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Original Article

Linezolid for the treatment of postneurosurgical infection caused by methicillin-resistant *Staphylococcus*

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ABSTRACT

Background: Postneurosurgical infection (PNSI) is a major problem. Linezolid is a bacteriostatic oxazolidinone antibiotic with a highly activity against Gram-positive cocci resistant to methicillin and a good cerebrospinal fluid penetration. The purpose of this study is to evaluate the efficacy of linezolid in the treatment of PNSI caused by methicillin-resistant *Staphylococcus* (MRS).

Methods: We conducted an observational study for all patients over 14 years old and diagnosed with MRS PNSI. Demographic, clinical, and laboratory information were collected prospectively.

Results: A total of 10 patients with PNSI (6 meningitis, 2 ventriculitis, and 2 subdural empyema) received linezolid. MRS isolated was *Staphylococcus aureus* in seven cases and *Staphylococcus epidermidis* in three cases. All isolated microorganisms were susceptible to vancomycin (minimum inhibitory concentration (MIC) = 2 mg/L) and linezolid (MIC = 1). The rate of microbiologic efficacy was 100% for patients with meningitis or ventriculitis. In the case of subdural empyema, focal infection had improved between 14 and 18 days. No adverse effects occurred during this study.

Conclusion: Our results suggest that linezolid as an alternative to vancomycin for the treatment of PNSI caused by MRS with a high rate of efficacy.

Keywords: Linezolid, Methicillin-resistant *Staphylococcus*, Neurosurgical infection

INTRODUCTION

Postneurosurgical infection (PNSI) is a major problem and frequently requiring high dose and prolonged antibiotic therapy.[16] Methicillin-resistant *Staphylococcus* (MRS) is the major Gram-positive organism causing PNSI and its incidence is increasing. Vancomycin is considered the treatment of choice in MRS PNSI; however, it has limited penetration into the cerebrospinal fluid (CSF) that depends on both the integrity of the blood–brain barrier and the inflammatory meningeal status.[21] Linezolid is a bacteriostatic oxazolidinone antibiotic with a highly activity against Gram-positive cocci resistant to methicillin.[6] The CSF penetration of linezolid is good and a CSF: plasma ratio of 0.7:1.6 *in vivo*.[25,28] In addition, the side effects of this antibiotic are rare and it was generally well tolerated by patients.[24] The purpose of this study is to evaluate the efficacy of linezolid in the treatment of PNSI caused by MRS.

METHODS

An observational, noncomparative, prospective study was performed at our center, tertiary care teaching hospital, between June 2017 and December 2018. The hospital has a 36-bed neurosurgery ward and six of these beds are in an intensive care unit. Our protocol was approved by the ethical and scientific committee of traumatology and severe Burns Center, Tunisia. Patients were included for the study if they were at least 14 years of age and diagnosed with MRS PNSI. Empirical therapy, consists of vancomycin (60 mg/kg/24 h) in combination with cefotaxime (200–300 mg/kg/24 h), was administered as soon as the infection was suspected and before microbiologic testing result. Linezolid was administered in the standard dosage of 2 × 600 mg/day, after the identification and susceptibility testing of MRS. If the duration of the treatment exceeds 14 days, linezolid intravenous administration is relayed by the oral route at the same dose (600 mg × 2/day). Demographic, clinical, and laboratory information were collected prospectively. Clinical information included procedure surgery, antibiotic combination, duration of treatment, days of hospitalization, and outcomes.

Definition of PNSI

PNSI was diagnosed according to the criteria of the Centers for Disease Control and Prevention,[10] adapted to the local protocol, and was classified into meningitis/ventriculitis and brain abscess/empyema. MRS meningitis/ventriculitis was determined as follows: (1) a positive MRS CSF culture and (2) increased white cells (CSF white blood cell count ≥100/mm^3) and decreased glucose (CSF glucose <2.5 mmol/L or ratio of CSF glucose to blood glucose <0.4) and increased lactate (CSF lactate >4 mmol/l) associated with fever and/or meningeal signs. MRS brain abscess/empyema was determined as follows: (1) MRS cultured from brain tissue or an abscess seen during a surgical operation and (2) fever, altered mental status, and/or focal neurologic deficits and suggestive computed tomography (CT) scans. Microbiologic success was defined, in the case of meningitis or ventriculitis, as the clearance of MRS from CSF on day 5 of treatment with linezolid. Brain abscess/empyema was defined as cured if CT showed no residual lesion and good neurological status.

Laboratory methods

CSF was obtained either by lumbar puncture or from extraventricular drainage reservoirs. All CSF samples were analyzed for leukocyte count, glucose, and lactate level and cultivated in aerobic media and anaerobic media. Identification of the etiological agents and susceptibilities to antibiotics was determined by Clinical Laboratory Standards Institute (CLSI) methods.[15]

Statistical analysis

A descriptive analysis was performed using SPSS software version 24. Quantitative variables were expressed as the median.

RESULTS

Among 240 patients operated during the study period, 19 had PNSI yielding a total incidence of 7.9%. A total of 10 cases of MRS PNSI were diagnosed. The median age was 48 years (range, 23–71) and 50% of patients were male. Meningitis was the most frequent infection, diagnosed in 6 cases (60%). This was followed by subdural empyema (20%) and ventriculitis (20%). Among the patients with postoperative meningitis, four had undergone surgery for supratentorial tumors, one for posterior fossa tumor, and one for Chiari I decompression. Two cases of ventriculitis occurred after the insertion of external ventricular drain for postoperative hydrocephalus and the patients with subdural empyema had undergone surgery for subdural hematoma. Only four patients received perioperative steroids (patient 2, 3, 4, and 6). Patient demographic data and type of PNSI are summarized in Table 1.

Laboratory data

The most common CSF abnormalities, for meningitis and ventriculitis, were pleocytosis (100%), hypoglycorrhachia (100%), and elevated lactate level (87%). The median CSF leukocyte count was 1224 cells/uL and the median of CSF lactate level was 9.8 mmol/l. CSF Gram stain was positive in 10% and culture was positive in all cases. MRS isolated were *Staphylococcus aureus* (MRSA) in seven cases and *Staphylococcus epidermidis* (MRSE) in three cases. Among the patient with PNSI caused by MRSE, two had an external ventricular drain and one had a CSF leakage. All isolated microorganisms were susceptible to vancomycin (minimum inhibitory concentration [MIC] = 2 mg/L), teicoplanin (MIC = 2 mg/L), and linezolid (MIC = 1) according to CLSI criteria [Table 2].

Antimicrobial treatment

All patients had been given vancomycin and cefotaxime before receiving linezolid. The median duration of vancomycin administration was 3 days. The median duration of antimicrobial treatment was 18 days (range, 14–42). Patients with MRS meningitis and ventriculitis had received intravenously linezolid for an average of 14 days. Into the two cases of subdural empyema, patients had received intravenously linezolid for 14 days then related by oral linezolid for 14–28 days. During linezolid therapy, two patients had received additional antibiotics for nosocomial

Table 1: Clinical, microbiological features, treatment modalities, and outcome of patients.

Patient No.	Age (years)/sex	GCS	Infection	CSF leukocyte cells/mm^3	CSF glucose/ lactate (mmol/l)	Procedure surgery	Pathogen	MIC (mg/l) vancomycin/ Linezolid	Treatment and duration (days)	Outcome
1	51/F	13	Ventriculitis	230	0.8/12	Pontocerebellar angle meningioma/EVD	MRSE	2/1	Linezolid (600 mg×2) IV, 14	Cured
2	26/M	14	Ventriculitis	156	1.3/8	Craniopharyngioma/ EVD	MRSE	2/1	Linezolid (600 mg×2) IV, 14 ceftazidime (2 g×3) IV, 10	Cured
3	23/M	14	Meningitis	360	1/6	Glioblastoma	MRSA	2/1	Linezolid (600 mg×2) IV, 14	Cured
4	38/F	15	Meningitis	290	0.9/9	Glioblastoma	MRSA	2/1	Linezolid (600 mg×2) IV, 14 colistin (3 MUI×3) IV, 15	Cured
5	47/M	15	Meningitis	410	1.8/10	Meningioma	MRSA	2/1	Linezolid (600 mg×2) IV, 14	Cured
6	58/F	13	Meningitis	189	1.5/21	Posterior fossa tumor	MRSE	2/1	Linezolid (600 mg×2) IV, 14	Cured
7	49/F	15	Meningitis	258	2/5	Meningioma	MRSA	2/1	Linezolid (600 mg×2) IV, 14	Cured
8	67/M	13	Subdural emppyema	-	-	Chronic subdural hematoma	MRSA	2/1	Linezolid (600 mg×2) IV 14 and OR 14	Cured
9	71/M	14	Subdural empyema	-	-	Chronic subdural hematoma	MRSA	2/1	Linezolid (600 mg×2) IV 14 and OR 28	Cured
10	58/F	7	Meningitis	8100	0.4/8	Chiari I decompression, LD	MRSA	2/1	Linezolid (600 mg×2) IV, 14	Cured

M: Male, F: Female, GCS: Glasgow come score, CSF: Cerebrospinal fluid, MIC: Minimum inhibitory concentration, EVD: Extraventricular drainage, LD: Lumbar drainage, MRSE: Methicillin-resistant *Staphylococcus epidermidis*, MRSA: Methicillin-resistant *Staphylococcus aureus*, IV: Intravenous, OR: Oral

pneumonia (patient 2 had received ceftazidime for *Pseudomonas aeruginosa* pneumonia and patient 4 had received colistin for *Acinetobacter baumannii* pneumonia) [Table 1].

Clinical and microbiologic efficacy

All patients with meningitis or ventriculitis had clearance of MRS from the CSF by day 5 of linezolid therapy. In patients with external ventricular catheter (patients 1 and 2), catheter was removed and followed by immediate replacement. In patients with subdural empyema, focal infection had improved on 14 days for patient 8 and on 18 days of linezolid therapy.

There were no in-hospital mortalities in our series and all patients were cured at the end of treatment. There were no severe hematologic, renal, or hepatic toxicity during treatment with linezolid.

DISCUSSION

Our study has shown that treatment with linezolid is a safe and effective alternative to vancomycin in patient with postneurosurgical ventriculitis, meningitis, and subdural empyemas caused by MRS.

MRS is the most common isolated organism in the PNSI.[13,18,29] In our study, the most commonly identified MRS was MRSA followed by MRSE. Often, the diagnosis of PNSI caused by MRSE is difficult and this is due to the contamination of the microbiological samples.[12,19] In the present study, MRSE was associated with shunt infection or CSF leakage.

The "gold standard" antimicrobial treatment of PNSI caused by MRS is vancomycin;[2] however, the penetration of vancomycin into CSF is poor with concentrations equal or less than 10% of those measured in plasma.[4] This concentration increases in the case of inflamed meninges.[20] In addition, recently, studies have shown that the incidence of MRS with elevated MIC is increasing and was associated with higher mortality.[5,11] In our study, all MRS isolated had a vancomycin MIC of 2 mg/L.

Linezolid, bacteriostatic oxazolidinone antibiotic, has a good penetration into the CSF, with a median CSF/plasma ratio of 0.77 and CFS concentration exceeded the MIC of the Gram-positive bacteria that cause PNSI.[4,14] Linezolid is recommended for the treatment of pneumonia and skin infection,[7] and currently, it is increasingly indicated in the treatment of PNSI. The European Federation of Neurological Sciences guideline on the management of community-acquired bacterial meningitis recommends linezolid for the treatment of methicillin-resistant staphylococcal meningitis.[3] Sipahi *et al*. reviewed in a

Table 2: Sensitivity pattern.

	MRSE *n* (%)	MRSA *n* (%)
Vancomycin	3 (100)	7 (100)
Linezolid	3 (100)	7 (100)
Teicoplanin	3 (100)	7 (100)
Lincomycin	1 (33)	3 (43)
Trimethoprim/sulfamethoxazole	2 (66)	2 (30)
Aminoglycoside	1 (33)	2 (30)
Chloramphenicol	1 (33)	1 (14)

MRSE: Methicillin-resistant *Staphylococcus epidermidis*, MRSA: Methicillin-resistant *Staphylococcus aureus*

retrospective cohort study 17 cases of methicillin-resistant staphylococcal postneurosurgical meningitis treated with linezolid (600 mg × 2). Microbiological efficacy rate was 88% by day 5 of linezolid treatment and there were no adverse events.[26] The same author compared in a retrospective study vancomycin with linezolid in the treatment of MRSA meningitis. Microbiologic success rates on day 5 were superior with linezolid (P = 0.044) and a vancomycin MIC of 2 mg/L was found in five strains of MRSA.[27] In our study, microbiologic success rates of linezolid in patients with meningitis or ventriculitis were 100%.

There are few cases in literature that have examined the efficacy of linezolid in the treatment of subdural empyemas. Maure *et al*. have treated successfully two cases of MRSA subdural empyema with linezolid as an adjunct to surgical therapy.[17] Bahubali *et al*. reviewed retrospectively 21 cases of MRSA intracerebral abscess treated with vancomycin or linezolid and have demonstrated that failure rate was lower with linezolid (25%) compared with vancomycin (43%).[1] In our series, the two cases of subdural empyema have evolved well with linezolid treatment. Due to its good bioavailability, linezolid is also effective when taken orally.[4] Martín-Gandul *et al*. evaluated the efficacy of oral linezolid in 77 patients with PNSI. In this study, stable patients were discharged with oral linezolid after a period of intravenous antimicrobial treatment. Seventy-two (93.5%) patients were cured at the end of treatment.[16] In the present study, patients 8 and 9 received oral linezolid for 14 and 28 days and were cured without recurrence.

The most common side effects after linezolid administration are gastrointestinal effects (nausea and vomiting) followed by hematological effects (anemia and thrombocytopenia) and lactic acidosis.[8,9,22] No adverse effects were detected in our patients.

The high consumption of linezolid in the intensive care unit is causing the increase of linezolid-resistant bacteria worldwide. Recently, Rodríguez-Lucas *et al*. were detected five cases of nosocomial ventriculitis by linezolid-resistant *S. epidermidis* in a Spanish hospital between 2013 and 2016.[23] A targeted prescription of linezolid, especially in PNSI, will preserve its effectiveness and avoid the emergence of more resistance.

Our study has some limitations. First, it was monocentric noncomparative observational study that included various PNSIs. Second, the small number of patients can limit our results on the efficacy of linezolid for the treatment of PNSI caused by MRS as well as underestimate the incidence of side effects.

CONCLUSION

Our results suggest that linezolid as an alternative to vancomycin for the treatment of PNSI caused by MRS with a high rate of efficacy. Orally linezolid may be a very interesting option for early discharge of patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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