

## SUPPLEMENTARY MATERIAL

### Protocol for management of tuberculous meningitis patients

Each suspicious TBM case underwent general physical and neurological examination when admitted. Chest radiography, brain MRI, T-SPOT.TB test (T-Spot) (Oxford Immunotec Limited, Abingdon, United Kingdom) and lumbar puncture were performed before treatment. CSF analysis included biochemistry, cytology, microbiology (including microscopy and culture for fungi and bacteria), and Cryptococcus latex agglutination titer. Ziehl-Neelsen staining of sediment and *M. tuberculosis* culture was performed. Upon TBM diagnosis, patients accepted anti-tubercular regimen which contained four first line drugs (isoniazid 0.6g/d, Rifampicin 0.45g/d, pyrazinamide 1.5g/d, ethambutol 0.75g/d ) and one of the second line drugs (para-aminosalicylic 8-12g/d or levofloxacin 0.5g/d ). Kanamycin 0.6g/d was used as an alternative when drug induced adverse reaction occurred. Some severe cases received linezolid supplementation regimen with a dosage of 1200 mg per day. Mannitol was used if headache or high intracranial pressure was present. Dexamethasone was regularly used to reduce the risk of death and long term severe disability. Patients had lumbar punctures every one or two weeks after treatment was initiated and CSF analysis was carried out. Glasgow Coma Scales (GCS) scores and temperature were evaluated for patients daily during treatment. Patients underwent baseline and serial safety evaluations weekly during hospitalization and monthly after discharge, including complete blood counts, electrolyte tests, liver and renal function tests. Clinical neurologic examinations were performed at baseline and monthly thereafter. A neurologist was called for consultation at entry and when patients complained of abnormal feeling or motor findings during linezolid treatment. To monitor patients for linezolid induced optic neuropathy, patients with any symptoms or abnormal findings were referred to an ophthalmologist. If linezolid attributed adverse reaction was suspected, the drug was discontinued.

31 **Data collection process**

32 Three doctors collected the data of all patients diagnosed as TBM from the electronic  
33 medical record system. Then all cases who met the 4 inclusion criteria below in our  
34 hospital from January 2010 to December 2012 were included in our study: (1)  
35 negative finding for bacteria/fungi in cerebrospinal fluid (CSF) smear and culture,  
36 negative latex agglutination test for cryptococcus in CSF. (2) confirmed TBM, highly  
37 probable TBM or probable TBM according to predefined diagnostic standard. (3)  
38 TBM Grade II or Grade III according to the modified MRC system. (4) previous  
39 treatment without linezolid before admission. Possible TBM cases, TBM Grade I  
40 cases and cases which lacked 1 of 3 lumbar punctures results were not included in the  
41 analysis. For all cases included in the analysis, Brain MRI reports were confirmed by  
42 an experienced radiologist and CSF culture results were confirmed by clinical  
43 microbiology laboratory again. If treatment information was not clear in the medical  
44 record system, attending physicians of related patients would be contacted to confirm  
45 the details of treatment.

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68 **Supplementary Table 1. Information related to the diagnosis for patients**  
69 **included in the study.**  
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Case	CSF culture results	CSF criteria supported evidence	Supporting criteria supported evidence	Diagnosis classification	MRC grade
<b>LZD+BR group</b>					
01	Negative	CSF/blood glucose ratio Protein concentration Lymphocytes proportion	Brain enhanced MRI	highly probable	III
02	Negative	CSF/blood glucose ratio Protein concentration	Brain enhanced MRI T-SPOT Pulmonary tuberculosis	highly probable	II
03	Positive	—	—	confirmed	II
04	Negative	CSF/blood glucose ratio Protein concentration Lymphocytes proportion	T-SPOT	highly probable	II
05	Positive	—	—	confirmed	II
06	Negative	CSF/blood glucose ratio Protein concentration Lymphocytes proportion	Brain enhanced MRI	highly probable	III
07	Negative	CSF/blood glucose ratio Lymphocytes proportion	Brain enhanced MRI	probably	II
08	Positive	—	—	confirmed	III
09	Positive	—	—	confirmed	II
10	Negative	CSF/blood glucose ratio Protein concentration	Brain enhanced MRI T-SPOT	highly probable	II
11	Negative	CSF/blood glucose ratio Protein concentration Lymphocytes proportion	Brain enhanced MRI T-SPOT	highly probable	II
12	Negative	CSF/blood glucose ratio Protein concentration	Brain enhanced MRI T-SPOT	highly probable	II
13	Negative	CSF/blood glucose ratio Protein concentration	T-SPOT	probable	II
14	Negative	CSF/blood glucose ratio Lymphocytes proportion	Brain enhanced MRI T-SPOT	highly probable	II
15	Positive	—	—	confirmed	II
16	Negative	CSF/blood glucose ratio Protein concentration Lymphocytes proportion	Brain enhanced MRI T-SPOT	highly probable	II
<b>BR group</b>					
01	Positive	—	—	confirmed	II
02	Negative	CSF/blood glucose ratio Protein concentration	Brain enhanced MRI T-SPOT	highly probable	II

03	Negative	CSF/blood glucose ratio Protein concentration Lymphocytes proportion	Brain enhanced MRI T-SPOT	highly probable	II
04	Negative	CSF/blood glucose ratio Lymphocytes proportion	T-SPOT	probable	II
05	Negative	CSF/blood glucose ratio Lymphocytes proportion	Brain enhanced MRI T-SPOT	highly probable	II
06	Negative	CSF/blood glucose ratio Protein concentration	Brain enhanced MRI T-SPOT Pulmonary tuberculosis	highly probable	III
07	Negative	CSF/blood glucose ratio Protein concentration Lymphocytes proportion	Brain enhanced MRI T-SPOT	highly probable	II
08	Positive	—		definite	II
09	Negative	CSF/blood glucose ratio Lymphocytes proportion	Brain enhanced MRI T-SPOT	highly probable	II
10	Negative	CSF/blood glucose ratio Lymphocytes proportion	Brain enhanced MRI T-SPOT	highly probable	II
11	Negative	CSF/blood glucose ratio Lymphocytes proportion	Brain enhanced MRI T-SPOT	highly probable	II
12	Negative	CSF/blood glucose ratio Lymphocytes proportion	T-SPOT	probable	II
13	Negative	CSF/blood glucose ratio Protein concentration Lymphocytes proportion	Brain enhanced MRI	highly probable	II
14	Negative	CSF/blood glucose ratio Protein concentration Lymphocytes proportion	Brain enhanced MRI T-SPOT	highly probable	III
15	Negative	CSF/blood glucose ratio Protein concentration Lymphocytes proportion	T-SPOT	highly probable	II
16	Negative	CSF/blood glucose ratio Protein concentration	Brain enhanced MRI T-SPOT	highly probable	II
17	Negative	CSF/blood glucose ratio Protein concentration Lymphocytes proportion	Brain enhanced MRI T-SPOT	highly probable	II

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79 **Supplementary Table 2. Background regimen and linezolid supplemented**  
 80 **regimen for patients included in the study.**

Case	Background regimen	Linezolid regimen		Dexamethasone
		Dosage(mg/d)	Days	Dosage(mg/d) <sup>a</sup>
<b>LZD+BR group</b>				
01	H,R,E,Z,M	1200(8d) 600(14d)	22	5
02	H,R,Z	1200	16	5
03	H,R,E,Z,L	1200	11	5
04	H,R,E,Z,L	1200	45	5
05	H,E,Z,L	1200	30	5
06	H,R,Z,P,M	1200	71	5-15
07	H,R,Z,P,L	1200	29	5
08	H,Z,E,P	1200(22d) 600(18d)	40	5-10
09	H,E,Z,L	1200(13d) 600(41d)	54	5-10
10	H,Z,P,L	1200	34	5-10
11	H,R,Z,E,P	1200	21	5
12	H,R,Z,E,L	1200	17	15 <sup>b</sup>
13	H,E,Z	1200	34	2-5
14	H,R,E,Z	1200	18	5-7.5
15	H,R,E,Z,P	1200	13	5
16	H,R,E,Z,L	1200	25	10
<b>BR group</b>				
01	H,R,Z,E,P		—	5
02	H,R,Z,E,P,M		—	2.5
03	H,R,Z,E,L		—	5-7.5
04	H,R,Z,E,L		—	3-5
05	H,R,Z,E,L		—	5
06	H,R,Z,E,L		—	5-7.5
07	H,R,Z,E,P		—	4-5
08	H,R,Z,E,P		—	2-4
09	H,R,Z,E,L		—	5
10	H,R,Z,E,P		—	5
11	H,R,Z,L,P		—	5
12	H,R,Z,E,L		—	2.5
13	H,R,Z,E,L		—	2.5
14	H,R,Z,E,L		—	4.5

15	H,R,Z,E,L	—	15
16	H,M,A	—	1.5
17	H,R,Z,E,L	—	1.5

81 Abbreviations: H, isoniazid; R rifmpicin; Z pyrazinamide; E, ethambutol; P, para-aminosalicylic  
82 acid; L, levofloxacin; A, amikacin; M, moxifloxacin; d, days.

83 <sup>a</sup> The range means the regulation of dosage during the initial treatment.

84 <sup>b</sup> This case accepted prednisone other than dexamethasone.

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