References


Successful Treatment of Vancomycin-Resistant Enterococcus Meningitis with Linezolid

R. Hachem, C. Afif, Z. Gokaslan, I. Raad

Enterococcus continues to be an unusual cause of bacterial meningitis, representing only 0.3% of cases of this disease [1]. This organism is associated with a high mortality rate, reaching 33% in one report [2]. Enterococcal meningitis usually occurs in the setting of chronic disease, immunosuppression, trauma or surgery of the central nervous system [3]. In the last few years, vancomycin-resistant enterococci (VRE) have emerged as a serious problem and the cause of various infections for which there are limited therapeutic options. Quinupristin/dalfopristin has been approved by the U.S. Food and Drug Administration for treatment of severe VRE faecium (VREF) infections; however, its penetration into the cerebrospinal fluid (CSF) is limited. We report a case of VREF meningitis in a patient with cancer who was successfully treated with linezolid, an oxazolidinone newly approved for the treatment of infections caused by resistant gram-positive organisms.

On 8 August 1999, a 62-year-old white male diagnosed 2 years earlier with renal cell carcinoma underwent a suboccipital craniectomy with extirpation of a right cerebellar metastatic lesion and placement of a right frontal ventriculostomy for obstructive hydrocephalus. The postoperative course was complicated by a non-Q wave myocardial infarct and Pseudomonas aeruginosa pneumonia that required intubation and broad-spectrum antibiotics. Four days later, the ventriculostomy was removed. The patient had progressive mental status changes and leakage of CSF from the suboccipital craniotomy incision. Upon insertion of a ventriculoperitoneal shunt, a routine CSF culture was performed; microscopic examination of the CSF showed leukocytosis and culture of the CSF yielded enterococci. On August 18, the patient was started on high-dose ampicillin and gentamicin. Two days later,
when the organism was identified as VREF and was isolated from other CSF cultures, intravenous linezolid was started at 600 mg every 12 h as a substitute for ampicillin (Table 1). Gentamicin (5 mg) was administered intraventricularly for two doses. Forty-eight hours after initiation of linezolid therapy, the patient became afebrile, his mental status improved, and the leukocyte count in the CSF decreased from a baseline of 250/mm³ to 8/mm³ (Table 1).

Subsequent CSF cultures were negative on day 5 and day 10 after initiation of therapy with linezolid. The patient’s clinical status progressively improved. Intravenous gentamicin was continued for 5 days. Linezolid was continued for 3 weeks, until the patient expired due to progression of his underlying malignancy, renal failure and gastrointestinal bleeding.

The pharmacokinetics of linezolid in blood and CSF were performed on day 5 of therapy and showed good CSF penetration with a CSF/plasma ratio of 0.8. Plasma levels collected at 5 h and 12 h after infusion were 6.66 μg/ml and 4.7 μg/ml, respectively. Corresponding CSF levels were 5.36 μg/ml and 3.8 μg/ml, respectively. Enterococci were identified in two steps: presumptive identification of Enterococcus was based on colony and Gram stain morphology; VREF isolates were then identified using standard methods (bioMérieux Vitek, USA) [4]. Antimicrobial susceptibility testing was performed according to National Committee for Clinical Laboratory Standards guidelines [5]. Using broth microdilution methods, the isolates were tested in cation-adjusted Mueller-Hinton broth. The minimal inhibitory concentration (MIC) was described as the lowest concentration of each agent that suppressed visible growth of the organism after incubation at 35°C for 18–20 h. Organisms were considered to be resistant if the MIC exceeded 4 μg/ml. The VRE isolate from our patient possessed high-level resistance to most currently available antimicrobial agents. The isolate was sensitive to quinupristin/dalfopristin and linezolid at an MIC of 2 μg/ml and to gentamicin at an MIC of 500 μg/ml.

VREF infection is associated with considerable morbidity and mortality. The organism frequently causes bacteremia, urinary tract infection, and wound abscess. VRE meningitis has rarely been documented and represents a therapeutic challenge because of limited treatment options [6, 7]. Enterococcal meningitis usually requires combination therapy and adequate CSF levels of antibiotics. Our patient started to improve clinically 48 h after the initiation of linezolid therapy. Therapeutic levels of linezolid were reached in the CSF, and we were able to sterilize the CSF after 3 days without removing the ventriculoperitoneal shunt.

We successfully treated a patient with VREF meningitis with linezolid in combination with gentamicin. Linezolid seems to have achieved adequate levels in the CSF, which correlated well with the response in this patient. Determination of the optimal duration of therapy and the need for synergistic aminoglycoside awaits further investigation.

### References