Outcomes of extended duration therapy for drug-susceptible cavitary pulmonary tuberculosis

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Background: Extending the continuation phase treatment duration is recommended to improve outcomes of drug-susceptible cavitary pulmonary tuberculosis (TB), but limited data are available on extended treatment outcomes.

Methods: We evaluated outcomes of 67 patients with drug-susceptible cavitary pulmonary TB who had received extended therapy. The primary endpoint of our study was the rate of a favorable outcome (cured or treatment completion without recurrence).

Results: Of the 67 patients, 40 (59.7%) were culture negative and 27 (40.3%) were culture positive two months after treatment initiation. The median treatment duration was 275 days. Extended duration therapy resulted in a 100% treatment success rate and 2.5% recurrence rate in patients with a negative culture at month 2. However, patients with a positive culture at month 2, showed a 74.1% treatment success rate and 8.0% recurrence rate (P<0.001 and P=0.554, respectively). In multivariable analyses, positive culture at month 2 was associated with greater odds of unfavorable outcomes (adjusted OR, 17.04, 95% CI, 1.68–177.92).

Conclusions: While extending the continuation phase was associated with favorable outcomes in pulmonary TB patients with negative culture at month 2, the same could not be achieved in those with positive culture at month 2, suggesting that this condition might not be overcome by merely extending the continuation phase.

Keywords: Pulmonary tuberculosis (pulmonary TB); cavitation; two-month culture; treatment outcome

Introduction

Most patients with drug-susceptible tuberculosis (TB) are successfully treated using the standard six-month treatment regimen consisting of isoniazid, rifampin, ethambutol, and pyrazinamide, with a treatment success rate of 90–95% (1). Previous studies have shown that treatment outcomes can be suboptimal in patients with additional risk factors, such as the following: being >10% below ideal body weight;

being an active smoker; and having diabetes mellitus, human immunodeficiency virus (HIV) infection, or signs of extensive disease observed on chest radiographs (2-7).

Besides the above factors, the most well-known risk factors for unfavorable treatment outcomes are cavitation on chest radiograph (3) and positive culture 2 months post-treatment initiation (hereafter positive culture at month 2) (3,8). In patients treated for six months, having both cavitation and positive culture after a two-month treatment

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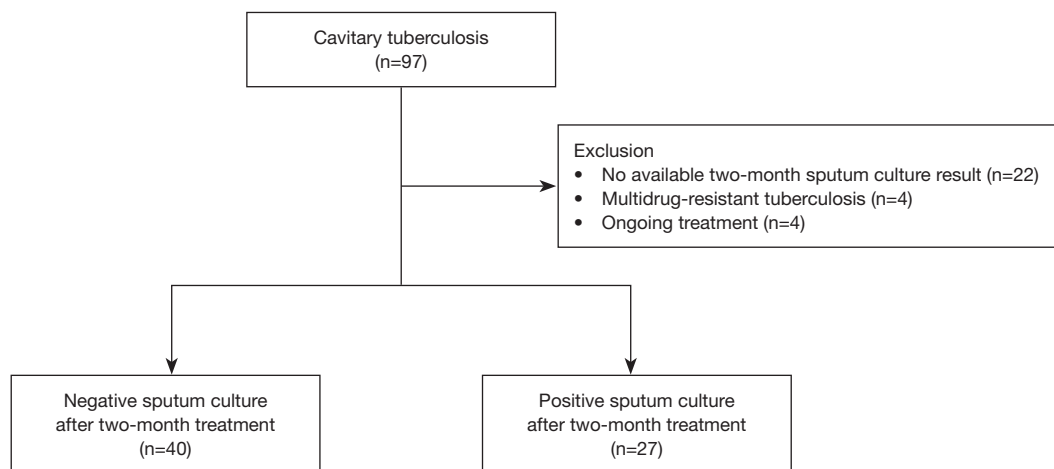
Figure 1 Flow chart of the study population.

is associated with an approximately 20% recurrence rate (7-9). Accordingly, the current guidelines have proposed extending the continuation phase of treatment with isoniazid and rifampin for an additional three months in these patients, corresponding to a total of nine months of therapy. It is also recommended to consider extending the continuation phase in patients with cavitation only (7). However, there is limited treatment outcome data available to support this recommendation.

Accordingly, we aimed to investigate the treatment outcomes in patients with drug-susceptible cavitary pulmonary TB who received treatment with an extended continuation phase.

Methods

Study population

We included all consecutive adult patients (age ≥18 years) with newly diagnosed or retreated drug-susceptible cavitary TB at Hallym University Kangnam Sacred Heart Hospital (a 577-bed referral hospital in Seoul, South Korea) between January 2012 and June 2017. During the study period, 1,288 patients were diagnosed with pulmonary TB, while 97 (7.5%) were diagnosed with cavitary pulmonary TB. After excluding patients with no available two-month sputum culture results (n=22), those initially diagnosed with multidrug-resistant TB (MDR-TB) (n=4), and those with ongoing treatment (n=4), 67 patients were included (*Figure 1*). Before commencing TB treatment, the attending physicians determined the baseline comorbidities. The

study protocol was approved by the Institutional Review Board (IRB) of Hallym University Kangnam Sacred Heart Hospital (IRB application no. 2018-07-007). All data were anonymized before analysis and the need for written informed consent was waived by the IRB due to the retrospective nature of this study.

Microbiologic and radiologic examination

Acid-fast bacilli (AFB) staining was performed on sputum samples with an auramine-rhodamine fluorescent stain, followed by confirmation with Ziehl-Neelsen-staining. Staining results were graded according to the American Thoracic Society/Centers for Disease Control and Prevention guidelines (10). Specimens in which the AFB smear results were categorized as grades ≥1+ were defined as smear positive. All clinical specimens were cultured on both solid and liquid media for six weeks. To this end, decontaminated samples were inoculated into mycobacterial growth indicator tubes (MGIT 960 system; Becton Dickinson, Sparks, MD) and 3% Ogawa agar (Shinyang, Seoul, Korea). All positive cultures were subjected to an AFB smear to confirm the presence of AFB and exclude contamination. Pulmonary TB was diagnosed based on sputum AFB smear or *Mycobacterium tuberculosis* (MTB) polymerase chain reaction (PCR) results. The PowerChek MTB/NTM Real-time PCR Kit (Kogene Biotech, Korea) was used to analyze sputum samples. Drug susceptibility testing (DST) was performed using the absolute concentration method with the Lowenstein-Jensen medium at the Korean Institute of Tuberculosis (11). Follow-up

sputum AFB smear and culture were performed monthly. All the procedures were performed in Class 2 biosafety cabinets.

With regard to the chest radiograph, the posteroanterior view or posteroanterior and lateral view chest radiography was performed in all patients at the time of TB diagnosis. The presence of cavitation was determined by a radiologist by formally interpreting the chest radiograph. Meanwhile, two of the authors (YS Sim and H Choi) examined the chest radiographs of the patients with cavitary TB for bilateral involvement, cavity number, and cavity size (the largest size was measured in patients with ≥2 cavities); a consensus was obtained.

Treatment regimen and outcomes

The standard treatment for drug-susceptible TB is comprised of the intensive phase with daily rifampin, isoniazid, ethambutol, and pyrazinamide for two months, followed by the continuation phase with daily rifampin and isoniazid with or without ethambutol for four months (7). The dosages for each of the medications were determined based on patients' body weight. Patients with body weight ≥50 kg received 600 mg of rifampin, 300 mg of isoniazid, 800 mg of ethambutol, and 1,500 mg of pyrazinamide (2,000 mg of pyrazinamide in those with bodyweight >70 kg); those with bodyweight <50 kg received 450 mg of rifampin, 300 mg of isoniazid, 800 mg of ethambutol, and 1,000 mg of pyrazinamide according to the Korean guideline for the treatment of TB (12). For patients with high risk for recurrence, including cavitation on chest radiography and positive culture at month 2, the continuation phase was extended to seven months, corresponding to nine months of total treatment duration. Moreover, the additional factors that should be considered when deciding to prolong treatment in patients with either cavitation or a positive culture at 2 months (but not both) included being >10% below ideal body weight; being an active smoker; having diabetes, HIV infection, or any other immunosuppressing condition; or having extensive disease on chest radiograph. In addition, the continuation phase could be extended based on the sputum AFB culture results at the discretion of the attending physicians.

Treatment outcomes were categorized as cured, treatment completion, treatment success, treatment failure, lost to follow-up, not evaluated, and recurrence (12,13). A patient was considered cured if the sputum culture was negative in the last month of treatment and at least two consecutive sputum cultures were negative before the end of treatment. Treatment completion was defined as completion of treatment (at least 180 doses) without the evidence of failure and non-adherence to treatment but not meeting the criteria of being cured. To ensure adherence to treatment in South Korea, through a public-private mix collaboration, the TB-specialist nurses were dispatched to health care facilities. They are responsible for providing patient education and monitoring any adverse effects during treatment. When the patients are lost to regular follow-up, the TB-specialist nurses encourage them to visit the hospital through telephone consultation or home visits (14,15). Treatment success was defined as both cured and completing treatment. Treatment failure was defined as having positive sputum culture results after 4 months of treatment (13). Lost to follow-up was defined as a lack of treatment initiation or treatment interruption for at least two consecutive months. Transferred patients with unknown treatment results were classified as not evaluated. Recurrence was defined as the diagnosis of pulmonary TB in a patient after initial treatment success (12,13). We defined a favorable outcome as treatment success with no evidence of recurrence during the follow-up period, and an unfavorable outcome as treatment failure or recurrence after initial treatment success. The patients should visit the hospital every 3 months for at least 1 year post-treatment completion to check for recurrence. The primary endpoint of our study was the rate of a favorable outcome.

Statistical analysis

Data are presented as the median and interquartile range (IQR) for continuous variables and as frequency (percentage) for categorical variables. Data were compared by the Mann-Whitney U test for continuous variables and by Pearson's chi-square test or Fisher's exact test for categorical variables. To evaluate the effect of a positive culture on the treatment outcomes at month 2, multivariable logistic regression analysis was performed after adjusting for age, sex, body mass index, cavity size, bilateral lung infiltrates, and treatment duration. All tests were two-sided, and P values of <0.05 were considered statistically significant differences. All statistical analyses were performed using IBM SPSS Statistics for Windows (version 23; IBM Corp., Armonk, NY, USA) and

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Table 1 Baseline characteristics of the study population

Characteristics	Total (n=67)	AFB culture at month 2		P value
		Negative (n=40)	Positive (n=27)	
Age, years	49 [39–62]	48 [34–56]	51 [46–71]	0.050
Sex, male	48 (71.6)	28 (70.0)	20 (74.1)	0.717
Body mass index, kg/m^2	20.2 (18.4–22.1)	20.1 (18.3–22.0)	20.2 (18.6–23.1)	0.399
Current smoker	30 (44.8)	20 (50.0)	10 (37.0)	0.295
Previous history of TB	18 (26.9)	10 (25.0)	8 (29.6)	0.675
Comorbidities				
Diabetes mellitus	13 (19.4)	7 (17.5)	6 (22.2)	0.632
Chronic pulmonary disease	7 (10.4)	4 (10.0)	3 (11.1)	1.0
Chronic liver disease	3 (4.5)	2 (5.0)	1 (3.7)	1.0
Malignancy	3 (4.5)	1 (2.5)	2 (7.4)	0.560
Disease severity				
AFB smear positivity	64 (95.5)	37 (92.5)	27 (100.0)	0.267
AFB smear grade				0.002
0	4 (6.0)	4 (10.0)	0 (0.0)	
1	12 (17.9)	12 (30.0)	0 (0.0)	
2	15 (22.4)	8 (20.0)	7 (25.9)	
3	20 (29.9)	10 (25.0)	10 (37.0)	
4	16 (23.9)	6 (15.0)	10 (37.0)	
Bilateral involvement	38 (56.7)	22 (55.0)	16 (59.3)	0.730
Cavity number	1.0 (1.0–1.0)	1.0 (1.0–1.5)	1.0 (1.0–1.0)	0.680
Cavity size, mm[a]	38.0 (30.0–56.0)	35.5 (30.3–47.8)	43.0 (25.0–64.0)	0.406

The data are presented as either median and interquartile range or number and percentage, as appropriate. [a], the largest size was measured in patients with ≥2 cavities. TB, tuberculosis; AFB, acid-fast bacilli.

STATA (version 14; Stata Corp., College Station, TX).

Results

Patient characteristics

The clinical characteristics of study participants are summarized in *Table 1*. None of the patients had HIV infection in this study. Among the 67 patients, 40 (59.7%) were culture-negative and 27 (40.3%) were culture-positive after two months of treatment. Patients with positive culture at month 2 showed significantly higher baseline AFB smear grades than those with a negative culture at month 2 (P=0.002). Although patients with negative culture at

month 2 were younger than those with positive culture at month 2 (48 *vs.* 51 years), this difference was not significant (P=0.050). There were no significant differences between the two groups in terms of smoking history, previous history of TB, comorbidities, bilateral lung field involvement on chest radiograph, cavity number, or cavity size on chest radiograph.

Treatment regimen and duration

Treatment regimen and duration for patients with drug-susceptible cavitary TB are summarized in *Table 2*. A standard anti-TB medication regimen was initiated in all patients, which consisted of rifampin, isoniazid, ethambutol, and pyrazinamide. Second line anti-TB medications were used in some patients

Table 2 Treatment regimen and treatment duration

	Total (n=67)	AFB culture at month 2		P value
		Negative (n=40)	Positive (n=27)	
Regimen of anti-TB drugs				
Rifampin	67 (100.0)	40 (100.0)	27 (100.0)	–
Isoniazid	67 (100.0)	40 (100.0)	27 (100.0)	–
Ethambutol	67 (100.0)	40 (100.0)	27 (100.0)	–
Pyrazinamide	67 (100.0)	40 (100.0)	27 (100.0)	–
Fluoroquinolone[a]	5 (7.5)	4 (10.0)	1 (3.7)	0.641
Injectable drugs[b]	2 (3.0)	2 (5.0)	0 (0.0)	0.512
Cycloserine	1 (1.5)	1 (2.5)	0 (0.0)	1.0
Duration of anti-TB drugs, days				
Rifampin	275 (259–301)	273 (207–284)	279 (272–362)	0.066
Isoniazid	275 (256–301)	273 (207–284)	279 (264–362)	0.114
Ethambutol	271 (176–280)	261 (177–280)	273 (138–280)	0.458
Pyrazinamide	70 (60–87)	70 (61–91)	70 (59–83)	0.450
Fluoroquinolone	56 (14–280)	152 (25–296)	14 (NA)	0.277
Injectable drugs	143 (NA)	143 (NA)	–	–
Cycloserine	14 (NA)	14 (NA)	–	–
Treatment duration, days	275 (259–301)	273 (207–284)	279 (272–362)	0.066

The data are presented as either median and interquartile range or number and percentage, as appropriate. [a], three patients received levofloxacin, and two patients received moxifloxacin; [b], one patient received intramuscular streptomycin, and the other patient received intramuscular streptomycin followed by kanamycin. AFB, acid-fast bacilli; TB, tuberculosis; NA, not applicable.

who had experienced side effects of standard medications, which included a fluoroquinolone in five (7.5%) patients (levofloxacin in three and moxifloxacin in two), injectable drugs in two (3.0%) (streptomycin in one and streptomycin followed by kanamycin in the other), and cycloserine in one (1.5%). There were no significant differences in TB treatment regimen between the patients regardless of culture conversion at month 2 after treatment initiation.

Patients were treated with rifampin, isoniazid, and ethambutol for approximately nine months, and pyrazinamide for approximately two months. Although patients with positive culture at month 2 were more likely to be treated for a longer duration, and receive rifampin for a longer duration than in those with negative culture at month 2, these differences were not significant (P=0.066, both for overall treatment duration and duration of rifampin use).

Treatment outcomes

As shown in *Table 3*, the rate of 2-month AFB smear positivity was significantly higher in patients with a positive culture at month 2 than in those with a negative culture at month 2 (74.1% *vs.* 30.0%; P=0.001). The proportion of patients with treatment success was significantly higher in patients with negative culture at month 2 than in those with a positive culture at month 2 [100% (40/40) *vs.* 74.1% (20/27); P<0.001]. The reasons for not achieving treatment success in patients with a positive culture at month 2 included treatment failure (18.5%, 5/27), follow-up loss, or not evaluated (7.4%, 2/27). In five patients categorized with treatment failure, three had negative cultures in 5 months, one had negative culture in 7 months, and the other had negative culture 9

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Table 3 Treatment outcomes

Outcomes	Total (n=67)	AFB conversion at month 2		P value
		Negative (n=40)	Positive (n=27)	
AFB smear positivity at month 2	32 (47.8)	12 (30.0)	20 (74.1)	0.001
Treatment outcomes				0.001
Cured	57 (85.1)	39 (97.5)	18 (66.7)	
Treatment completed	3 (4.5)	1 (2.5)	2 (7.4)	
Treatment failure[a]	5 (7.5)	0 (0.0)	5 (18.5)[a]	
Follow-up loss	1 (1.5)	0 (0.0)	1 (3.7)	
Not-evaluated	1 (1.5)	0 (0.0)	1 (3.7)	
Follow-up duration, months	15.8 (6.3–39.3)	22.3 (10.1–41.2)	9.7 (3.0–19.3)	0.004
Recurrence after treatment success[a]	3 (4.5)	1 (2.5)	2 (8.0)[a]	0.554
Favorable treatment outcomes[b]	58 (86.6)	39 (97.5)	19 (70.4)	0.002
Unfavorable treatment outcomes[c]	9 (13.4)	1 (2.5)	8 (29.6)[a]	0.002
Development of acquired drug resistance				
Rifampin	1 (1.5)	0 (0.0)	1 (3.7)	0.403
Isoniazid	1 (1.5)	0 (0.0)	1 (3.7)	0.403
Ethambutol	0 (0.0)	0 (0.0)	0 (0.0)	–
Pyrazinamide	0 (0.0)	0 (0.0)	0 (0.0)	–

The data are presented as either median and interquartile range or number and percentage, as appropriate. [a], one patient who had experienced treatment failure also had a relapse after treatment completion. This case was counted as a single event of an unfavorable outcome; [b], favorable treatment outcomes were defined as treatment success with no evidence of recurrence during follow-up period; [c], unfavorable treatment outcomes were defined as treatment failure or recurrence after initial treatment success. AFB, acid-fast bacilli.

months after treatment initiation.

The proportion of patients with favorable treatment outcomes was significantly higher in patients with a negative culture at month 2 than in those with a positive culture [97.5% (39/40) *vs.* 70.4% (19/27); P=0.002]. The recurrence rate after treatment success was 2.5% (1/40) in patients with a negative culture at month 2 and 8% (2/25) in those with a positive culture at month 2, respectively (P=0.554). The median follow-up duration post-treatment completion was 15.8 months (IQR, 6.3–39.3 months). Each follow-up duration was 22.3 months (IQR, 10.1–41.2 months) in patients with a negative culture at month 2, and 9.3 months (IQR, 3.0–19.3 months) in those with a positive culture at month 2, respectively (P=0.004). Among patients with negative culture at month 2, one patient had recurrence after treatment success. The patient was a 49-year-old man with a low BMI (17.4 kg/m^2), current smoking history, and bilateral disease on the initial chest radiograph.

The effect of positive culture at month 2 on treatment outcomes

As shown in *Table 4*, regardless of the definition of unfavorable treatment outcome, patients with positive culture at month 2 were more likely to have unfavorable treatment outcomes than those with negative culture at month 2 (unadjusted OR, 16.42, 95% CI, 1.91–140.07; adjusted OR, 17.04, 95% CI, 1.68–172.92 for unfavorable outcomes defined as treatment failure, follow-up loss, not evaluated, or recurrence after initial treatment success, unadjusted OR, 12.32, 95% CI, 1.38–109.7l; adjusted OR,18.69, 95% CI, 1.05–333.05 for unfavorable outcomes defined as treatment failure or recurrence after initial treatment success).

Disease course of patients with initial treatment failure

Clinical characteristics and treatment regimens of five patients with initial treatment failure are provided in

Table 4 Crude and adjusted odds ratio for the unfavorable treatment outcomes in patients with positive culture at month 2 over those with negative culture at month 2

	AFB culture at month 2[a]			AFB culture at month 2[b]		
	Negative (n=40)	Positive (n=27)	P value	Negative (n=40)	Positive (n=25)	P value
Crude model	References	16.42 (1.91–140.07)	0.011	References	12.32 (1.38–109.71)	0.024
Adjusted model[c]	References	17.04 (1.68–172.92)	0.016	References	18.69 (1.05–333.05)	0.046

The patient who had both treatment failure and recurrence after treatment completion was counted as one case. [a], unfavorable outcomes were defined as treatment failure, follow-up loss/not evaluated, or recurrence after initial treatment success; [b], unfavorable outcomes were defined as treatment failure or recurrence after initial treatment success, except for those with follow-up loss/not evaluated (n=2); [c], age, sex, body mass index, cavity size, bilateral lung infiltrates, and treatment duration were factors in the adjusted model. AFB, acid-fast bacilli.

Supplementary *Table S1*. DST performed using *M. tuberculosis* grown on month 4 sputum cultures did not reveal any new drug resistance. After detecting treatment failure, all five patients received a treatment regimen composed of isoniazid and rifampin with or without ethambutol, which was the standard continuation phase regimen. Three patients achieved culture conversion after extending the duration of therapy, one patient developed MDR-TB at 5.5 months after treatment initiation, and one patient was lost to follow-up 5.8 months after culture conversion, which was achieved 8.7 months from treatment initiation. Of the three patients who had achieved treatment success after prolonged treatment, recurrence was observed in one patient 37.7 months after treatment completion.

Discussion

The present study evaluated treatment outcomes of an extended treatment regimen of 67 patients with drug-susceptible cavitary pulmonary TB. At month 2, two-thirds of patients had negative sputum culture, and one-third had positive sputum culture. The rate of favorable treatment outcomes were significantly higher in patients with negative culture at month 2 compared to those with a positive culture. The extended treatment regimen showed favorable treatment outcomes in patients with a negative culture at month 2; however, it might not be enough to overcome unfavorable outcomes in those with a positive culture at month 2.

Several studies using qualitative smears and cultures have shown that patients with cavitary TB have higher mycobacterial loads in their sputum (16-20), which may result in a high recurrence rate, ranging up to 20% in cavitary TB patients, especially in those with a positive culture at month 2 (7-9). These study results suggest that the current six-month standard therapy is not an adequate treatment duration for cavitary pulmonary TB despite drug-susceptibility. Thus, the current treatment guidelines recommend extending the continuation phase therapy for three months in cavitary TB patients with a positive culture at month 2, and considering an extended continuation phase therapy in TB patients with only cavitation (7). However, there have been insufficient data to support this recommendation.

From this perspective, our study provided informative data about the treatment outcomes of an extended treatment regimen in these patients. Supporting the current expert recommendation, the recurrence rate after extended treatment was about 4.6% (2.5% in patients with a negative culture at month 2 and 8.0% in patients with a positive culture at month 2) in this study, which is lower than the previous results (ranging up to 20%) in patients who received a six-month treatment (8). The factors related to recurrence including age, underlying comorbidities, and disease severity in this study were comparable with those of the previous study conducted by Jo and colleagues (8). Moreover, a recent meta-analysis reported that the subgroup of patients with both cavitation and positive 2-month smear positivity had shown a relapse risk of at least 10% (21). Thus, the extended treatment duration may have a significant role in decreasing the recurrence rate. In addition, the Korean Government public-private mix collaboration policy (explained in the Methods section in detail) (14,15), which has been settled since 2011, may have an additional role in decreasing the recurrence rate by enhancing medication adherence.

Unfortunately, the treatment success rate was significantly different depending on the culture results at month 2. While patients with negative culture at month 2 showed a high treatment success rate (100%), comparable with those

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of drug-susceptible TB in previous reports (1,22), patients with positive culture at month 2 showed only a 74% treatment success rate. Thus, due to a high treatment failure rate, despite the low recurrence rate, it could be postulated that cavitary pulmonary TB with positive culture at month 2 may not be successfully treated by only extending the duration of continuation therapy. Previous studies have also shown that positive smear and/or culture at month 2 (23-25) is associated with treatment failure. Although a more severe disease condition, i.e., the presence of cavitation and positive culture at month 2, is suggested to be associated with a higher risk of treatment failure, few data have been available; a previous study showed that treatment failure and recurrence rates are higher in patients with both cavitation and positive culture at month 2; however, the study did not separately evaluate treatment failure from recurrence (2). To the best of our knowledge, this is the first study showing that both the presence of cavitation and positive culture at month 2 are significantly associated with treatment failure.

In this study, five patients among those with positive culture at month 2 experienced treatment failure, defined as persistently positive culture results after four months of treatment (7,12). Although maintaining the continuation phase therapy led to culture conversion in three patients, one patient was lost to follow-up, and one patient acquired MDR-TB. Some researchers have raised concerns that lengthy TB treatment might increase the development of drug resistance (26,27). Supporting this perspective, one fifth developed MDR-TB during extended treatment for cavitary TB in this study. Thus, although it could be postulated that extending the continuation phase therapy might be helpful to reduce the recurrence rate, we should be careful not to facilitate the development of MDR-TB. We believe that reinforced 2-month intensive phase regimen may shorten the treatment duration as well as prevent the development of drug resistance in patients with unfavorable outcomes. Future research highlighting new regimens is needed to overcome the drug resistance issue.

Our results, along with the findings of previous studies, strongly suggest that an augmented treatment regimen may be needed for the treatment of cavitary pulmonary TB in patients with positive culture at month 2. Considering the poor penetration of first line oral anti-TB drugs in cavitary lesions (28-30), augmentation of the treatment regimen with second line drugs such as moxifloxacin may be helpful (29). A previous study using an animal model revealed that moxifloxacin showed a high tissue-plasma ratio of distribution in cavitary lesions (nine in cavity caseum and 16 in the

cavity wall), while tissue-plasma ratios of isoniazid, rifampin, and pyrazinamide were relatively unsatisfactory (29). In addition, a recently published article by Strydom and colleagues investigated TB drugs' distribution in the patient's lung lesions and suggested a mechanistic model for regimen and dose optimization (31). We may incorporate such a promising tool into practice, which will lead to more tailored regimen to overcome subtherapeutic drug concentrations in cavities.

The extended continuation phase was an acceptable strategy for the treatment of cavitary pulmonary TB patients with negative culture at month 2. Since treatment outcomes were much better in cavitary TB patients with negative culture at month 2 than those with positive culture at month 2, we could postulate that a six-month standard regimen may be enough for some of the patients with negative culture at month 2. However, as all patients with cavitary TB received extended treatment in this study, we could not evaluate the treatment outcomes of the standard six-month therapy. Thus, further studies comparing the treatment outcomes of standard six-month therapy versus extended continuation phase therapy in cavitary pulmonary TB are needed.

This study has several limitations. First, it was a retrospective study with a relatively small sample size from a single referral hospital. For example, cavity size was larger in patients with a positive culture at month 2 than in those with a negative culture at month 2, which might have resulted in culture positivity at month 2 and hence treatment failure. However, the difference in cavity size was not statistically significant, probably due to the small sample size. Second, because genotyping was not available, this study could not discriminate relapse due to reactivation from recurrence due to exogenous reinfection (32). Third, although there was no significant difference in the recurrence rate between patients with positive and negative culture at month 2, the statistical insignificance may be due to the relatively small study population. However, this limitation does not change our study findings regarding the potential role of an extended continuation regimen. Studies with a larger number of patients are needed to confirm these findings.

In conclusion, the culture result at month 2 is the most critical factor affecting treatment outcomes in patients with drug-susceptible cavitary TB. Patients with negative culture at month 2 showed favorable treatment outcomes comparable with those of drug-susceptible TB without cavitation. In contrast, patients with positive culture at

month 2 showed unfavorable treatment outcomes with a higher treatment failure rate, which was not overcome by merely extending the continuation phase. This study suggests that an augmented treatment regimen might be needed in cavitary pulmonary TB patients with positive culture at month 2.

Acknowledgments

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the Institutional Review Board (IRB) of Hallym University Kangnam Sacred Heart Hospital (IRB application no. 2018-07-007).

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Table S1 Clinical characteristics and treatment regimens in five patients with initial treatment failure

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, years	72	60	60	78	63
Sex	Female	Male	Male	Male	Male
Body mass index, kg/m^2	22.8	20.6	23.3	18.0	16.7
Smoking history	Never	Ex-smoker	Current	Never	Current
Comorbidities					
Diabetes mellitus	Yes	Yes	No	No	No
Chronic pulmonary disease	No	Yes	No	No	No
Chronic liver disease	No	No	No	No	No
Malignancy	No	No	No	Yes	No
Disease severity					
AFB smear	Positive	Positive	Positive	Positive	Positive
Bilateral involvement	Yes	Yes	Yes	No	Yes
Treatment regimen					
Overall	2HREZ/9HR	2HREZ/12HRE	2HREZ/10HRE	2HREZ/10HRE	3HREZ/2HRE
Before confirmation of treatment failure	2HREZ/2HR	2HREZ/2HRE	2HREZ/2HRE	2HREZ/2HRE	3HREZ/2HRE
After confirmation of treatment failure	7HR	10HRE	8HRE	8HRE	MDR-TB
Final treatment outcomes					
Treatment success	Yes	No	Yes	Yes	No
Treatment failure	No	No	No	No	Yes
Follow-up loss	No	Yes	No	No	No
New drug resistance	No	No	No	No	Yes to HR
Recurrence	Yes	Unknown	No	No	–
Follow-up duration after treatment success, days	1,131	–	551	161	–

AFB, acid-fast bacilli; H, isoniazid; R, rifampin; E, ethambutol; Z, pyrazinamide; MDR, multidrug-resistant; TB, tuberculosis.