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Case report

Successful treatment of methicillin-resistant *Staphylococcus aureus* osteomyelitis with combination therapy using linezolid and rifampicin under therapeutic drug monitoring

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ABSTRACT

Linezolid is an effective antibiotic against most gram-positive bacteria including drug-resistant strains such as methicillin-resistant *Staphylococcus aureus*. Although linezolid therapy is known to result in thrombocytopenia, dosage adjustment or therapeutic drug monitoring of linezolid is not generally necessary. In this report, however, we describe the case of a 79-year-old woman with recurrent methicillin-resistant *S. aureus* osteomyelitis that was successfully treated via surgery and combination therapy using linezolid and rifampicin under therapeutic drug monitoring for maintaining an appropriate serum linezolid concentration. The patient underwent surgery for the removal of the artificial left knee joint and placement of vancomycin-impregnated bone cement beads against methicillin-resistant *S. aureus* after total left knee implant arthroplasty for osteoarthritis. We also initiated linezolid administration at a conventional dose of 600 mg/h at 12-h intervals, but reduced it to 300 mg/h at 12-h intervals on day 9 because of a decrease in platelet count and an increase in serum linezolid trough concentration. However, when the infection exacerbated, we again increased the linezolid dose to 600 mg/h at 12-h intervals and performed combination therapy with rifampicin, considering their synergistic effects and the control of serum linezolid trough concentration via drug interaction. Methicillin-resistant *S. aureus* infection improved without reducing the dose of or discontinuing linezolid. The findings in the present case suggest that therapeutic drug monitoring could be useful for ensuring the therapeutic efficacy and safety of combination therapy even in patients with osteomyelitis who require long-term antibiotic administration.

1. Introduction

Linezolid is an antibiotic classified as an oxazolidinone and is effective against most gram-positive bacteria including drug-resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci, vancomycin-resistant *S. aureus*, and vancomycin-resistant enterococci [1,2]. However, linezolid is known to cause thrombocytopenia, particularly when used for more than 2 weeks [3]. Maintenance of a serum linezolid trough concentration (C_{min}) between 2 and 7 μg/mL immediately before each administration has been suggested as a step for improving safety outcomes while retaining appropriate efficacy [4]. A more recent report recommends maintaining C_{min} between 3.6 and 8.2 μg/mL [5].

Combination therapy using rifampicin and agents such as linezolid has been shown to be more effective than monotherapy [1,6]. However, the concomitant use of rifampicin and linezolid may

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result in drug interactions that decrease serum linezolid concentration [2,4] and pose a risk of therapeutic failure [4]. To our knowledge, no previous studies have assessed the efficacy of therapeutic drug monitoring (TDM) in combination therapy using linezolid and rifampicin.

In this report, we document a case of MRSA osteomyelitis successfully treated with combination therapy using linezolid and rifampicin under TDM for appropriate control of serum linezolid concentration.

2. Case report

This study was performed in conformity with the Helsinki Declaration after approval by the Ethical Review Board of University of Toyama (approval number: clinical 24-118), and the patient provided informed consent regarding the publication of medical data. Patient privacy was fully protected and personal information was handled such that patients could not be identified. The patient was a 79-year-old woman who underwent total left knee implant arthroplasty because of osteoarthritis in November 2013. In December 2013, she developed surgical wound infection and MRSA was detected in the effusion from the wound. Antimicrobial therapy against MRSA was performed using vancomycin and daptomycin, but the infection could not be controlled and caused patellar tendon rupture and cutaneous fistula. Despite suturing the patellar tendon, performing continuous perfusion, and maintaining antimicrobial therapy, the discharge of pus from the wound persisted. She was then transferred to the orthopedic department of our hospital for further treatment in May 2014.

On admission day, her vitals were as follows: body temperature, 37.9 °C; blood pressure, 116/69 mmHg; heart rate, 111 bpm; and SpO_2, 97% (room air). She was 140.2 cm tall and weighed 58.5 kg. Her left knee had an open wound and the patella was exposed (Fig. 1). Her laboratory findings (Table 1) were as follows: white blood cells, 8410/μL with 54.5% neutrophils; erythrocytes, 357 × 10^4/μL; hemoglobin, 10.8 g/dL; platelets, 34.2 × 10^4/μL; C-reactive protein, 1.71 mg/dL; serum total protein, 7.0 g/dL; albumin, 2.8 g/dL; lactate dehydrogenase, 181 IU/L; aspartate aminotransferase, 33 IU/L; alanine aminotransferase, 34 IU/L; ɤ-glutamyltransferase, 45 IU/L; blood urea nitrogen, 11 mg/dL; creatinine, 0.4 mg/dL; hemoglobin A1c, 8.2%; and procalcitonin, 0.05 ng/mL.

MRSA was isolated from the effusion on admission, and the patient was diagnosed with MRSA arthritis in the left knee. Minimum inhibitory concentration of anti-microbial agents against MRSA isolate are as follows: vancomycin, 2 mg/L; teicoplanin, ≤2 mg/L; arbekacin, 4 mg/L; linezolid, ≤1 mg/L; daptomycin, >1 mg/L; and rifampicin, ≤1 mg/L. We initiated intravenous drip infusion of linezolid at a conventional dose of 600 mg/h at 12-h intervals. On day 6, she underwent surgery for the removal of the artificial left knee joint, which had been implanted 6 months before, and for the placement of vancomycin-impregnated bone cement beads. MRSA was isolated from both the joint fluid and bone marrow aspirate collected during surgery, and hence, the patient was diagnosed with MRSA osteomyelitis. After initiation of linezolid therapy, we performed TDM to maintain an appropriate linezolid C_{min}. The measurement of serum and wound exudate linezolid concentrations by high-performance liquid chromatography (HPLC) has been described previously [7]. The bulk powder of linezolid for HPLC was provided by Pfizer Inc., and the lower limit of quantification of linezolid using this method was 0.1 μg/mL, with intra-/inter-day precision being below 5.0%. Previous studies have shown a relationship between thrombocytopenia and overexposure to linezolid, as well as between clinical failures and underexposure to linezolid [4]. Maintenance of C_{min} between 2 and 7 μg/mL [4] or between 3.6 and 8.2 μg/mL [5] has been suggested as the target range.

Table 1
Laboratory datas on admission.

Blood index	
WBC	8410/μL
Neutrophils	54.5%
Erythrocytes	357 × 104/μL
Hemoglobin	10.8 g/dL
Platelets	34.2 × 104/μL
CRP	1.71 mg/dL
Total protein	7.0 g/dL
Albumin	2.8 g/dL
LDH	181 IU/L
AST	33 IU/L
ALT	34 IU/L
ɤ-GTP	45 IU/L
BUN	11 mg/dL
Creatinine	0.4 mg/dL
HbA1c	8.2%
Procalcitonin	0.05 ng/mL

WBC, white blood cells; CRP, C-reactive protein; LDH, lactate dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ɤ-GTP, ɤ-glutamyltransferase; BUN, blood urea nitrogen; HbA1c, hemoglobin A1c.

The patient's platelet count decreased to 16.1 × 10^4/μL on day 8, and the measured C_{min} on days 5 and 8 were high at 15.1 and 13.9 μg/mL, respectively. Although intraoperative bleeding might also have caused the decrease in platelet count, we still reduced the linezolid dose to 300 mg/h at 12-h intervals on day 9. On day 15, her C_{min} decreased to 2.2 μg/mL, but she developed a fever (body temperature, 38.3 °C). Linezolid therapy at the decreased dosage was insufficient and could have exacerbated the MRSA infection. Although we considered increasing the linezolid dose to 600 mg/h at 12-h intervals, we feared it might again result in a decrease in platelet count. Therefore, we initiated combination therapy using oral rifampicin (450 mg/day) and intravenous drip infusion of linezolid (600 mg/h at 12-h intervals) on day 16, taking into consideration not only the synergistic effects of this combination but also the control of C_{min} via the drug interaction to decrease the serum linezolid concentration.

After the combination therapy, we could maintain C_{min} within an optimal range of 3.7–7.2 μg/mL (Fig. 2). The patient's fever subsided quickly, and her inflammatory response diminished as the leukocyte count decreased to 5000/μL. The redness of and pus discharge from the wound disappeared, and we discontinued the combination therapy on day 75.

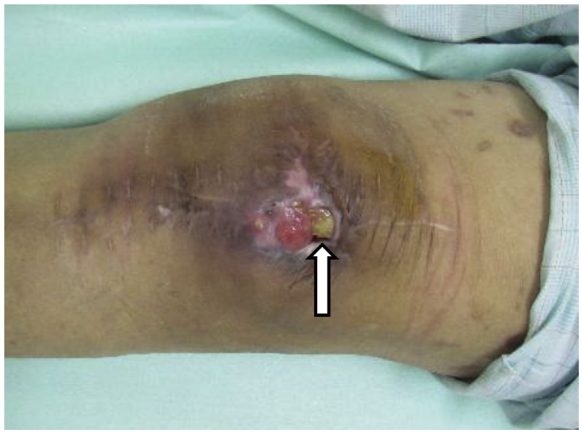

Fig. 1. Photograph acquired on admission shows the left knee with an open wound and exposed patella (white arrow).