Short Communication

Linezolid as a Potentially Effective Drug for the Treatment of Multidrug-Resistant Tuberculosis in Japan

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SUMMARY: Linezolid (LZD) is classified as a WHO group 5 drug used in the treatment of tuberculosis (TB). Although its efficacy and long-term safety have not yet been established, it is being increasingly used in the treatment of multidrug resistant tuberculosis (MDR-TB) and extensive multidrug-resistant tuberculosis (XDR-TB). The current study is a single-center retrospective clinical analysis of hospitalized M/XDR-TB patients in Fukujiji Hospital involving 26 patients (18 men and 8 women) consecutively treated with combinations of anti-TB drugs including LZD from 2009 to 2015. The sputum culture results were negative after using LZD for an average period of 28.0 ± 12.0 (average $\pm$ SD) days. LZD was reduced or withdrawn in 11 cases due to adverse effects. Nineteen cases including 3 XDR-TB patients were operated on, and their TB was treated following surgery. The average time from the initiation of LZD therapy to surgery was 87.6 ± 38.7 (average $\pm$ SD) days. Favorable clinical outcome was maintained in 23 surviving patients, while 3 patients died during treatment because of end stage cancer and aspiration pneumonia. Our study showed that LZD might be clinically effective in the treatment of M/XDR-TB patients in Japan.

The World Health Organization (WHO) estimated that there were approximately 500,000 cases of multidrug-resistant tuberculosis (MDR-TB) in 2014 (1). Linezolid (LZD), which is a group 5 anti-TB drugs, should only be used as prescribed by TB specialists, since its effectiveness has not yet been established. In this study, we report our findings following the treatment of MDR-TB or extensive multidrug-resistant (XDR)-TB in patients with LZD in Japan. Our findings showed that patients responded positively. Therefore, we propose that LZD might be an effective TB drug for the treatment of M/XDR-TB patients in Japan, similar to findings reported in other countries.

Our study is a retrospective clinical study of 26 MDR-TB positive, hospitalized patients in Fukujiji Hospital between 2009 and 2015 who were treated with LZD. This study was approved by the research and ethics committee of Fukujiji Hospital. During the treatment period, the sputum samples were examined via Ziehl-Neelsen staining, and cultured in 2% Ogawa medium for up to 8 weeks, according to the standard laboratory guidelines in Japan. The susceptibility of *Mycobacterium tuberculosis* (Mtb) to the first-line drugs including isoniazid (INH), rifampicin (RIF), ethambutol (EMB), streptomycin (STR), and

pyrazinamide (PZA) was tested using Mycobacteria Growth Indicator Tube 960 SIRE (Becton Dickinson, Sparks, MD, USA) and PZA kits (Becton Dickinson), as recommended by the WHO (2). The susceptibility of Mtb to second-line drugs including kanamycin (KM), levofloxacin (LVFX), cycloserine (CS), ethionamide (ETH), para-aminosalicylic acid (PAS), enviomycin (EVM) was tested with Welpack[®]S (Japan BCG Laboratory, Tokyo, Japan) (3) which is conducted in 1% Ogawa medium.

According to the current guidelines for the systematic management of drug-resistant tuberculosis in Japan (4), we considered LZD for the treatment of MDR-TB patients in Fukujiji Hospital. These patients have a high probability of failure with the currently available drugs including PZA, EMB, LVFX, KM, ETH, PAS, CS, and other alternative agents due to drug resistance, adverse drug reactions, and estimated high risk of default. M/XDR-TB patients who could not take further medications, or who could not receive alternative second-line drugs were excluded from this study. According to the above principles, all 26 patients received oral LZD (or intravenously if their condition did not permit oral administration) at a dosage of 600–1,200 mg daily combined with other anti-TB drugs at the beginning of treatment. Patients were monitored carefully for side effects. If side effects occurred, the dose of LZD was tapered or withdrawn.

Of the 26 patients, 7 were MDR-TB cases (susceptible to KM and LVFX), 12 were MDR-TB cases with resistance to injectable drugs or fluoroquinolones (pre-XDR-TB), and the remaining were XDR-TB cases. Among these patients, 18 (69%) were male patients. The average age was 47.5 ± 18.5 years, (range 18–85

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Table 1. Characteristics of each patient and response to drug treatment

Patients No.	Sex	Age	Type of MDR-TB	Cavity	ETH ¹⁾	EMB ¹⁾	STR ¹⁾	KM ¹⁾	EVM ¹⁾	PZA ¹⁾	LVFX ¹⁾	CS ¹⁾	PAS ¹⁾	High dose INH ¹⁾	concomitant anti-TB drug
1	M	59	Pre-XDR	No	+ ²⁾	+	+	- ³⁾	-	+	+	-	-	-	KM, CS, PAS, H ^h ⁴⁾
2	M	71	Pre-XDR	Yes	+	-	+	-	-	-	+	-	-	-	EMB, KM, PZA, CS, H ^h
3	M	67	Pre-XDR	Yes	+	-	-	-	-	+	+	-	-	+	ETH, STR, CS, PAS
4	M	43	XDR	Yes	+	+	+	+	+	+	+	-	-	-	CS, PAS, H ^h
5	M	85	Pre-XDR	No	-	-	+	-	-	-	+	-	-	+	EMB, KM, PZA, CS
6	F	26	XDR	No	+	+	+	+	-	-	+	-	+	+	EVM, ABPC/SBT
7	M	27	Pre-XDR	Yes	+	+	+	-	-	+	+	-	-	+	KM, CS, PAS
8	F	33	Pre-XDR	Yes	+	+	+	-	-	+	+	-	-	+	KM, CS, PAS
9	F	53	MDR	Yes	-	+	+	-	-	+	-	-	-	+	ETH, KM, LVFX
10	M	46	XDR	Yes	+	+	+	+	+	+	+	-	+	+	CS, RBT
11	M	39	XDR	Yes	+	+	+	+	-	+	+	+	+	+	EVM, STFX, AMPC/CVA, CFZ
12	F	27	MDR	Yes	-	+	+	-	-	+	-	-	-	+	ETH, KM, LVFX, CS, PAS
13	M	54	MDR	Yes	+	+	+	-	-	+	-	-	-	+	LVFX, CS, KM, PAS
14	M	39	XDR	Yes	+	+	+	+	-	+	+	-	+	+	EVM, CS, CFZ
15	M	61	XDR	Yes	-	+	+	+	-	+	-	+	-	+	EVM, MINO, CAM
16	M	44	Pre-XDR	Yes	+	+	-	-	-	+	+	-	-	+	KM, CS
17	M	56	Pre-XDR	No	-	+	+	-	-	+	+	-	-	+	ETH, KM, CS, PAS
18	M	27	MDR	Yes	-	-	+	-	-	+	-	-	-	+	ETH, KM, LVFX, CS, PAS
19	F	18	MDR	Yes	+	-	+	-	-	+	-	-	-	-	EMB, KM, LVFX, CS, PAS, H ^h
20	M	82	MDR	Yes	-	+	+	-	-	-	-	-	+	-	ETH, KM, LVFX, CS, PAS
21	F	26	Pre-XDR	Yes	-	+	+	-	-	+	-	-	-	+	ETH, KM, LVFX, CS, PAS
22	F	32	Pre-XDR	Yes	+	+	-	-	+	-	+	-	-	-	KM, PZA, CS, PAS, H ^h , RBT
23	F	29	Pre-XDR	No	-	+	+	-	-	+	+	-	-	+	ETH, KM, CS, PAS, RBT
24	M	72	XDR	No	+	+	+	+	-	+	+	-	-	-	ETH, PAS, CFZ
25	M	63	Pre-XDR	Yes	-	+	-	+	-	-	-	-	+	-	ETH, STR, LVFX, PAS, H ^h
26	M	57	MDR	Yes	+	+	+	-	-	-	-	-	-	-	ETH, KM, LVFX, CS, PAS, H ^h , RBT

¹⁾ INH, isoniazid; RIF, rifampicin; EMB, ethambutol; STR, streptomycin; PZA, pyrazinamide; KM, kanamycin; LVFX, levofloxacin; CS, cycloserine; ETH, ethionamide; PAS, para-aminosalicylic acid; EVM, enviomycin; AMPC/CVA, amoxicillin/clavulanate; RBT, rifabutin; ABPC/SBT, ampicillin/sulbactam; STFX, sitafloxacin; CFZ, clofazimine; MINO, minocycline; CAM, clatithromycin.

²⁾ ‘+’ indicates drug resistance.

³⁾ ‘-’ indicates drug sensitivity.

⁴⁾ ‘H^h’ indicates high dose INH.

years; Table 1). Six patients were treated with 1,200 mg of LZD as the normal starting dosage, while the other 20 patients were started with 600 mg, following the alternative dosage previously reported (5,6). The duration of LZD-containing treatment was 270.0 ± 60.0 (average $\pm$ SD) days in Fukujiji hospital. The average hospitalization time was 126.0 ± 57.0 days. The sputum culture results were negative after using LZD for an average period of 28.0 ± 12.0 days. The sputum cultures tested negative throughout the follow-up period; 5 cases transferred to another institution and were tested negative at the time of transfer. There were no recurrent cases after treatment. In this series, Mtb were susceptible to 5 drugs on average. Student t test showed that there was no significant relationship between the total LZD dosage and incidence of adverse effects ($t = 1.017$, $p = 0.320$). Furthermore, the total LZD dosage showed no relationship to drug susceptibility (over 5 drugs or 5 or fewer drugs) ($t = 1.364$, $p = 0.205$). The 2 fatal cases were excluded from these analyses (Table 2; Case No. 2, No. 3). Among the 26 patients, 19 (73%) underwent surgical treatment including single lobar resection (10 cases), 2-lobe resection (1 case), and pneumonectomy (8 cases). Despite the pres-

ence of widespread lesions that were indicated for pneumonectomy, all 19 surgical patients were successfully treated. The postoperative sputum cultures were negative for all patients. The average time from the initiation of LZD therapy to surgery was 87.6 ± 38.7 days. Treatment with LZD induced complete recovery from MDR-TB, as confirmed by consistently negative culture results during a culture period of 8 weeks. The dose of LZD was reduced or withdrawn in 11 (42%) cases, due to side effects that included myelosuppression in 10 (anemia, 6 cases; leukopenia, 7 cases; thrombocytopenia, 2 cases), severe anorexia in 2, and suspected liver toxicity in 2 cases (Table 2). The dose of LZD was reduced from 1,200 mg daily to 600 mg or to 1,200 mg every other day in 6 cases, and from 600 mg to 300 mg daily or to 600 mg every other day in 5 cases. Other adverse effects such as neuropathy were not observed in our study.

To our knowledge, this is the first clinical report in Japan showing successful treatment of a number of M/XDR-TB patients with a LZD-containing regimen. The efficacy of LZD in treating M/XDR-TB was previously reported (7,8). In our study, all specimen cultures were converted post treatment, except for 1 fatal case,

Table 2. LZD doses and associated treatment outcomes

Patients No.	Total LZD dose (g)	LZD dose until appearance of adverse effect (g)	Side effect	Sputum culture results at the start and end of LZD treatment	Sputum culture results before and after operation	Clinical outcome ¹⁾
1	146	23	Myelosuppression	(N/N)	(N/N)	Outpatient
2	14	—	None	(N/N)	—	Died because of stomach cancer
3	60	—	None	(P/P)	—	Died because of colon cancer
4	392	72	Severe anorexia	(P/P)	(P/N)	Outpatient
5	357	36	Myelosuppression	(P/N)	—	Outpatient
6	432	—	None	(N/N)	(N/N)	Outpatient
7	198	—	None	(P/N)	(N/N)	Hospital transferred
8	234	18	Myelosuppression	(P/N)	(P/N)	Outpatient
9	72	—	None	(P/N)	(N/N)	Hospital transferred
10	54	18	Myelosuppression	(P/N)	(N/N)	Hospital transferred
11	72	—	None	(N/N)	(N/N)	Hospital transferred
12	126	—	None	(P/N)	(P/N)	Outpatient
13	90	90	Suspicion of liver toxicity	(P/N)	(N/N)	Outpatient
14	324	—	None	(P/N)	(N/N)	Outpatient
15	198	90	Suspicion of liver toxicity	(P/N)	(N/N)	Outpatient
16	144	—	None	(P/N)	(N/N)	Outpatient
17	198	—	None	(P/N)	(N/N)	Outpatient
18	126	—	None	(P/N)	(N/N)	Hospital transferred
19	162	54	Myelosuppression	(P/N)	—	Outpatient
20	36	36	Myelosuppression	(P/N)	—	Died because of aspiration pneumonitis
21	162	—	None	(P/N)	(N/N)	Outpatient
22	54	13	Anemia	(P/N)	(N/N)	Outpatient
23	54	18	Myelosuppression	(P/N)	—	Outpatient
24	18	18	Anorexia	(P/N)	(N/N)	Outpatient
25	54	36	Myelosuppression	(N/N)	—	Outpatient
26	54	36	Myelosuppression	(P/N)	(N/N)	Outpatient

¹⁾: Clinical outcomes show maintenance of negative sputum culture results in outpatients. At the time point in which patients were transferred to other hospitals, the sputum culture results were negative.
P, Positive; N, negative.

where treatment had been discontinued in the late terminal stage. In patients with a localized TB lesion, surgery has been reported as an effective management method for M/XDR-TB (9). All XDR-TB patients who underwent surgical resection following LZD treatment were clinically cured. For case No. 11 (Table 1), the patient with XDR-TB was only administered a single anti-TB drug. Without the administration of LZD, this patient could not have undergone surgery; the patient was clinically cured following right pneumonectomy.

In 1 meta-analysis, there was no statistically significant difference in the treatment outcome between patients receiving over or under 600 mg daily LZD doses (8). Except 1 patient who died of cancer, all cases in our study converted to negative sputum culture irrespective of the total dose of LZD. As the benefits of vitamin B6 administration are not established, it was not used in our study. However, another publication reported that when vitamin B6 was included in the treatment regimen, there was no LZD-associated myelosuppression in any of the patients (10). Therefore, usage of vitamin B6 with LZD might be considered.

This study has some limitations. Firstly, this is a single-site, one-arm clinical trial. It was difficult to prove to what extent the other concomitant anti-TB drugs influenced treatment outcomes. Second, there might have been a selection bias as 19 (73%) patients had localized lesions. However, there were 8 (31%) patients who

underwent pneumonectomy indicating more serious disease compared to the 10 (38%) patients for whom lesions were localized to only 1 lobe.

Because LZD has been increasingly used for the treatment of M/XDR-TB in recent years, the establishment of usage guidelines for LZD should be considered in order to prevent the development of LZD resistance in Mtb and other bacteria. In this study, surgery might have also played an important role in curing M/XDR-TB patients since sputum culture conversion was observed postoperatively. Our study and previously reported data have shown that LZD might be effective in the treatment of M/XDR-TB, suggesting that reclassifying LZD into a new WHO group of anti-TB drugs may be appropriate.

Conflict of interest None to declare.

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