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Highlights:

- Treating MDR-TB is complicated, long and expensive
- Bedaquiline (BQ) is a new active drug to treat MDR-TB
- No study evaluated safety and effectiveness of surgery in BQ-treated patients
- 57 BQ-exposed cases resistant to 7 drugs (median) underwent surgery in 9 countries
- 60% of cases initiated BQ after surgery, 36.4% before and completed it afterwards
- 90% culture-converted and 69.1% achieved treatment success at the end of treatment

Outcomes of patients with drug-resistant-tuberculosis treated with bedaquiline -containing regimens and undergoing adjunctive surgery

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Running title (max 50 characters): MDR-TB cases treated with bedaquiline and surgery

Declarations of interest: none

Abstract (199/200 words)

Objectives: No study evaluated the contribution of adjunctive surgery in bedaquiline-treated patients. This study describes treatment outcomes and complications in a cohort of drug-resistant pulmonary tuberculosis (TB) cases treated with bedaquiline-containing regimens undergoing surgery.

Methods: This retrospective observational study recruited patients treated for TB in 12 centres in 9 countries between January 2007 and March 2015.

Patients who had surgical indications in a bedaquiline-treated programme-based cohort were selected and surgery-related information was collected. Patient characteristics and surgical indications were described together with type of operation, surgical complications, bacteriological conversion rates, and treatment outcomes. Treatment outcomes were evaluated according to the time of surgery.

Results: 57 bedaquiline-exposed cases resistant to a median of 7 drugs had indication for surgery (52 retreatments; 50 extensively drug-resistant (XDR) or pre XDR-TB). Sixty percent of cases initiated bedaquiline treatment following surgery, while 36.4% underwent the bedaquiline regimen before surgery and completed it after the operation. At treatment completion 90% culture-converted with 69.1% achieving treatment success; 21.8% had unfavourable outcomes (20.0% treatment failure, 1.8% lost to follow-up), and 9.1% were still undergoing treatment.

Conclusions: The study results suggest that bedaquiline and surgery can be safely and effectively combined in selected cases with a specific indication.

Key words: TB, MDR-TB; XDR-TB, surgery; pulmonary rehabilitation

Text Word count: 1679 words

Introduction

With over 490,000 multidrug-resistant tuberculosis cases (MDR-TB; TB caused by *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin) occurring globally each year, 6.2% of which are XDR-TB (extensively drug-resistant TB: MDR-TB with additional resistance to fluoroquinolones and one second-line injectable), the 'white plague' remains a major clinical and public health priority *(1-4)*.

Although higher success rates are achievable *(1,2)*, the overall proportion of treatment success is sub-optimal, adverse events common, and treatment duration long and expensive *(1-4)*. Currently, scientific debate focuses on the role of new medications (bedaquiline and delamanid), *(5-15)* and repurposed drugs for the optimal management of difficult-to-treat M/XDR-TB cases *(16-19)*.

Few studies are presently available on the programmatic use of bedaquiline *(1,4-7)* and no study has evaluated the contribution of adjunctive surgery in bedaquiline-treated patients (*20,21)*. The aim of this study is to describe treatment outcomes and complications in a cohort of drug-resistant pulmonary TB cases treated with bedaquiline-containing regimens having indication for surgical intervention (the vast majority of them have been operated).

Materials and methods

This retrospective observational study recruited patients treated for TB in 12 centres in 9 countries from January 2007 to March 2015.

Patients who had surgical indications in a bedaquiline-treated programme-based cohort *(2)* were selected and surgery-related information collected. Patient characteristics and surgical indications were described together with type of operation, surgical complications, bacteriological conversion

rates, and treatment outcomes (per World Health Organization (WHO) definitions) *(2)*. Treatment outcomes were evaluated according to the time of surgery. The cases not operated (two out of 57) were removed from outcome analysis.

An ad hoc electronic form (Excel, Microsoft) was used to collect clinical and epidemiological variables. Qualitative and quantitative variables were described with absolute and relative (percentages) frequencies and medians (interquartile ranges) for the non-parametric distribution, respectively. Chi-squared and Mann-Whitney tests were used to perform statistical comparisons of qualitative and quantitative variables. A two-tailed p-value less than 0.05 was considered statistically significant. The statistical software Stata version 15 (StataCorp, Texas, USA) was used to carry out all statistical computations.

Results

Fifty-seven cases of drug-resistant TB managed with both surgical indication and bedaquiline-containing regimens were included (52 from the original study plus 4 added from the Russian Federation and 1 from Italy) as follows: Russian Federation (39), South Africa (5), India (4), Italy (3) and Peru (2); Argentina, Australia, Greece, and Sweden contributed with one case.

Overall, 5 cases were new and 52 had been previously treated for M/XDR-TB (37 failures, 15 relapses).

The majority were male (66.7%) with a mean (SD) age of 36.4 (11.8) years; 5.3% were HIV co-infected. Out of 41 cases with information on co-morbidities and risk factors, 2 reported hepatic failure, 2 drug addiction, 2 alcohol abuse (>40 mg/day), one diabetes, and one renal failure.

Out of the 57 cases enrolled, 31 had XDR-TB, 19 pre-XDR-TB (12 MDR with additional resistance to a fluoroquinolone and 7 to a second-line injectable), 6 MDR-TB, and one (poly-resistant) was resistant to isoniazid and streptomycin.

Overall, isolates were phenotypically-resistant to a median of 7 (IQR 5-10) drugs.

Clinical-radiological characteristics were indicative of severe disease. Of 57 cases with radiological details available, 46 (80.7%) had cavities (20 bilateral; 26 mono-lateral), and the remaining nodular lesions. Ten cases reported lung complications following TB disease, such as bronchiectasis, 10 destroyed lungs, 3 recurrent haemoptysis, and 2 each bronchial fibrostenosis, pleural empyema, and aspergilloma (4.7%).

The median (IQR) duration of anti-TB therapy was 18 (13-28) months. The median (IQR) number of prescribed active drugs was 5 (4-7) and 6 (5-7) before and after surgery (Table 1).

Pre-surgical treatment regimens included linezolid (48.8%), a carbapenem (12.2%), and clofazimine (9.8%) in addition to bedaquiline. No case underwent combined bedaquiline and delamanid treatment *(22-27)*. A single patient reported a QTc interval of 515 msec (week 8) reverting spontaneously without any consequences.

The indications for surgery (non-mutually exclusive) were localised disease allowing resection (35/39, 89.7%), failed bacteriological conversion (21/42, 50.0%), and disease worsening (15/42, 35.7%).

Twenty-five out of 34 cases had FEV_1 (Forced Expiratory Volume in 1 sec) ≥80% of predicted.

Prior to surgery 20/42 (47.6%) and 23/42 (54.8%) were still sputum smear- and culture-positive, respectively.

The most common types of operation performed were lobectomy, segmentectomy, and pneumonectomy (Table 2). All cases were operated with the exception of two cases (one worsening and dying before surgery; one still waiting for it while completing the bedaquiline cycle); they were removed from outcome analysis (the denominator for outcome analysis was 55, Table 2). Three patients underwent bilateral surgery. Postero-lateral thoracotomy was the commonest approach for the surgical intervention (34 (89.5%) of the 38 cases with information).

Most cases (33/55, 60%) initiated bedaquiline treatment following surgery, while 20/55 (36.4%) were administered a bedaquiline including regimen before surgery and completed it after the operation. Only two cases, enrolled more recently, completed bedaquiline before surgery. One of

the two cases was prescribed delamanid after the operation, having been admitted for an additional 110 days. Delamanid was necessary to ensure the minimum number of effective drugs in the late post-surgery phase. One case was still waiting for surgery while completing the bedaquiline cycle at the moment the data collection was completed.

No significant differences were found between timing of surgery and final treatment outcomes. The median (IQR) anti-TB chemotherapy duration was 8 (5-13) months before and 10 (7-14) after surgery.

Based on data distribution of the variable 'surgery time' in relation to the start of anti-TB chemotherapy, an artificial threshold, based on the median value of the non-parametric distribution, of 244 days (8 months) was found to compare success rates of patients operated before or after it: 13 (68.4%) cases achieved treatment success when surgery was performed before and 16 (88.9%) after the threshold (P= 0.23). In other words, patients were more likely to achieve treatment success when their operation was performed 8 months or more after starting anti-TB chemotherapy.

Based on data distribution of the variable 'bedaquiline initiation' in relation to the time of surgery, an artificial threshold (chosen following the computation of the median value of the variable) was found at 114 days, with 10 (90.9%) cases achieving treatment success before and 11 (100%) after it (P= 1.0).

The median (IQR) number of surgery-related hospital admission-days was 70 (33.5-108).

Three cases were successfully re-operated because of complications. No post-operative death was notified. Out of 38 patients, 29 (76.3%) did not report post-operative surgical complications, while 3 had empyema (7.9%), 2 failed to re-expand the lung completely (5.3%), and one each (2.6%) had failure to re-expand the lung and bronchopleural fistula, pneumothorax, bleeding and a fistula.

A total of 90% patients achieved sputum smear- and 90.5% culture-conversion after surgery, with 69.1% treatment success, 20.0% failure, and 1.8% lost to follow-up (Table 2).

Discussion

We describe for the first time the use of adjunctive surgery in severe M/XDR-TB cases treated with bedaquiline-containing regimen achieving satisfactory outcomes and high bacteriological conversion rates.

Although the treatment success in this sample (69.1%) was lower than in the larger cohort previously reported (77%) *(2)*, it is still 10% higher than that reported by WHO *(1)*. In a large systematic review and meta-analysis of 1,572 MDR-TB cases undergoing surgery, long-term treatment success was higher (87%, with high results heterogeneity), and 3-6% all-cause mortality was observed *(21)*. However, in this study *(21)* the treatment success rate was lower (69%) in 73 XDR-TB (e.g. those with a resistance pattern comparable to that of our cohort) while, overall, the cases were less severe than in our cohort (mean number of resistances <4.9). The authors described an additional advantage when operating cases with >4.7 resistances, which more closely resembles our cohort *(21)*.

The study has limited size and retrospective design. Data were collected from a real-world scenario and several variables could not be collected in some settings due to the different care models adopted in high- and low-income countries. For example, we cannot describe the outcomes of the patient who, at the moment the data collection was completed, was waiting for the surgical operation.

However, useful information was obtained collating different surgical experiences, providing a scientific framework for further studies. It is important to underline that, because of historical reasons (bedaquiline approved in 2012) this study takes a picture of severe MDR-TB cases undergoing chemotherapy first, followed by surgery, and by bedaquiline treatment; in 20 patients surgery was performed during bedaquiline treatment. It is possible that earlier use of bedaquiline might have prevented the need for surgery in some of the cases, but our data do not allow to investigate this hypothesis.

We are unable to quantify the degree to which the use of surgery or bedaquiline contributed to overall treatment outcomes.

However, these study results offer several insights, which may be helpful for future management of difficult-to-treat patients:

1) When surgery was performed, about 50% of the patients were still sputum smear- and culture-positive. The combined action of surgery and bedaquiline is likely to be responsible for a 40% additional bacteriological conversion, as at the end of treatment >90% of the cases were bacteriologically negative. The final success rate was high (38/55, 69.1% with a cure rate of 65.5%) considered the severe resistance profile of the cases in our cohort.
2) There is agreement that patients need to start chemotherapy first; surgery may be indicated for selected cases after a few (3 or more) months of treatment, ideally with evidence of sputum/culture-conversion *(3,20,21)*, to reduce lesion size, interrupt bacterial replication, and reduce the risk of bacillary spread when operating. In theory, the initial effective antibiotic regimen (including a sufficient number of active drugs) could reduce the bacterial load and the extension of the histological lesions, while lowering the infectious risk for surgeons and increasing the probability of surgical success (small sized lesions are easier to manage) *(20,21)*.

   The study results do not provide evidence on optimal surgical timing, although the highest treatment success was achieved after 4-8 months of chemotherapy (statistically not significant). A larger sample size would allow a better assessment of the efficacy of surgery combined with antibiotic therapy in selected cases.
3) Bedaquiline was well tolerated *(2,5-7)*, the proportion of surgery-related complications modest and no surgery-related death was observed. Overall, the possibility to combine surgery and bedaquiline in selected cases with a severe pattern of drug-resistance seems to be justified from a safety perspective.

4) As no patient was treated at the same time with bedaquiline and delamanid, the study cannot shed light on the safety of the two new drugs combined administration (particularly in terms of QT interval prolongation (*22-27).* A single case was prescribed bedaquiline and delamanid sequentially, with a long interval between them (12 months); the patient had no QT interval changes.
5) The amount of resources to support surgery (70 days in emergency and surgical departments, weaning, subsequent pulmonary rehabilitation) *(28)* is considerable, although the overall cost of treating these patients is so high that marginal cost-effectiveness from surgery may still plausibly be realized.

In conclusion, the results of this study suggest that bedaquiline and surgery can be safely and effectively combined in selected cases with a specific indication. Prospective, well designed and adequately sized studies are necessary to better understand when to use bedaquiline and when to operate difficult-to-treat TB cases for whom indication exists.

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Table 1. Clinical characteristics (pre- and post- operative) of a retrospective multicentre cohort of drug-resistant tuberculosis cases treated with bedaquiline-containing regimens and adjunctive surgery

	Pre-surgery	***Post-surgery***
Median (IQR) n. of active drugs administered	5.0 (4.0-7.0)	6.0 (5.0-7.0)
Median (IQR) anti-TB treatment duration (months)	8.0 (5.0-13.0)	10.0 (7.0-14.0)
Anti TB regimen administered n (%)	42/42* (100.0)	55/55 (100.0)
Bedaquiline administered n (%)	*23/42*¶ (54.8)*	*33/55 (60.0)*
Delamanid administered n (%)	*0/41* (0.0)*	*1/55 (1.8)*
Linezolid administered n (%)	*20/41* (48.8)*	*36/55 (65.5)*
Clofazimine administered n (%)	*4/41* (9.8)*	*11/53* (20.7)*
Carbapenems administered n (%)	*5/41* (12.2)*	*11/55 (20.0)*
Fluoroquinolones administered n (%)	*32/41* (78.0)*	*41/53* (77.4)*
Second-line injectables administered n (%)	*18/41* (43.9)*	*23/55 (41.8)*
Sputum positive n (%)	20/42* (47.6)	18/20* (90.0)
Culture positive n (%)	23/42* (54.7)	19/21* (90.5)

Legend: IQR: interquartile range; TB: tuberculosis; *: denominator corresponds to total number of TB patients for whom data are available; ¶: numerator includes 20 patients who were administered bedaquiline before surgery and completed it after the operation

Table 2. Type of surgical intervention and final treatment outcomes of a retrospective multicentre cohort of drug-resistant tuberculosis cases treated with bedaquiline-containing regimens and adjunctive surgery

Type of surgical intervention	
Lobectomy, n (%)	15/55 (27.2)
Segmentectomy, n (%)	12/55 (21.8)
Pneumonectomy, n (%)	8/55 (14.5)
Lobectomy/thoracoplasty, n (%)	5/55 (9.0)
Pneumonectomy/thoracoplasty, n (%)	4/55 (7.2)
Thoracoplasty, n (%)	3/55 (5.4)
Insertion of endobronchial valves, n (%)	2/55 (3.6)
Segmentectomy/lobectomy, n (%)	1/55 (1.8)
Segmentectomy/phrenic nerve interruption, n (%)	1/55 (1.8)
Segmentectomy/decortication, n (%)	1/55 (1.8)
Extra-pleural plombage, n (%)	1/55 (1.8)
Open window thoracotomy, n (%)	1/55 (1.8)
Embolization, n (%)	1/55 (1.8)
Final treatment outcomes	
Cured, n (%)	36/55 (65.5)
Treatment completed, n (%)	2/55 (3.6)
Treatment success, n (%)	*38/55 (69.1)*
Treatment failed n (%)	11/55 (20.0)
Died, n (%)	-
Lost to follow-up, n (%)	1/55 (1.8)
Still on treatment, n (%)	5/55 (9.1)