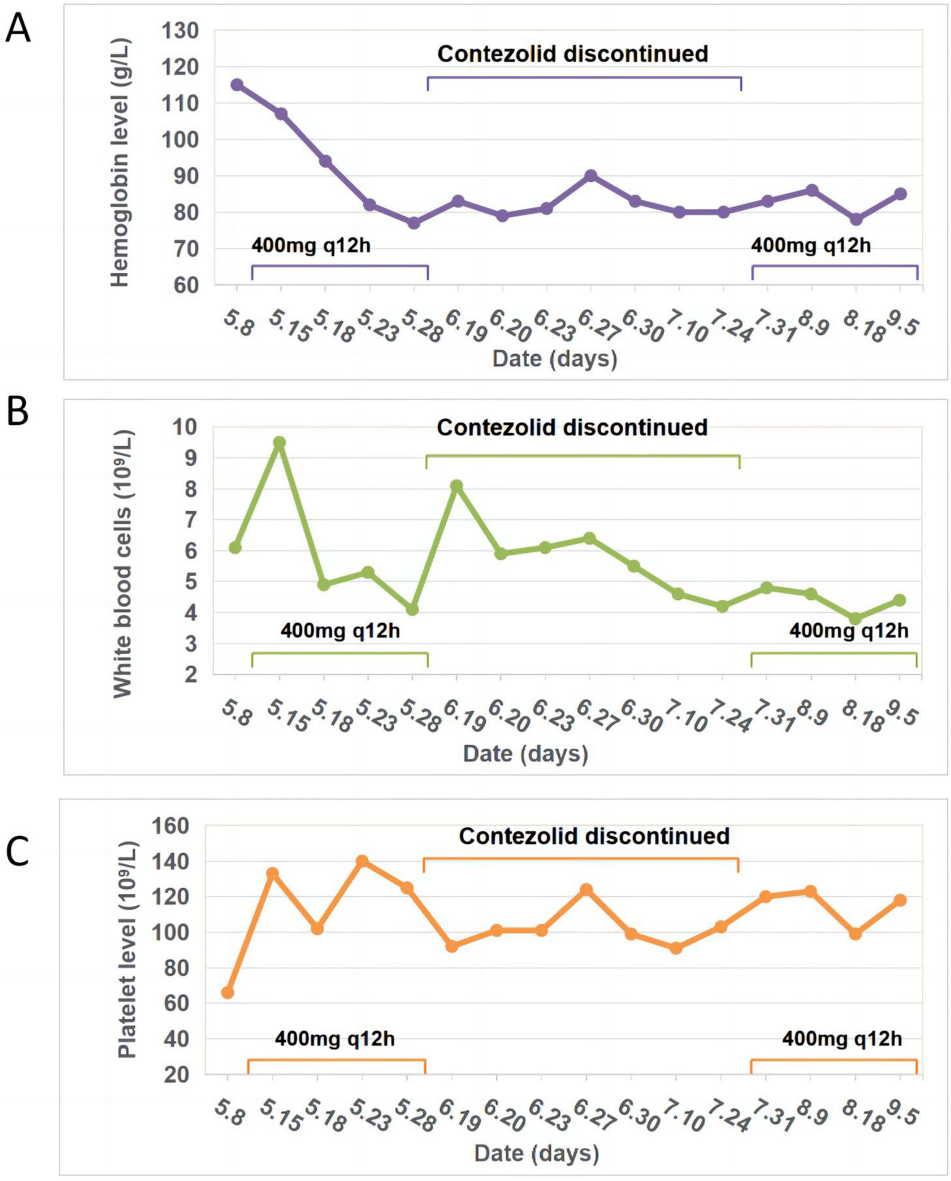

Figure 3 Changes in hemoglobin (**A**), white blood cells (**B**), and platelet (**C**) levels during the whole course of treatment. The normal ranges for hemoglobin, white blood cells, and platelet levels are 120–170 g/L, 3.5×10^9–9.5×10^9/L and 100×10^9–300×10^9/L, respectively.

not spread further. The hemogram, renal and liver function were stable. The timeline of the overall treatment process is presented in Table 1.

Blood concentrations of CZD, cycloserine, and bedaquiline during the patient's treatment were monitored by liquid chromatography-mass spectrometry method. The linear ranges of the assays for determining CZD, cycloserine, and bedaquiline concentrations were 0.25–50 μg/mL, 5–200 μg/mL, and 1–40 μg/mL, respectively, with the precision and accuracy meeting the requirements of the China Food and Drug Administration regulations.

Discussion

This study reported the therapeutic efficacy and safety of CZD in an elderly patient with TB and renal insufficiency. CZD is a fully synthetic oxazolidinone antimicrobial agent that can be used to treat infections caused by aerobic gram-positive bacteria. In vitro studies have shown that the antibacterial action mechanism of CZD is the same as that of other oxazolidinones, which is to inhibit bacterial growth by inhibiting bacterial protein synthesis. CZD has potential

Table 1 The Timeline of the Overall Treatment Process

Time	Laboratory Profile	Imaging Examination	Treatment
May 8th	NR	NR	moxifloxacin (0.4 g, qd, iv.), 10% potassium chloride (10 mL, tid, po.), spironolactone (20 mg, qd, po.), valsartan (80 mg, qd, po.), furosemide (20 mg, qd, iv.), atorvastatin (20 mg, qd, po.)
May 9th	WBC: 6.1×10^9/L; RBC: 3.55×10^{12}/L; Hgb: 115 g/L; PLT: 66 ×10^9/L; Scr: 128.1 μmol/L; BUN: 6.11mmol/L; TB: 31.8 μmol/L; DB: 15.3 μmol/L; ALT: 32 U/L; AST: 36 U/L; ALP: 133 U/L; CRP (hs): 102.7 mg/L; K+: 3.45 mmol/L TB acid-fast bacilli smear test: positive	CT: diffuse miliary nodules, multiple fibrous foci and air sacs in both lungs, and pleural effusion on both sides.	Adding: cefoperazone/sulbactam (2.0 g, q12h, iv.)
May 10th	NR	NGS (sputum): Mtb was resistant to isoniazid, rifampicin, and streptomycin	bedaquiline (400 mg, qd, for 2 weeks; 200 mg, W3D, for the following 22 weeks, po.), contezolid (400 mg, q12h, po.), cycloserine (0.25 g, q12h, qod), moxifloxacin (400 mg, qd, po.). Discontinue: cefoperazone/sulbactam.
May 16th	WBC: 9.5×10^9/L; RBC: 3.27×10^{12}/L; Hgb: 107 g/L; PLT: 133 ×10^9/L; Scr: 218.4 μmol/L; BUN: 11.87 mmol/L; TB: 21.7 μmol/L; DB: 11.7 μmol/L; ALT: 13 U/L; AST: 34 U/L; ALP: 139 U/L; CRP (hs): 37.59 mg/L; K+: 5.04 mmol/L	Xpert MTB/RIF: Mtb complex group: positive, Mtb was resistant to rifampicin.	Discontinue: spironolactone.
May 18th	WBC: 4.9×10^9/L; RBC: 2.82×10^{12}/L; Hgb: 94 g/L; PLT: 102 ×10^9/L; Scr: 216.8 μmol/L; BUN: 11.07 mmol/L; TB: 28.1 μmol/L; DB: 16.3 μmol/L; ALT: 7 U/L; AST: 29 U/L; ALP: 128 U/L; CRP (hs): 41.31 mg/L; K+: 4.94 mmol/L C_{2h} of bedaquiline: 1.5 μg/mL C_{2h} of cycloserine: 31.26 ug/mL	NR	Continue anti-MDR-TB treatment regimen
May 24th	WBC: 5.3×10^9/L; RBC: 2.46×10^{12}/L; Hgb: 82 g/L; PLT: 140 ×10^9/L; Scr: 196.6 μmol/L; BUN: 12.39 mmol/L; TB: 29.2 μmol/L; DB: 17.1 μmol/L; ALT: 13 U/L; AST: 56 U/L; ALP: 171 U/L; CRP (hs): 25.71 mg/L; K+: 4.11 mmol/L C_{2h} of bedaquiline: 2.7 μg/mL	NR	/
May 25th	C_{trough} of contezolid: 1.82 μg/mL	NR	/
May 29th	WBC: 4.1×10^9/L; RBC: 2.26×10^{12}/L; Hgb: 77 g/L; PLT: 125 ×10^9/L; Scr: 159.5 μmol/L; BUN: 11.44 mmol/L; TB: 16.6 μmol/L; DB: 9.7 μmol/L; ALT: 11 U/L; AST: 49 U/L; ALP: 166 U/L; CRP (hs): 20.75 mg/L; K+: 3.77 mmol/L	NR	Discontinue: contezolid.
May 30th	NR	NR	The patient was discharged. Continue anti-MDR-TB treatment and receive weekly tests of the blood, liver and kidney functions.
1 week after discharge (June 7th)	Hgb: 78 g/L; PLT: 100 ×10^9/L; Scr: 160 μmol/L; BUN: 9.41 mmol/L; TB: 20.1μmol/L; DB: 14.17 μmol/L; ALT: 8 U/L; AST: 43 U/L; ALP: 115 U/L; K+: 2.78 mmol/L	NR	/

(*Continued*)

Table 1 (Continued).

Time	Laboratory Profile	Imaging Examination	Treatment
2 weeks after discharge (June 14th)	Hgb: 73 g/L; PLT: 78 $\times10^9$/L; Scr: 153 μmol/L; BUN: 10.64 mmol/L; TB: 16.7 μmol/L; DB: 11.92 μmol/L; ALT: 9 U/L; AST: 34 U/L; ALP: 117 U/L; K+: 3.35 mmol/L	NR	/
3 weeks after discharge (June 19th)	WBC: 8.1×10^9/L; RBC: 2.39×10^{12}/L; Hgb: 83 g/L; PLT: 92 $\times10^9$/L;	NR	/
Second admission (June 20th)	WBC: 5.9×109/L; RBC: 2.32×1012/L; Hgb: 79 g/L; PLT: 101 ×109/L; Scr: 145.7 μmol/L; BUN: 8.7 mmol/L; TB: 21.0 μmol/L; DB: 12.8 μmol/L; ALT: 15 U/L; AST: 42 U/L; ALP: 142 U/L; CRP (hs): 51.62 mg/L; K+: 3.18 mmol/L	CT: Bilateral pulmonary tuberculosis accompanied by intrapulmonary spread, and was more serious than the previous test results; Pleural effusion increased on both sides.	furosemide (20 mg, qd, iv.), valsartan (80 mg, qd, po.), atorvastatin (20 mg, qN, po.), potassium chloride (0.5g, tid, po.), Suspend: anti-TB treatment regimen.
July 10th	WBC: 4.6×10^9/L; RBC: 2.3×10^{12}/L; Hgb: 80 g/L; PLT: 91 $\times10^9$/L; Scr: 193.1 μmol/L; BUN: 12.4 mmol/L; TB: 15.5 μmol/L; DB: 9.7 μmol/L; ALT: 23 U/L; AST: 32 U/L; ALP: 141 U/L; CRP (hs): 30.86 mg/L; K+: 4.6 mmol/L	NR	Adding: folic acid (5mg, qd, po.), enteral nutrition emulsion (200mL, bid, po.).
July 26th	WBC: 4.2×10^9/L; RBC: 2.31×10^{12}/L; Hgb: 80 g/L; PLT: 103 ×10^9/L; Scr: 154.1 μmol/L; BUN: 11.04 mmol/L; TB: 10.1 μmol/L; DB: 6.7 μmol/L; ALT: 23 U/L; AST: 27 U/L; ALP: 165 U/L; CRP (hs): 26.54 mg/L; K+: 2.29 mmol/L	CT: Bilateral pulmonary tuberculosis accompanied by intrapulmonary spread; Pleural effusion on both sides, more obvious absorption than before	Adding anti-TB treatment, including: contezolid (400 mg, q12h, po.), moxifloxacin (400mg, qd, po.), cycloserine (0.25g, q12h, po.) Adding: Iron proteinsuccinylate oral solution (40mg, bid, po.), vitamin B6 (10mg, tid, po.), bicyclol (25mg, tid, po.)
August 3rd	C_{trough} of contezolid: 1.27 μg/mL C_{2h} of contezolid: 3.88 μg/mL C_{4h} of contezolid: 6.32 μg/mL C_{6h} of contezolid: 8.99 μg/mL C_{10h} of contezolid: 3.14 μg/mL	NR	/
August 23rd	NR	CT: Bilateral pulmonary tuberculosis accompanied by intrapulmonary spread, was similar to before; Right pleural effusion, more obvious absorption than before.	The patient was discharged. Continue anti-MDR-TB treatment
2-month after discharge (October 20th)	WBC: 5.5×10^9/L; RBC: 2.26×10^{12}/L; Hgb: 78 g/L; PLT: 97 ×10^9/L; Scr: 229.1 μmol/L; BUN: 16.03mmol/L; TB: 12.0 μmol/L; DB: 8.4 μmol/L; ALT: 5 U/L; AST: 22 U/L.	CT: Bilateral pulmonary tuberculosis accompanied by intrapulmonary spread, obviously absorbed than before; Right pleural effusion, more obvious absorption than before.	/
3-month after discharge (December 6th)	WBC: 3.8×10^9/L; RBC: 2.38×10^{12}/L; Hgb: 83 g/L; PLT: 113 ×10^9/L; Scr: 190.8 μmol/L; BUN: 12.78 mmol/L; TB:5.6 μmol/L; DB: 3.7 μmol/L; ALT: 5 U/L; AST: 26 U/L.	CT: Bilateral pulmonary tuberculosis accompanied by intrapulmonary spread, was similar to before; The pleural effusion was almost completely absorbed.	/
6-month after discharge (February 10th of 2024)	WBC: 4.7×10^9/L; RBC: 2.44×10^{12}/L; Hgb: 86 g/L; PLT: 110 ×10^9/L; Scr: 142.7 μmol/L; BUN: 13.2 mmol/L; TB:6.8 μmol/L; DB: 1.5 μmol/L; ALT: 6 U/L; AST: 25 U/L.	CT: Bilateral pulmonary tuberculosis accompanied by intrapulmonary spread, was similar to before.	/

Abbreviations: WBC, white blood-cell counts; RBC, red blood-cell counts; Hgb, hemoglobin; PLT, platelet; Scr, serum creatinine concentration; BUN, serum urea nitrogen level; TB, total bilirubin; DB, direct bilirubin; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; CRP, C-reactive protein; K+, serum K+ concentration; CT, computer tomography; C_{trough}, trough concentration; NGS, next generation sequencing; Xpert MTB/RIF, detection of Mycobacterium tuberculosis and rifampicin resistance.

antibacterial activity in the treatment of tuberculosis, especially drug-resistant tuberculosis. Current domestic and foreign research results show that it has similar anti-tuberculosis activity to linezolid in vivo, animals and patients, and more importantly, it has a lower incidence of adverse reactions such as hematologic toxicity, neurotoxicity, and lactic acidosis than linezolid in the long-term application process.[13,14] Currently, very few cases have been reported about contezolid for

the treatment of TB; however, the published two cases all reported the potential clinical value of contezolid in the treatment of TB. Kang et al reported the case of an 87-year-old female patient, during the treatment of TB pleurisy, she occured thrombocytopenia and gastrointestinal hemorrhage induced by isoniazid, as well as thrombocytopenia induced by linezolid, so the drugs were switched to CZD and cycloserine, after 4 weeks treatment, the patients' bilateral pleural effusions had significantly reduced, the body temperature were fluctuated in the normal range, and a gradual increase in platelets from 68×10^9/L to 324×10^9/L, and no significant adverse reactions were observed during the treatment with CZD.[15] The study conducted by Guo et al also confirmed the therapeutic efficacy of CZD in treating TB meningitis. In this case, the treatment was switched to CZD (800 mg, twice a day) from linezolid due to numbness in the feet and low WBC counts. Following the change in medication, the patient's condition stabilized without symptoms such as fever and headache. Furthermore, the WBC counts returned to normal, and the numbness in the feet was relieved.[16]

The results reported in our study were similar to those in above literature. The manufacturer's instructions of CZD suggested that the dosage of CZD (800mg, twice a day) does not need to be adjusted for older patients (65–75 years old), patients with mild renal insufficiency, and patients with mild-to-moderate hepatic insufficiency.[10] However, considering the patient in this study was 90 years old and had comorbid CKD, the clinician prescribed CZD empirically 400 mg, twice a day. After 2 weeks of treatment, his body temperature recovered to normal, with alleviated cough and expectoration, and no weakness in the limbs. Moreover, the result of sputum culture for Mtb was negative, and the patient's condition was subsequently stabilized.

Meanwhile, considering the patient was older, with chronic comorbidities including hypertension, CAD 3 period, and CKD, as well as the existence of high-risk factors including low platelet counts and low hemoglobin levels, CZD was chosen directly for treatment since the fewer adverse effects instead of linezolid. During the treatment of CZD, the patient's PLT and WBC levels fluctuated within normal ranges, but the Hgb level decreased significantly. Clinicians thought this situation might be related to CZD, so it was discontinued. The decreased Hgb level may be caused by (1) the patient has a poor appetite, nutrient intake was reduced, resulting in a corresponding decrease of hemoglobin synthesis; (2) the patient has renal insufficiency (with increased creatinine and decreased renal function), which was associated with insufficient secretion of erythropoietin; (3) The effects of other drugs.[17–19] Moreover, the CZD treatment was later continued again for 1 month, during which the Hgb level remained stable. Therefore, CZD may be not the direct cause of the decreased Hgb level in the patient. These results were similar to what has been reported in the prior studies.[15,20] A pooled analysis of clinical studies on the treatment of phase II and phase III complicated skin and soft tissue infections with CZD showed that the risk of thrombocytopenia was significantly lower in the contezolid-treated group than in the linezolid-treated group, and the difference was more pronounced in patients treated for ≥11 days.[20] However, since our patient had not previously received linezolid treatment and had CKD and other underlying diseases, CZD cannot definitively be deemed to have had less adverse impacts on hematologic system than linezolid. Therefore, clinical observational studies with more patients must be conducted.

CZD is absorbed rapidly after oral administration, and reaches its peak concentration about 2.5 h. It is widely distributed in the body after oral administration in healthy subjects, and the plasma protein binding rate is about 90%. CZD is mainly metabolized as an oxidative ring-opening dihydropyridine metabolite (M2), and currently the metabolic mechanism of CZD in vivo has not been fully understood.[13] This study firstly reported the changes of CZD concentration on pre-dose (trough concentration level) and 2, 4, 6, and 10 hours post-dose in elderly patients with TB and renal insufficiency. Guo et al[16] reported that the blood CZD concentrations at 7 hours post-administration were 9.64 μg/mL and 9.36 μg/mL at weeks 7 and 11 of CZD treatment (800mg, twice a day), respectively. In the present study, the blood CZD concentration of the patient was 8.99 μg/mL at 6 hours post-administration after 1 week of CZD continuous treatment, which is similar to the findings of Guo et al. However, considering that CZD was administered at a dose of 400 mg, twice a day in this study, future studies were needed to further validate the PK profile of CZD administrated at different doses.

In conclusion, this study demonstrated the therapeutic efficacy and safety of CZD in treating MDR-TB and analyzed the changes in its PK characteristics in elderly patients with renal insufficiency. For patients who cannot tolerate the adverse effects of linezolid, who must be treated for a long period, or who have comorbid underlying diseases and/or

mixed infections that require the administration of multiple drugs, more rigorously designed prospective and real-world studies should be conducted to further clarify the application value of CZD in drug-resistant TB.

Conclusion

This case study demonstrated the therapeutic efficacy and safety of contezolid in the treatment of MDR-TB and evaluated its PK characteristics in elderly patients with renal insufficiency to provide a reference for the clinical application of contezolid. Further prospective PK studies are needed to confirm our findings and provide information for clinical management.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author Jinmeng Li on reasonable request.

Ethics Approval and Consent to Participate

This study was supported by the Ethics Committee of Hangzhou Red Cross Hospital (No.: 2023YS017) and was carried out in accordance with the ethical standards of the Declaration of Helsinki.

Consent for Publication

Written and informed consent was obtained from the patient and the Hangzhou Red Cross Hospital for publication of this Case Report and any accompanying images.

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Disclosure

The authors report no conflicts of interest in this work.

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