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CASE SERIES

Contezolid for the Treatment of Drug-Resistant Tuberculosis in China: A Clinical Case Series

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Background: Linezolid (LZD) is a cornerstone medication in the treatment of drug-resistant tuberculosis (DR-TB). However, it frequently triggers adverse effects such as bone marrow suppression, optic neuropathy, and peripheral neuropathy, all of which can impact treatment outcomes and prognosis. Contezolid (CZD), a novel oxazolidinone antibiotic, exhibits comparable antimicrobial efficacy against Mycobacterium tuberculosis as LZD, but with potentially enhanced safety profiles.

Case Presentation: This report presents five cases (Cases 1–5) of LZD intolerance, wherein CZD served as an effective alternative treatment. In Cases 1–3, LZD administration resulted in bone marrow suppression, primarily manifested as anemia. Transitioning to CZD therapy led to a rise and stabilization of hemoglobin (HGB) levels in Cases 1–2, and a return to baseline values in Case 3. In Case 4, CZD treatment alleviated symptoms of LZD-induced peripheral neuritis, although complete resolution was not achieved, hinting at potential irreversibility of this type of peripheral neuropathy. In Case 5, direct CZD anti-TB therapy was initiated for recurrent leukopenia and neutropenia, resulting in no further severe myelosuppression and successful recovery.

Conclusion: These case studies suggest that CZD could represent an effective and safe option for anti-TB therapy, especially for patients intolerant to LZD.

Keywords: contezolid, linezolid, drug-resistant tuberculosis, myelosuppression, peripheral neuropathy

Introduction

The 2023 World Health Organization (WHO) report indicates that tuberculosis (TB) remains a global public health threat.[1] Compared with those of drug-sensitive TB, treatment regimens for drug-resistant tuberculosis (DR-TB) are characterized by longer durations, heavier economic burdens, and increased drug toxicity, leading to a higher likelihood of severe adverse events and poorer treatment outcomes.[2]

LZD, the initial oxazolidinone antibiotic used to treat DR-TB, still demonstrates effective activity against drug-resistant *M. tuberculosiss* both in vitro and in vivo.[3,4] However, reports indicate a heightened incidence of adverse events (AEs) among DR-TB patients receiving LZD treatment, with peripheral neuropathy being the most prevalent, affecting approximately 81%, followed by bone marrow suppression at a rate of around 48%. Among these cases, 37% experience varying degrees of anemia.[5] A prospective study also indicated that the cumulative incidence rates of anemia and peripheral neuropathy events within 6 months of LZD use were 39% (95% confidence interval [CI], 31–47) and 20% (95% CI 14–27), respectively.[6] These AEs are believed to be associated with LZD's ability to bind to human mitochondrial 16S rRNA, sharing a homologous target site with *M. tuberculosiss*.[7] Prolonged use of the treatment may increase the occurrence of AEs, which can limit its effectiveness due to toxic effects.

CZD is a novel oxazolidinone antibiotic drug that has been approved by the China State Drug Administration for the treatment of complex skin and soft tissue infections.[8,9] Animal experiments indicate that the minimum inhibitory

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concentration (MIC) range of CZD against *M. tuberculosiss* (0.25–1.0 μg/mL) is similar to that of LZD (0.25–1.0 μg/mL), suggesting comparable activity against tuberculosis between CZD and LZD.[10] CZD functions by preventing the formation of the functional 70S initiation complex necessary for bacterial replication.[8] CZD makes modifications to the structure of LZD, addressing concerns related to bone marrow suppression and MAO inhibition associated with LZD. This adjustment significantly reduces the potential for these AEs, thereby enhancing its safety profile.[11] Additionally, animal experiments indicate that CZD could potentially replace LZD in regimens containing bedaquiline and pretomanid, as well as in other anti-TB regimens.[12] Therefore, In China, CZD has begun to be used experimentally for the treatment of tuberculosis. Several case reports have demonstrated successful treatment outcomes with CZD in patients with TB who are intolerant to LZD, with no significant occurrences of myelosuppression or peripheral neuropathy.[13–15] However, detailed case reports in patients with DR-TB are currently lacking.

Here, we present 5 cases of drug-resistant tuberculosis where CZD was prescribed as an alternative treatment due to AEs associated with LZD. Additionally, we provide detailed descriptions of the changes in Hemoglobin (HGB), White Blood Cell (WBC), Neutrophil (NEUT), and symptoms of peripheral nerve inflammation observed during the patients' treatment. Our cases serve as a reference for considering CZD as an alternative therapy for DR-TB patients intolerant to LZD.

Case 1

A 52-year-old female with a history of pulmonary tuberculosis for over 6 months underwent standard isoniazid/rifampicin/pyrazinamide/ethambutol (HRZE) treatment (Supplementary Table 1). However, her pulmonary lesion absorption remained unsatisfactory. On July 12, 2022, testing was performed using Middlebrook 7H9 liquid medium in the BACTEC MGIT 960 culture detection system (Becton, Dickinson and Company, USA). The *M. tuberculosis* sputum cultures and drug susceptibility testing (DST) revealed resistance to H/R/E/levofloxacin (LFX)/moxifloxacin (MFX)/amikacin (AM)/streptomycin (S)/kanamycin (CM), diagnosing the patient with pre-extensively drug-resistant tuberculosis (pre-XDR TB). According to the 2019 "Comprehensive Guide for Drug-Resistant Tuberculosis", the prescribed treatment regimen included Bedaquiline (BDQ), LZD, Clofazimine (CFZ), Cycloserine (CS), Prothionamide (PTO), and Pyrazinamide (Z).[16] On 16th September, the patient presented to our department with symptoms of cough, sputum production, chest tightness, fever, and fatigue for one week. Upon admission, her WBC count was 5.74×10^9/L, with a NEUT ratio of 77.2%, red blood cell(RBC) count was 2.63×10^{12}/L, HGB was 73g/L, platelet(PLT) count was 254×10^9/L, C-reactive protein(CRP) level of 14.22 mg/L, and normal procalcitonin(PCT) levels (<0.040 ng/mL). The patient received antimicrobial therapy with piperacillin and tazobactam sodium injections at 4.5 g q8h during TB treatment. On the evening of September 19, she developed a high fever of 40°C and transient confusion. Further investigations revealed severe anemia (HGB, 56 g/L; RBC, 1.95×10^9/L; Reticulocyte (RET), 4×10^9/L) and an elevated PCT level of 0.42 ng/mL. A chest computed tomography (CT) scan indicated worsened lesions, suggesting a possible TB-complicated bacterial infection. We have ruled out anemia caused by chronic diseases or other reasons. Severe anemia was considered to be related to the anti-TB medication (LZD), which led to discontinuation of LZD. The patient received a blood transfusion and supportive therapy to correct anemia, and Meropenem 1.0 g q8h was initiated as antimicrobial therapy. After 6 days, her anemia improved, with HGB rising to 94g/L. The LZD dosage was reduced to 0.3 g once daily. However, the patient continued to experience fatigue, and routine blood tests revealed moderate anemia during this period. On November 18, 2022, CZD was initiated as continuous treatment. A follow-up blood test on January 4, 2023, showed an HGB of 94 g/L, indicating gradual improvement in anemia symptoms. The patient's HGB and RET gradually increased and remained above 100 g/L from May 25, 2023 (Figure 1) (Supplementary Figure 1). Regular chest CT scans were conducted to monitor treatment efficacy (Figure 2), revealing increased absorption of lesions compared to earlier scans. Over the past six months, chest CT scans indicated that pulmonary lesions remained largely stable, however, structural damage had occurred in the lungs, such as partial lesion destruction and cavitation shadows, which were irreversible and unabsorbable. Furthermore, five consecutive sputum Mycobacterium cultures returned negative results, indicating a favorable treatment response.

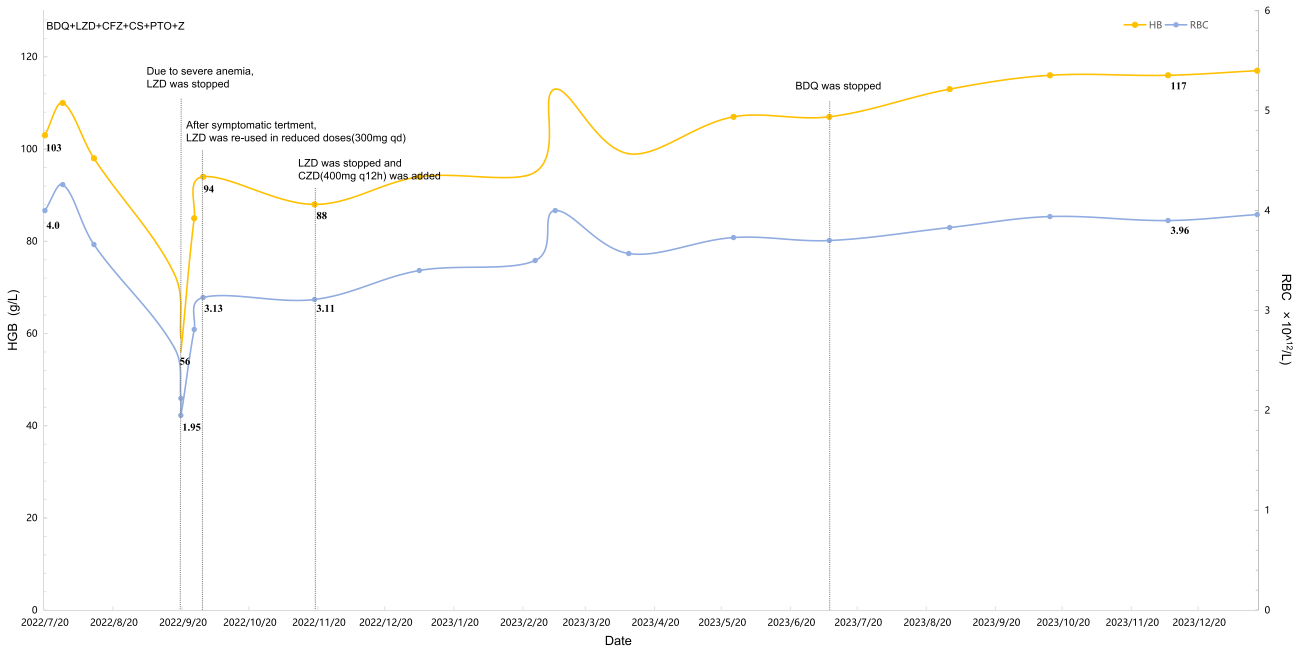

Figure 1 Case1: Changes in blood routine-related indices throughout treatment.

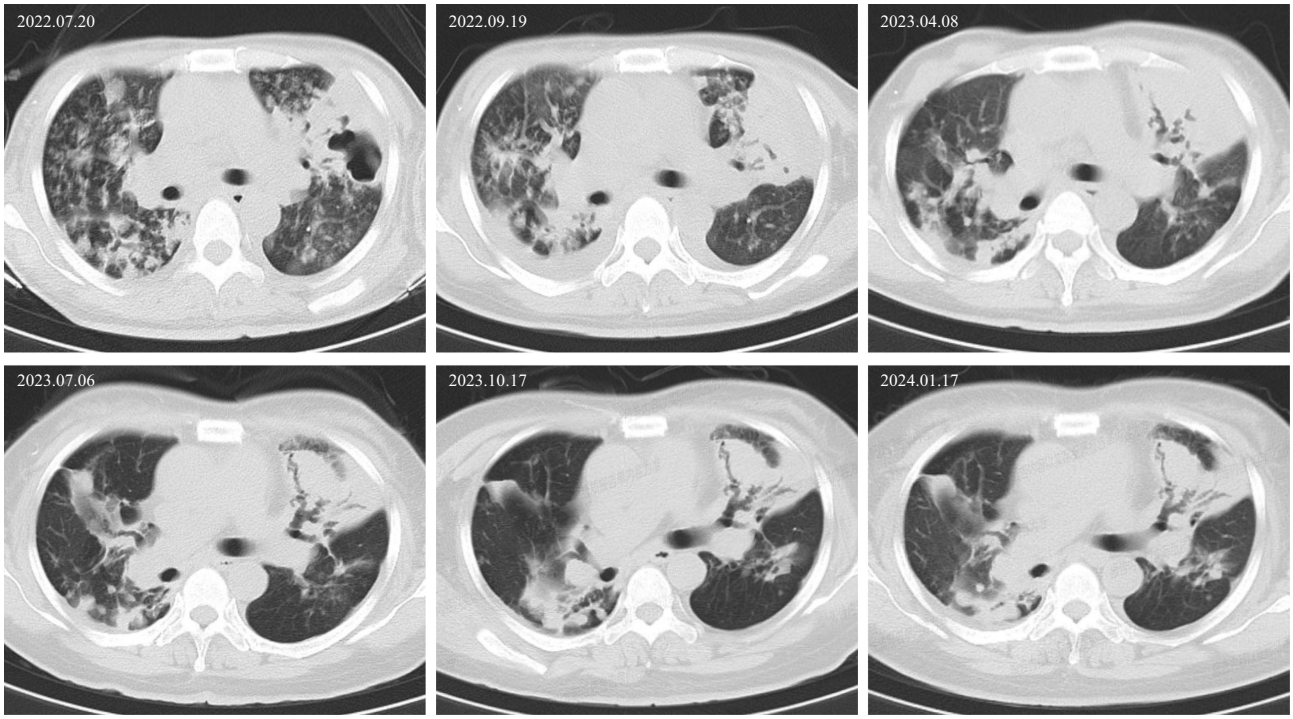

Figure 2 Case 1: The dynamic changes in computed tomography scans of the patient following corresponding treatment. Starting from July 6, 2023, the lesions began to stabilize.

Case 2

A 43-year-old woman presented with a history of recurrent cough and sputum for over a year and intermittent fever for the past two months. A chest CT revealed destruction of the left lung, lesions in the right lung with bilateral pleural effusion, and detection of *M. tuberculosis* by sputum smear. The patient received HRZE treatment for 10 days; however, intermittent fever persisted. On 26th September 2022, the sputum culture results indicated positivity for *M. tuberculosis*, intermediate susceptibility to Lfx, and resistance to H/R/Mfx, resulting in a diagnosis of pre-XDR-TB. Blood routine showed that HGB was 97g/L, and RBC count was $3.24*10^{12}$/L.

Due to economic reasons, the use of BDQ was declined. Considering that this is a new case of TB in which LFX was not previously administered, the following treatment regimen was established on 8th October: LFX-LZD-CFZ-CS-Z-AM. The patient revisited our department on December 28 due to chest tightness and palpitations lasting a week. Her HGB level was 82 g/L, blood potassium was 3.12 mmol/L, and electrocardiography revealed frequent premature ventricular beats and prolonged QTc (corrected for heart rate: QTcF 491ms). We have ruled out anemia caused by chronic diseases or other reasons. We considered that the anemia was related to LZD, which led to its discontinuation. The patient received potassium supplementation, nutritional support, and symptomatic treatment for myocardial function. On 18th January 2023, a follow-up electrocardiogram revealed a normalized QTcF of 416ms. On 10th January, the anti-TB treatment was adjusted to CZD. AM therapy was discontinued after 36 weeks, and BDQ was added on September 8th. Regular blood testing showed a gradual increase in HGB levels from 82g/L on December 29, 2022, to over 100g/L on January 29, 2024, with the highest level recorded as 111g/L on November 27, 2023 (Figure 3). Follow-up chest CT showed improvement and stabilization of the lesions. Three consecutive sputum cultures yielded negative results. The patient experienced significant improvement in palpitations and chest tightness, indicating the effectiveness of the treatment.

Case 3

The patient, a 44-year-old woman with a 25-year history of drug-resistant tuberculosis (DR-TB), had been irregularly taking medication, including intermittent use of MFX and other drugs. On August 23, 2022, she experienced worsening cough and sputum symptoms. *M. tuberculosis* sputum cultures and DST indicated resistance to H/R/LFX/MFX/Streptomy(S) and intermediate resistance to E, suggestive of pre-XDR-TB. Routine blood examinations revealed moderate anemia (Hemoglobin, 88 g/L), and chest CT revealed bilateral TB lesions, bronchiectasis, cavities, and destruction of the left lung. The patient was initiated on the following treatment regimen: BDQ-LZD-CFZ-CS-PA (Pasiniazid). Due to severe anemia (HGB 56g/L, RET 42× 10^9/L) on March 27, 2023, LZD therapy was promptly discontinued. With blood transfusions and supportive nutritional therapy, the Hemoglobin rose to 68 g/L by April 5, 2023. We have ruled out anemia caused by chronic diseases or other reasons. Therefore, we attribute the anemia to LZD-induced hematologic toxicity. As a result, the patient's treatment regimen was adjusted to CZD. By November 1, 2023, the HGB had risen to 102 g/L (Figure 4). Six consecutive negative sputum cultures and improvement and stabilization of chest CT lesions suggested the effectiveness of the treatment.

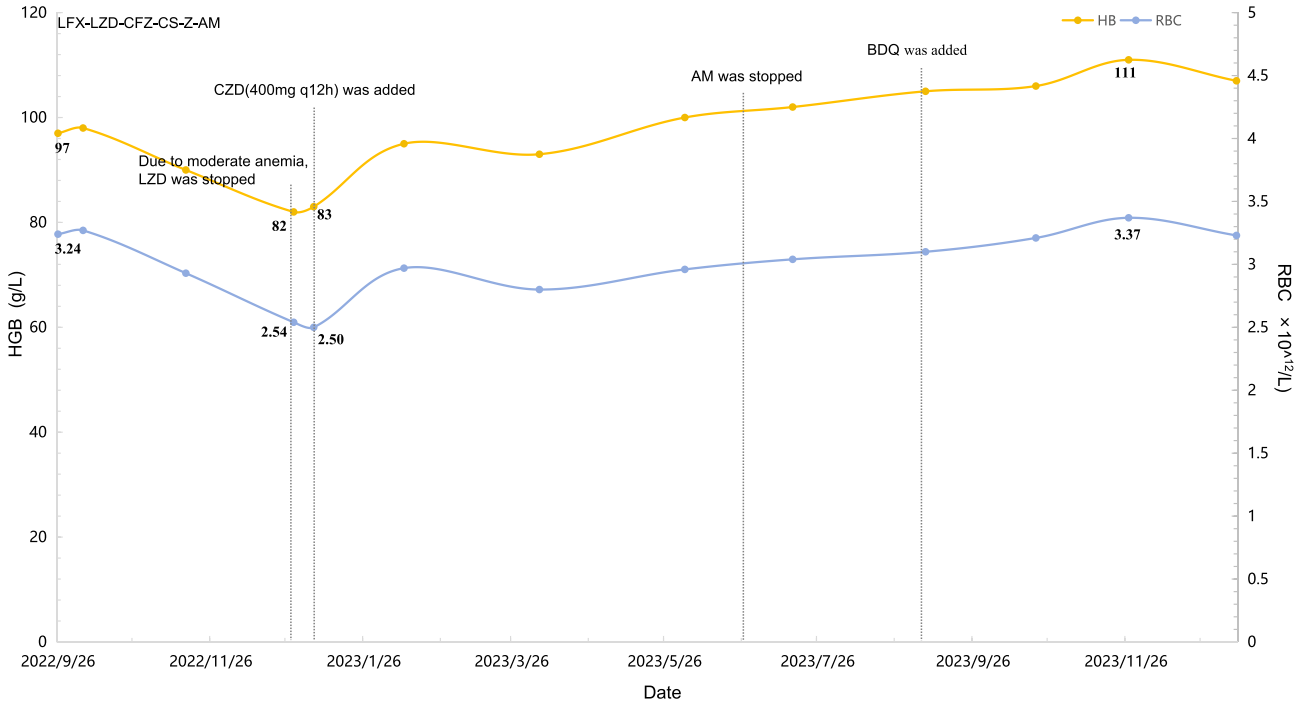

Figure 3 Case 2: Changes in blood routine-related indices throughout the treatment.

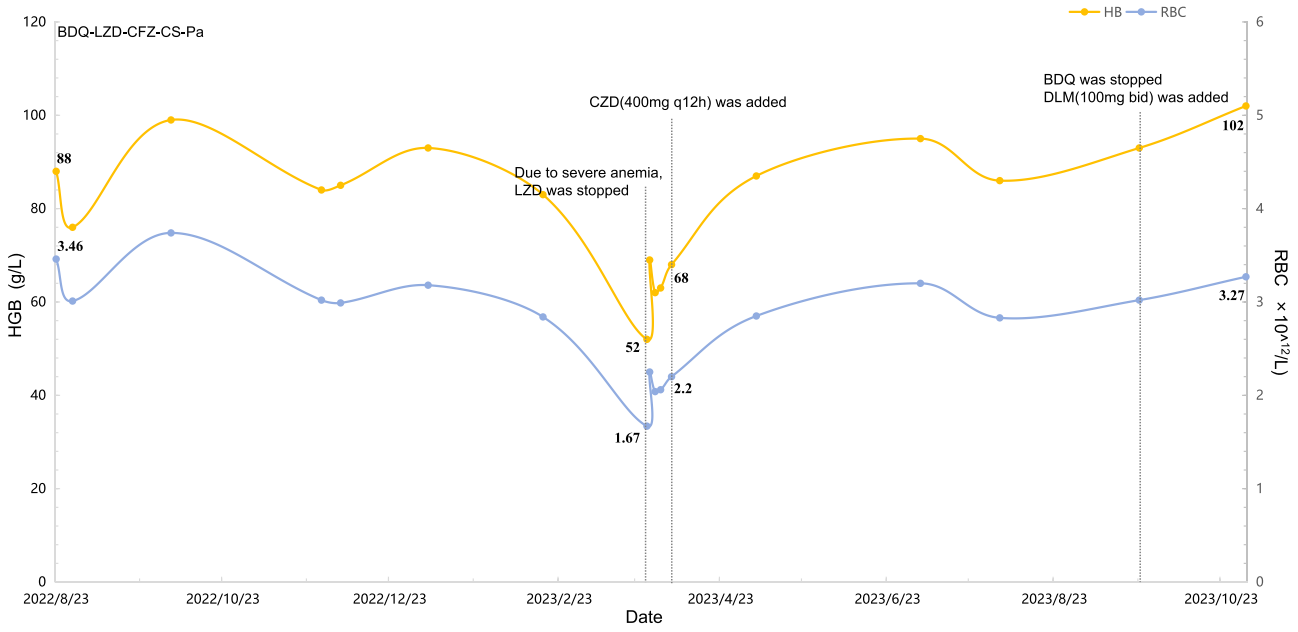

Figure 4 Case 3: Changes in blood routine-related indices throughout treatment.

Case 4

On August 19, 2021, a 16-year-old boy presented to our department with a one-year history of recurrent cough and sputum. Tracheal endoscopy biopsy revealed extensive caseous necrosis, with acid-fast staining positive. The patient was diagnosed with rifampicin-resistant tuberculosis (RR-TB) based on the culture of *M. tuberculosis* from sputum and lavage fluid, along with DST. A treatment regimen consisting of LFX-LZD-CFZ-CS-PTO (prothionamide) was established on August 28, along with localized treatment through multiple bronchoscopies. On January 25, 2022, the patient reported abnormalities including altered sensation, numbness, and decreased perception in both lower limbs. Consequently, the LZD dosage was adjusted to 0.3 g once daily. By March 5, increased discomfort in both lower limbs and tingling sensations in both feet prompted a neurological consultation, which suggested drug-induced peripheral neuritis. This led to the discontinuation of H and LZD and the addition of nutritional nerve medications (vitamin B12, vitamin B1, and vitamin B6). LFX was ceased on May 17 due to Achilles tendonitis. Following some improvement in peripheral neuritis, LZD and H were reintroduced. However, on September 3, the patient's symptoms of pain in both lower extremities had worsened, hindering normal walking. Consequently, LZD was replaced with CZD in the anti-TB regimen. Although the patient's lower limb pain gradually improved, numbness and decreased perception persisted. The symptoms of peripheral neuritis did not completely resolve. After over a year of treatment, sputum cultures returned negative results on more than six occasions throughout the treatment period. The patient was considered cured on February 23, 2023 (Figure 5).

Case 5

A 48-year-old woman with a 7-year history of Sjogren's syndrome was diagnosed with pulmonary and bronchial TB in 2021 based on the culture of *M. tuberculosis* in BALF and pathologic examination of bronchial biopsy. She was initially treated with HRE-Mfx for TB; however, the medication was discontinued several times due to recurrent leukopenia and hypokalemia. The patient has no other discomfort symptoms, and a thorough series of tests have ruled out other causes of leukocyte reduction such as tuberculosis bone marrow infiltration. On September 11, the treatment was switched to HP(rifapentine)E. Subsequently, on September 17, due to persistent leukopenia, the treatment was further modified to Mfx-Cs-E. Following culturing and DST of BALF for *M. tuberculosis*, resistance to H/R/Sm was identified, leading to the diagnosis of MDR-TB. Considering the patient's recurrent leukopenia and neutropenia, we took into account the potential adverse effects of LZD-induced myelosuppression, which could exacerbate the decline in leukocyte and granulocyte counts. Consequently, we opted for CZD therapy directly, formulating the treatment regimen as LFX-CFZ-CS-AM-CZD. AM treatment was halted after 22 weeks due to challenges with injectable medications. Remarkably, the patient's WBC and neutrophil counts showed no further decline throughout nearly two years of treatment, remaining

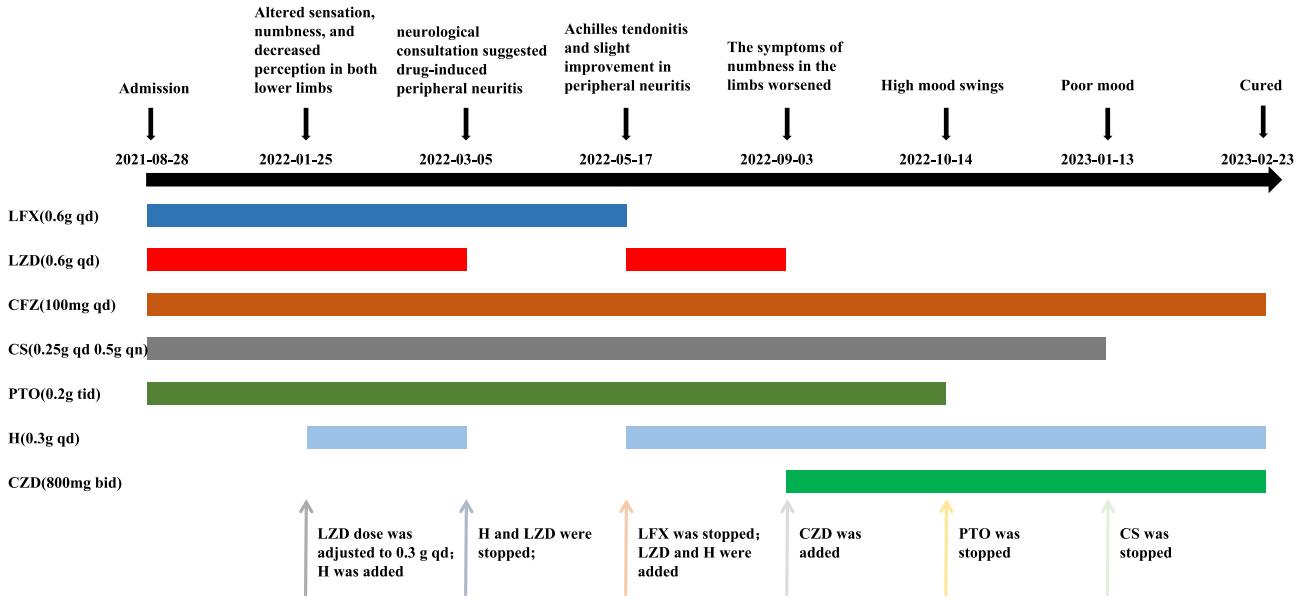

Figure 5 Case 4: DR-TB treatment regimen used in patient and correlated with side effects and interventions.

stable at 2–3*10^9/L for WBC and above 1.0*10^9/L for neutrophils, with HGB consistently maintained above 80g/L, and at the time of discontinuation, HGB level was recorded at 117g/L (Figure 6). Additionally, the patient achieved eight consecutive negative sputum cultures and was declared cured on January 11, 2023.

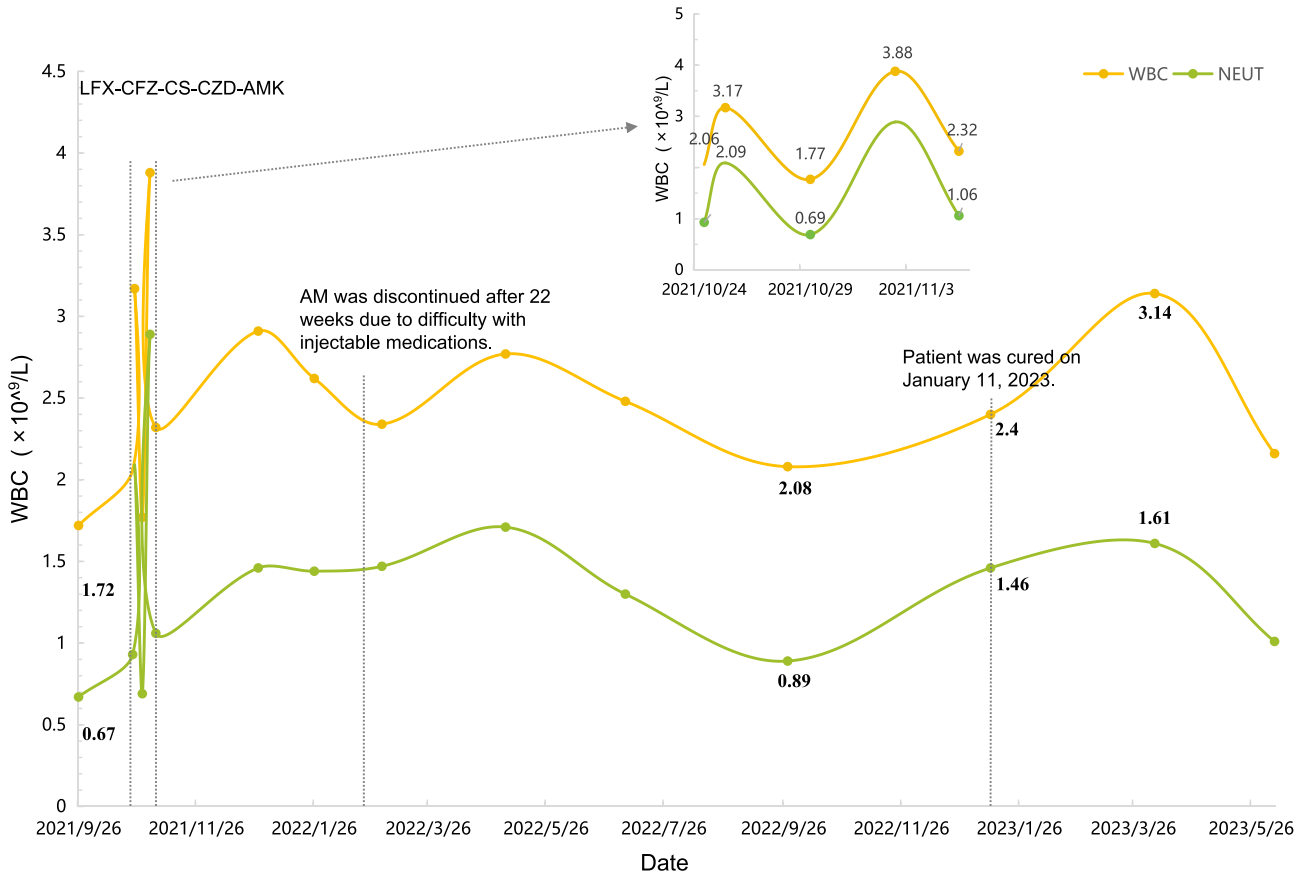

Figure 6 Case 5: Changes in blood routine-related indices throughout treatment.

Discussion

The persistent transmission of DR-TB remains a formidable challenge to global tuberculosis prevention and control efforts. Presently, treatment protocols for DR-TB are inadequate, with sluggish progress in developing new drugs.[17] The global success rate in treating DR-TB stands at a mere 60%.[1] Hence, there is an urgent call for the development of new, effective, and safe drugs to combat this disease. CZD is a novel oxazolidinone antibiotic drug with activity similar to that of LZD against *M. tuberculosis*. Importantly, by adjusting its molecular structure, CZD manages to circumvent AEs such as myelosuppression and MAO inhibition.[11] Preclinical and clinical studies have indicated that CZD's safety profile may be superior to that of LZD.[10,18] Therefore, CZD emerges as a promising alternative treatment for patients intolerant to LZD.

Prolonged treatment with LZD in Cases 1–3 resulted in intolerable bone marrow suppression. Severe anemia developed after 2 and 6 months of LZD use in Cases 1 and 2, respectively. Following the switch to CZD for anti-TB treatment, noticeable improvements in symptoms were observed. HGB levels gradually increased and stabilized at approximately 100 g/L. In Case 3, the patient experienced moderate anemia after 3 months of LZD use. Upon transitioning to CZD, HGB levels gradually returned to initial values. Furthermore, the treatment outcomes for these three patients were satisfactory. These cases underscore the importance of promptly discontinuing LZD and switching to CZD when patients develop LZD-related anemia. In DR-TB patients with anemia, direct consideration of CZD over LZD may be warranted. This is similar to the effect on HGB observed in Wang et al's study.[19] However, in cases 1–3 and 5, we observe that the effects of LZD and CZD on PLT do not appear to be significantly different. Additionally, we documented changes in patient WBC and NEUT counts, along with improvements in peripheral neuropathy symptoms.

After 5 months of LZD use, Case 4 developed peripheral neuropathy. Despite halving the LZD dosage, there was persistent worsening of numbness in both lower limbs. Following the switch to CZD treatment, there was some improvement in peripheral neuropathy symptoms, but complete relief was not achieved, indicating that LZD-induced peripheral neuropathy may be irreversible. Importantly, CZD-containing treatment regimens do not exacerbate peripheral neuritis. Given the irreversible nature of peripheral neuropathy, clinicians should promptly consider transitioning to CZD as an alternative treatment when mild LZD-related peripheral neuropathy occurs. In Case 5, the patient underwent direct CZD anti-TB therapy for recurrent leukopenia and neutropenia. Throughout the treatment, leukocyte and neutrophil levels did not significantly decrease, and the patient achieved a cure. This suggests that CZD is also safe and effective in DR-TB patients with leukopenia and neutropenia.

The study suggests that oral CZD may offer better safety and satisfactory antimicrobial activity compared to LZD in the treatment of DR-TB. Based on relevant research, CZD could potentially serve as a replacement for LZD within the treatment regimen for DR-TB.[19,20] However, since the DR-TB treatment regimen also included other anti-TB drugs, the efficacy of CZD treatment alone could not be accurately assessed. Moreover, the present study only investigated five cases. Large-scale randomized controlled trials are still required to validate the effectiveness and safety of CZD in treating drug-resistant pulmonary TB.

Conclusion

The study reported 5 cases of DR-TB where treatment was switched to CZD due to AEs related to LZD (anemia, leukopenia, and peripheral neuropathy) during the initial treatment. The adjustment of treatment medications led to positive clinical outcomes. This preliminary evidence confirms the safety and efficacy of CZD in managing drug-resistant tuberculosis.

Abbreviations

WHO, World Health Organization; DR-TB, drug-resistant tuberculosis; MDR-TB, multi-drug-resistant tuberculosis; RR-TB, rifampicin-resistant tuberculosis; pre-XDR-TB, pre-extensive drug-resistant tuberculosis; LZD, linezolid; CZD, contezolid; AEs, adverse events; BALF, bronchoalveolar lavage fluid; WBC, white blood cell; NEUT, neutrophil; RBC, red blood cell; HGB, hemoglobin; PCT, procalcitonin; AM, amikacin; BDQ, bedaquiline; CFZ, clofazimine; CS, cycloserine; H, isoniazid; LZD, linezolid; LFX, levofloxacin; MFX, moxifloxacin; PTO, prothionamide; R, rifampicin; Z, pyrazinamide; E, ethambutol; S, streptomy; CM, cinkanamycin; PA, Pasiniazid; RET, Reticulocyte.

Data Sharing Statement

All data generated or analyzed were included in this published article.

Ethics Approval Statement

The studies involving human participants were reviewed and approved by Anhui Provincial Chest Hospital (approval no. KJ2024-036). Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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