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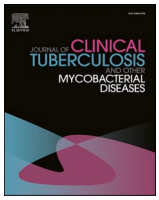

The use of BPaL containing regimen in the MDR/PreXDR TB treatments in Thailand

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ABSTRACT

The primary objective of this study was to evaluate the real-world effectiveness, side effects and challenges associated with the implementing of the groundbreaking BPaL-containing regimen in Thailand. Another aim was to investigate the characteristics and severity of the disease, the presence of abnormal extensive lesions in chest X-Rays and the influence of cavitation on sputum conversion. Material and method: The case series study included patients at TB clinic of Central chest institute of Thailand between August 2021-April 2023. All 28 Patients fullfilled the diagnostic criterial for MDR-TB by molecular tests and/or sputum culture. Sputum molecular test, utilizing GeneXpert MRB/XDR or Genotype MTBDRsl assay, was conducted. The 8 Pre-XDR patients who exhibited quinolone resistance and the 2 MDR-TB patients who encountered side effected from quinolone drugs were treated with BPaL regimen, while the remainder received BPaLM regimens. Results: Among the 28 patients, 23 (82.1 %) successfully completed the treatment with favorable outcomes. However, one patient from the BpaL regimen died due to severe destroy lung lesion, and four patients from the BpalM regimen discontinued treatment. The investigation into the correlation between extension lesion, cavitation lesions, and culture conversion unveiled that the group with extension lesions and cavitation $\geq$4 cm had a diminished probability of achieving sputum culture conversion within 8 weeks in comparison to the group without attributes. The associated risk ratio was 0.56 (95 % CI, 0.14–2.27), p = 0.14. Although the study report minimal side effects, 6 patients (22.2 %) experienced peripheral neuropathy and a notable adverse reaction identified was optic neuritis, affecting 2 cases (7.1 %). Summary: The administration of the BPaL-containing regimen resulted in rapid sputum conversion within 8 weeks and had minimal side effects.

1. Introduction

MDR-TB (Multidrug- resistance Tuberculosis) was one of the main problems in healthcare system of Thailand. The treatment for MDR-TB involved long durations and multiple drugs, leading to various side effects that needed to be addressed. The introduction of the 6-month regimens of BPaL containing regimen (BPaL and BPaLM provided a new chance for treating MDR-TB[1].

The BPaL regimen is well know from the Nix-TB study conducted in 2020[2]. The study focused on patients with preXDR-TB and MDR-TB who faced challenges in treatment using standard drug regimens and experienced side effects. The BPaL regimen included the use of Linezolid at a high dose of 1200 mg throughout the 26-week treatment, along with daily administration of pretomanid at a dose of 200 mg for 26 weeks and bedaquiline at a dose of 400 mg once daily for the initial 2 weeks, followed by 200 mg three times a week for 24 weeks. The favorable outcomes for XDR-TB and MDR-TB were 89 % (95 %CI 79–95) and 92 % (79–98 %), respectively. However, it was found that there were significant side effects associated with the use of Linezolid at a dose of 1200 mg, reaching up to 54 % in grade 3–4.

In the subsequent TB- PRACTECAL study, which examined patients with MDR-TB for 24- week period of BPaLM treatment, the Linezolid dose was reduced to 600 mg daily for 16 weeks, followed by 300 mg daily for 8 weeks[3]. Pretomanid and Bedaquiline were administered at the same dose as in the BPaL regimen of the Nix-TB study. Additionally, moxifloxacin at a dose of 400 mg per day was added to the BPaLM

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regimen. The favorable outcomes in the modified intention- to treat population was 89 %, and serious side effect in grade 3 or higher were observed in 25 % of the group. Sputum conversion was achieved in 88 % of the population at 12 weeks.

The treatment of drug-resistance Tuberculosis using the shorter all oral 9- month regimen has a recommendation against choosing this treatment in cases where extensive lesion is shown[4]. The truncated TB study, which explored short- course 2-month regimens in patients with drug- susceptible TB, had limitations in selecting patients with direct smear result in the 1–2 + range and cavitation less than 4 cm [5].

However, The BPaL containing (Bpal/BpalM) regimens did not have such limitations. In the protocol amendment, it was mentioned that patients on the BPaL regimen who did not achieve conversion in 3 months could extend their treatment to 9 months, raising questions about patient selection suitability. The primary objective of this study was to to assess the real-life success, side effects and challenges of implementing the pioneer BPaL containing regimen in Thailand. Additionally, the study aimed to investigate the characteristics and severity of the disease, such as bacterial counts identified via direct smear tests, the presence of abnormal extensive lesions in chest X-Rays and the effect of cavitation on sputum conversion.

2. Material and method

The case series report included patients at TB clinic of Central chest institute of Thailand between August 2021-April 2023, based on the inclusion criteria of the regimen. All Patients met the diagnostic criterial for MDR-TB though molecular test such as Xpert MTB/RFF ultra/genotype MTBDR (1st) assay and/or phenotypic drug sensitivity test by standard culture. However, patients with extrapulmonary disease such as TB meningitis and skeletal TB, pregnancy individuals, those with low body weight (BW <35 Kg), and those who had been using at least one drug from this regimen one month before enrolling, were excluded. Underlying disease was recorded, and anti-HIV testing was conducted. The study was approved by the ethical committee of Central Chest Institute of Thailand.

Chest X-Ray was performed on all patients to demonstrate cavitation and the extension of lesion. “Extension lesion” referred to lesion that covers more than two lobes of the total Chest X-Ray lobes. Cavitation was measured at its maximum diameter.

Sputum molecular test using GeneXpert MRB/XDR or Genotype MTBDRsl assay were performed on all MDR-TB patients to distinguish Pre-XDRTB from MDR-TB. Patients who did not show quinolone resistance in the molecular test were enrolled in BPaLM regimen, while others were in BPaL regimen. For patients who previously had issues or encountered problem while taking the BPaLM regimen, the medication was switched to BPaL. The drug dosages used in BPaL containing regimen were as follows:

- Bedaquiline at a dose of 400 mg once daily for the initial 2 weeks, followed by 200 mg three times a week for 24 weeks.
- Linezolid at a dose of 600 mg once daily for 26 weeks, and the dose may be decreased or stopped due to side effects after 8 weeks of treatment.
- Pretomanid at a dose of 200 mg once daily for 26 weeks.
- Add M (Moxifloxain) 400 mg once daily in quinolone susceptibility for 26 weeks

Sputum samples were collected for smear microscopy (fluorescence microscope) and culture using solid culture (culture 2 % Ogava and Löwenstein-Jensen media) at baseline and up to treatment visits, such as week ±1, 2, 4, 6, 8 and then monthly until 6 months. After completing the treatment, Chest X-rays were performed at follow-up visits every 3–6 months for at least 1 year. Direst smear and culture were performed if recurrent disease was suspected favorable outcomes were defined by clinical, chest X-ray and laboratory responses including negative sputum culture.

2.1. Statistical analysis

Statistical analysis was conducted using Strata 15.1. Continuous variables were reported as Median (IQR), mean ± SD and categorical variables were presented as frequency (percentage). Survival analysis and the Kaplan-Meier method were utilized to determine the time to sputum culture conversion. The relationship between extensive lesion and cavity size was presented as a risk ratio.

3. Results

The 28 patients were included in the BPaL/BPaLM regimen. Most of the patients were seronegative. Additionally, One-third of the patients had extensive lesions, with lesion more than two lobes observed in their chest X-rays and one- fourth showed cavitation. The characteristic data is presented in Table 1.

The 8 Pre-XDR patients and the 2 MDR-TB patients who experienced quinolone drug side effected received BPaL regimen. After treatment for two weeks, one patient who received the BPaL regimen died due to destroy lesion and respiratory failure. The patients had TB empyema and pneumothorax. Among the patients treated with BPaL regimen, 9 completed their treatment with only one completing the one- year follow up with no recurrent, six patients were still undergoing treatment. During the follow-up period, two patient was lost to follow-up, one was followed up for 6 months, one was followed up for 3 months with no recurrent and ongoing follow-up care, and four patient is awaiting a 3-month follow up.

On the other hand, the 18 MDR-TB patients received the BPaLM regimen. One patient discontinued the treatment after 4.5 months. Another patient changed to an individual longer course regimen of MDR-TB because they experienced blurred vision after using Linezolid for 2 weeks. This patient had underling diabetes mellitus (DM) and was afraid to continue with Linezolid regimen. One patient discontinued the regimen after 3 months of treatment due to a change in residence. Additionally, one patient discontinued the regimen after 1.5 months of

Table 1
Characteristics of the 28 Drug-resistant TB patients.

Characteristics	No (%) or Median (IQR)
Age, yr	46 (32.5–51)
Female (No (%))	14(50 %)
Body mass index, Kg/m2	21 (16.3–23)
Positive HIV status	0 (0 %)
Smoking history	7(25 %)
Underlying dis	
DM	5 (17.9%)
Vascular disease/valvular disease	4 (14.3%)
Airway disease (asthma/COPD)	2 (7.1%)
Other: Anemia of chronic disease, gout	2 (7.1%)
Baseline positive smear	19 (67.9 %)
1+	11(39.3%)
2–3+	8(28.6%)
Type of disease	
Extensive lesion of CXR more than two lobes	8(28.6%)
Cavitation, diameter	6 (21.4%, 6.1 cm (3.7-7.0 cm)
Extrapulmonary disease with or without pulmonary involvement	2 (7.1 %)
Previous treatment of TB	18(64.3%)
failure to treatment TB	4(14.3%)
recurrent TB	14(50%)
Tuberculosis type	
RR-TB	5(17.8%)
MDR-TB	14(50.0%)
Pre XDR-TBTB	8(28.5%)
TB(Xpert MTB/RFT: Rf resistance, culture DST: Rf not resistance)	1(3.57%)

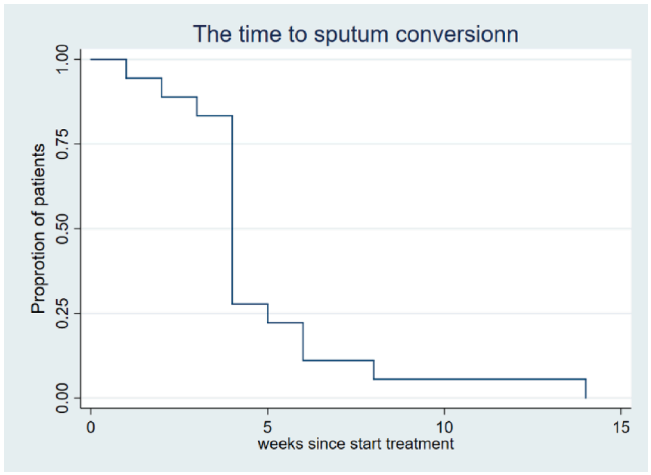
treatment due to a change in working place and the subsequent loss medication 3.5 months. The patient also changed to an individual longer course regimen. Four-teen patients completed their treatment. During the follow-up period, one patient was lost to follow-up, two was followed up for 6 months, seven was followed up for 3 months with no recurrent and ongoing follow-up care, and four patient is awaiting a 3-month follow up, as shown in Fig. 1.

In the treatment with the BPaL-containing regimen, the mean time (±SD) to sputum culture conversion was found to be 4.48 (±1.88) weeks, with only 1 case having a sputum conversion time of more than 8 weeks as shown in the Graph 1. The status of Treatment outcomes, follow-up and sputum conversion to negative was shown in Table 2. There was only one pre-XDR-TB patient with an extensive lesion (covering approximately 80 % of the abnormal chest X-ray area) and a large cavity (8.5 cm) who underwent extended treatment for 9 months due to delayed sputum conversion to 14 weeks.

The study on the relationship between extension lesion and cavitation lesion compared to culture conversion revealed that It was the group with extension lesions and cavitation ≥4 cm had a lower likelihood of sputum culture conversion within 8 weeks compared to the group without such conditions, with a risk ratio of 0.56 (95 % CI, 0.14–2.27), p = 0.14 as shown in the Table 3.

Side effects observed from using the BPaL containing regimen.

- The most common side effects were nausea and dizziness, occurring in 4 out of the 22 patients. These symptoms were usually present in the early 2–3 weeks but improved over time.
- One patient from the BPaLM regimen experienced prolongation of the QT interval (Maximum Qtcf interval ≥500 msec) twice, at 2 months and 4 months after starting treatment. After stopping all medications for about 1 week, the patients resumed the same regimen. There was no electrolyte imbalance between episodes.
- Six patients experienced peripheral neuropathy. Four cases were from the BPaLM regimen. Two patients had mild symptoms: one after 14 weeks of treatment, and the other had underlying condition (DM). Both were managed with supportive treatment and high-dose vitamin B6 was found to be sufficient. The third patient had symptoms after 16 weeks, with no improvement, and discontinued the treatment after 18 weeks. The fourth patient had moderate symptoms after 20 weeks, leading to a dose reduction (300 mg) until stop medication. Two cases were from the Bpal regimen. The first patient developed moderate symptoms after 20 weeks, prompting a dose reduction (300 mg) before eventually discontinuing the medication. The second patient had severe symptoms after 15 weeks, leading to a dose reduction (300 mg, 1 month) and ultimately discontinuation of linezolid.
- Three patients experienced blurred vision. One patient from BPaL regimen also had diabetes and non-specific blurred vision. Two of them developed suspected optic neuritis (diagnosis by ophthalmologist) and required treatment discontinuation, one from BPaLregimen, and the other from BPaLM regimen. All patients who had optic neuritis were females, aged 39 and 26 years, with BMI of 16.3 and, 15.4, respectively. The duration of blurred vision started 23 weeks



Graph 1. The time of sputum culture conversion in patients with baseline positive culture (20 patients).

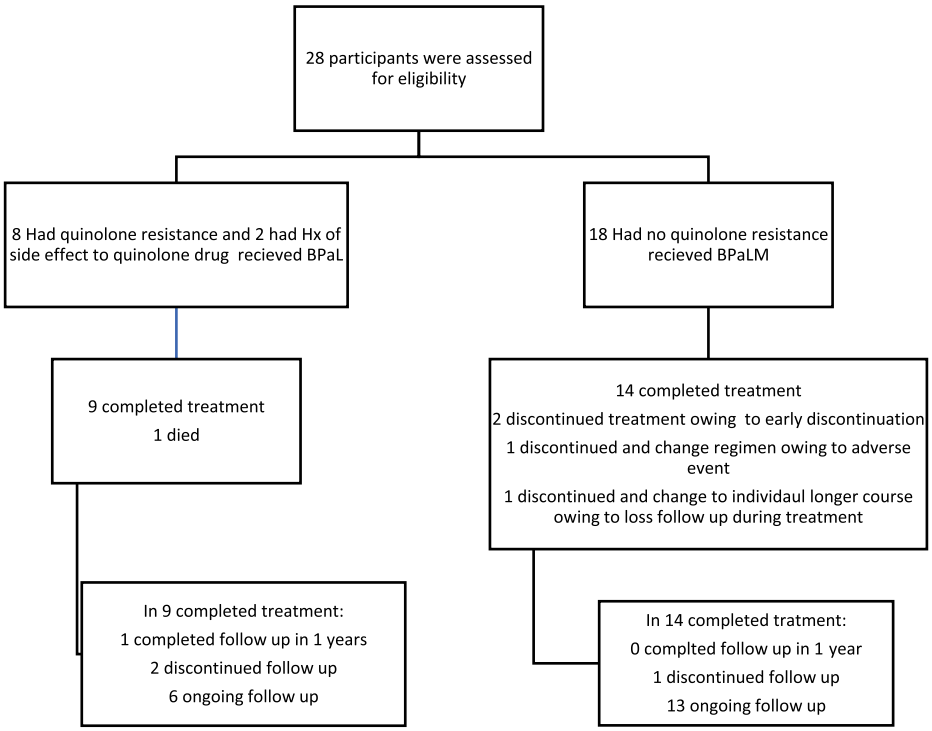


Fig. 1.

Table 2
Treatment outcomes and Follow-up.

	BPaL regimen, N = 10	BPaLM regimen N = 18
Outcomes– no (%)		14 (77.7 %)
Favorable outcome	9 (90 %)	0 (0 %)
Failure	0 (0)	1 (5.6 %)
Change regimen	0 (0)	3 (16.7 %)
Loss to follow up	0 (0)	0(0 %)
Died	1 (10 %)	
1-year follow-up after treatment –no		1
Completed	1 (11.1 %)	0 (0 %)
Loss	2 (22.2 %)	1 (7.1 %)
Ongoing	6 (66.7 %)	13 (92.9 %)
Sputum culture conversion at 4 week, n (%)	4 (40 %)	18 (100 %)
Sputum culture conversion at 8 week, n (%)	8 (80 %)	18 (100 %)

Table 3
Relationship between severe disease compared to culture conversion within 8 weeks.

	Risk ratio (RR)	95 % confidence interval	p-value
Extensive lesion of CXR (more than two lobes)	0.9	0.40–2.00	0.79
Cavitation ≥4 cm	0.85	0.47–1.55	0.53
Extensive lesion of CXR และ Cavitation ≥4 cm	0.56	0.14–2.27	0.14
Baseline smear positive: 3+ and more	0.76	0.48–1.28	0.21
BMI ≤18	0.82	0.57–1.19	0.19
Underlying dis: DM	0.92	0.57–1.47	0.69

and 16 weeks after treatment, respectively. The recovery time after stopping treatment in all patients were 2 weeks.

- No patients had severe anemia (Hb <8 g/dl) or thrombocytopenia/ neutropenia.
- Two patients experienced hand tremors; one had a history of tremors after consuming coffee, and the other had a history of depression.
- Two patients experienced palpitations, both having valvular heart disease. One patient had mitral valve regurgitation and required mitral valve replacement after about 1 week of medication, while the other had aortic stenosis.

4. Discussion

Based on the NIX-TB study, it was found that the treatment success rate was high when using the BPaL regimen for both XDR-TB and MDR-TB, with success rates of 89 % (95 % CI 79–95) for XDR-TB and 92 % (79–98 %) for MDR-TB. Similarly, in the TB-PRACTECAL study, the treatment success rate for MDR-TB patients using the BPaLM regimen was also high at 89 %. These findings demonstrate the effectiveness of the BPaL containing regimen in treating drug-resistant tuberculosis. This study was a cross-sectional study that included a total of 28 patients. Among them, 23 patients completed the treatment, and all 23 of them achieved favorable treatment outcome. However, it appears that the BPaLM regimen had some patients who discontinued treatment, whereas the BPaL regimen had no patients who discontinued. In the BPaL group, there were some patient deaths, possibly due to the severity of lung damage before starting the treatment.

Due to utilization of BPaL-containing regimen, the treatment duration for MDR-TB patients has been reduced, leading to faster sputum conversion. According to the finding of this study, the average time for sputum conversion was merely 4.4 weeks. There was one case that experienced sputum conversion after 8 weeks. In this patient, extension lesions involvement (approximately 5 lobes of the abnormal lesion) and cavitation size 8.5 cm were observed. Based on the results of the NIX-Tb study, it is recommended to extend the treatment from 6 months to 9 months for patients who remain culture positive by the third month. Consequently, in these patients, the treatment duration was extended to 9 months. No correlation was established between the duration of sputum conversion and disease severity due to the limitation in the number of cases. The group displaying extensive lesion and large cavitation (≥4 cm) had a decreased likelihood of sputum conversion within 8 weeks compared to the group without such conditions, with a risk ratio of 0.56 (95 % CI, 0.14–2.27), p = 0.14. From this finding of this study, it may be possible to anticipate the need for extended treatment duration in individuals with extensive lesion and large cavitation, thereby contributing to more effective management of MDR-TB cases. However, other factors such as a high bacterial load at baseline detected through direct smear, comorbidities like DM, and malnutrition cannot reliably be predictive of delayed sputum conversion.

From the study of using the BPaL based regimen in the NIX-TB study, it was found that the side effects from using linezolid at a dose of 1200 mg reached up to 54 % in grade 3–4. Peripheral neuropathy occurred in 81 % of all patients, with severity ranging from mild to moderate. Meanwhile, optic neuritis was found in only 2 cases (2 %) of the patients. In the TB-PRACTECAL study, reducing the linezolid dose to 600 mg resulted in a decrease in serious side effects in grade 3 or higher, with only 25 % of the group experiencing them. Peripheral neuropathy was observed in 9 % of the patients, and no patients had optic neuritis. The ZeNix trial studied by adjusting the linezolid dose from 600 mg for 9 weeks to a reduced dose of 300, 0 mg in response to adverse events [6]. The study showed favorable outcomes for patients who received a fixed dose of 600 mg for 26 weeks and for those who received the dose for 9 weeks followed by a dose reduction based on side effects, with success rates at 91 % and 84 %, respectively. These rates are high and closely to the study results of TB-PRACTECAL, which showed a success rate of 89 %. The occurrence of grade ≥3 side effects in the groups that received a fixed dose and dose adjustment were 20 % and 24 %, respectively, with peripheral neuropathy observed in 24 % and 13 %, respectively. This study had one patient who died within 2 weeks of starting the treatment, and thus, it was not possible to assess side effects in this case. There were also no patients with anemia (Hb <8 gm/dl). Six out of 27 patients (22.2 %), who had the side effect of peripheral neuropathy, were nearly equal to the rate of patients who received a fix 600 mg dose of Linezolid in the ZeNix studies. However, this study found optic neuritis in 2 out of 27 patients (7.4 %), which is a higher rate compared to other studies. Both patients who experienced optic neuritis were females of younger age and lower BMI. Due to the limited number of patients in this study, there are limitations in analyzing this relationship. Therefore, there is a need for further consideration in adjusting the medication dose more quickly or reducing the dose to 300 mg in the last 1–2 months of treatment, especially in younger female patients with lower body weight. Summary: The administration of the BPaL-containing regimen resulted in rapid sputum conversion within 8 weeks and had minimal side effects.

CRediT authorship contribution statement

Piamlarp Sangsayunh: . **Thanyanuch Sanchat:** Data curation, Formal analysis, Investigation. **Charoen Chuchottaworn:** . **Krisana Cheewakul:** Data curation. **Sirijit Rattanawai:** Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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