Pulmonary resection combined with isoniazid- and rifampin-based drug therapy for patients with multidrug-resistant and extensively drug-resistant tuberculosis

Seung-Kyu Park a,b,*, Jin-Hee Kim a, Hyungseok Kang a, Jeong Su Cho a, Raymond A. Smego Jr c

a National Masan Tuberculosis Hospital, 486 Kapodong, Masan City, Republic of Korea
b International TB Research Center, Masan, Republic of Korea
c Medical University of the Americas, Nevis, West Indies

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KEYWORDS
Tuberculosis; MDR-TB; Drug resistance; Resectional surgery

Summary
Objective: To evaluate the clinical efficacy of pulmonary resection and postoperative use of a first-line drug regimen for patients with well-localized, cavitary pulmonary multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB).
Methods: This was a prospective case study set in the National Masan Tuberculosis Hospital in Masan, Republic of Korea. From February 1998 to May 2004, 19 patients with well-localized, cavitary pulmonary MDR-TB or XDR-TB were enrolled and followed prospectively through April 2007. After radical surgical resection, patients were treated with anti-tuberculous therapy consisting of isoniazid (H), rifampin (R), ethambutol (E), pyrazinamide (Z), and streptomycin (S) (3HREZS/3HRES/6HRE).
Results: All recovered isolates of Mycobacterium tuberculosis were resistant to isoniazid and rifampin, and to a mean of 4.7 anti-tuberculous drugs (range 2–8 drugs). Seventeen patients had MDR-TB and two had XDR-TB. Surgical procedures included: lobectomy (14 patients), lobectomy plus segmentectomy or wedge resection (four patients), and pneumonectomy (one patient). The median time to postoperative sputum smear and culture conversion was 2 days (range 1–23 days). Fifteen (78.9%) subjects, including both with XDR-TB, had durable cures (mean follow-up period 53.2 months). One patient failed to convert her sputum and was successfully switched to second-line therapy. Another patient developed active disease again 68 months after cure, likely due to re-infection with a new M. tuberculosis strain. Two patients were lost to follow-up after hospital discharge.

* Corresponding author. Tel.: +82 55 249 3791; fax: +82 55 242 1135.
E-mail address: pulmo116@nmh.go.kr.com (S.-K. Park).

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Conclusion: Resectional lung surgery combined with isoniazid- and rifampin-based antituberculous chemotherapy can be an effective treatment strategy for patients with well-localized, cavitary pulmonary MDR-TB and XDR-TB.

Introduction

Multidrug-resistant tuberculosis (MDR-TB), defined as in vitro resistance to at least both isoniazid and rifampin, has become an emerging global public health crisis. Strains of multidrug-resistant Mycobacterium tuberculosis are often resistant to other anti-tuberculous agents in addition to isoniazid and rifampin. When such an isolate is resistant to any second-line injectable agent (e.g., amikacin, capreomycin, or kanamycin) and any fluoroquinolone, the strain is termed extensively drug-resistant tuberculosis (XDR-TB). In Korea, there is a high burden of both MDR-TB and XDR-TB. Between 2000 and 2004, among 11,939 clinical samples reported to the World Health Organization/International Union Against Tuberculosis and Lung Disease (WHO/IUATLD) Supra-National Reference Laboratory Network, 1298 (10.9%) were MDR-TB and, of these, 15.4% were XDR-TB. The management of MDR-TB and XDR-TB requires extended treatment and expensive and potentially toxic drug regimens, and often results in higher rates of treatment failure and death compared to drug-sensitive disease. Reported cure or treatment completion rates for MDR-TB using second-line agents have ranged from 44% to 83%. Treatment failure is especially common with patients co-infected with XDR-TB and HIV, where mortality approaches 100%.

In the past decade, surgical intervention has re-emerged as an important adjunct in the management of MDR-TB. Lung resection combined with antituberculosis chemotherapy for MDR-TB has shown success rates of 89–96%. With increasing rates of XDR-TB worldwide, resectional surgery will likely become increasingly utilized in these patients with very limited chemotherapeutic options. At our institution, we have observed that many patients treated for MDR-TB and XDR-TB require extended treatment and expensive and potentially toxic drug regimens, and often results in higher rates of treatment failure and death compared to drug-sensitive disease. Reported cure or treatment completion rates for MDR-TB using second-line agents have ranged from 44% to 83%. Treatment failure is especially common with patients co-infected with XDR-TB and HIV, where mortality approaches 100%.

Methods

This was a prospective case study. All patients were treated at the National Masan Tuberculosis Hospital (NMTH) in Masan, Republic of Korea. The hospital is a 430-bed facility that serves as a national referral center for individuals with recurrent and/or drug-resistant tuberculosis. Approximately 95% of hospitalized patients have pulmonary disease, and about 50% have MDR-TB. Anti-tuberculous agents typically used to treat MDR-TB at NMTH, as part of standardized or individualized combination regimens, include pyrazinamide, ethambutol, prothionamide, cycloserine, streptomycin or kanamycin, para-aminosalicylic acid, and ofloxacin.

The Institutional Review Board of NMTH approved this study and informed consent was obtained from all participants and one of their family members before entry into the study. One of the authors was responsible for obtaining informed consent from all study participants, and this involved explaining to each patient and his/her family, in detail, the purpose of this study, the risk of operation, and the potential necessity of changing the drug regimen to second-line drugs during the course of postoperative chemotherapy. In most cases, this required at least three interviews. The final decision to participate in this study was left entirely to the patients.

Between February 1998 and May 2004, 107 patients with MDR-TB underwent some type of surgical procedure at NMTH. All patients had preoperative chest X-rays and high-resolution chest computed tomography (HRCT). In order to confirm radical resectability, HRCT was performed in each patient within at least one month before operation, and one of the authors examined the lung intra-operatively by direct palpation in order to evaluate for any other lesion(s) that could not be detected by HRCT prior to surgery. Where radical removal of the lesion was not considered feasible, patients were excluded from the study. Eighty-three cases had radical resectional surgery and received second-line anti-tuberculosis therapy before and after surgery. Five cases were not considered to be radically resectable at the time of surgical lung examination and were excluded from the study and treated with second-line anti-tuberculosis drugs postoperatively. The remaining 19 subjects were enrolled as the study cohort. All of these patients were HIV-seronegative and were shedding M. tuberculosis resistant to both isoniazid and rifampin at the time of diagnosis. All had preoperative chest X-rays and HRCT that demonstrated well-localized, cavitary pulmonary tuberculosis that was confined to only the portion of lung that was subsequently removed surgically. Two subjects were believed to have primary MDR-TB, while 17 had secondary or acquired MDR-TB according to their treatment history and drug susceptibility testing results over time. Preoperative sputum acid-fast bacilli (AFB) smear status was positive in 10 subjects and negative in nine. For the latter group, each had chest X-rays that demonstrated one or more thick-walled cavities, and each also had a history of one or more episodes of active tuberculosis in the same anatomic area. None of the study subjects had ever received any second-line anti-tuberculous chemotherapy for their disease previously.

After resectional surgery, postoperative regimens for all 19 patients consisted of 3HRZES/3HRES/6HRE, even for documented MDR-TB, rather than other second- and third-line...
agents in the belief that such therapy would minimize drug adverse events and optimize tolerance and adherence. After operation, sputum smears and cultures were obtained every day for one week, then every second week for one month, and then monthly for the entire follow-up period. Chest X-rays were obtained every month and HRCT was obtained twice, i.e., at 6 months after surgery and at the end of chemotherapy. Postoperatively, sputum negativity was defined as serially-negative sputum smears and cultures.

Drug susceptibility testing of all M. tuberculosis strains was performed in our laboratory using an absolute concentration method described by Canetti and colleagues,\(^{22,23}\) using Loewenstein—Jensen (L—J) medium. Drugs and their critical concentrations for resistance were as follows: isoniazid 0.2 \(\mu g/ml\), rifampin 40 \(\mu g/ml\), ethambutol 2 \(\mu g/ml\), streptomycin 10 \(\mu g/ml\), kanamycin 40 \(\mu g/ml\), prothionamide 40 \(\mu g/ml\), cycloserine 30 \(\mu g/ml\), para-aminosalicylic acid 1 \(\mu g/ml\), ofloxacin 2 \(\mu g/ml\). Pyrazinamide susceptibility was determined using a pyrazinamidase test. Resistance was indicated by the growth of more than 1\% of the colonies on drug-containing medium.

**Results**

Patient characteristics and clinical outcomes for all 19 patients are shown in Table 1. The male:female ratio for the study cohort was 15:4. The mean patient age was 31.1 years (range 20—46 years). Recovered isolates of M. tuberculosis were resistant to a mean of 4.7 anti-tuberculous drugs (range 2—8 drugs). All 19 study isolates displayed in vitro resistance to isoniazid and rifampin, and XDR-TB was present in two cases. Resistance to the first-line agents ethambutol, streptomycin, and pyrazinamide was seen in 73.7\%, 36.8\%, and 26.3\% of isolates, respectively; 10 of 19 subjects (52.6\%) had isolates that were resistant to at least two of these three agents. Some strains showed resistance to second-line anti-tuberculous drugs that the patients had not knowingly been exposed to previously. Resistance rates for second-line drugs were as follows: para-aminosalicylic acid 47.4\%, ofloxacin 26.3\%, kanamycin 21.1\%, prothionamide 21.1\%, and cycloserine 15.8\% (Table 2).

Surgical procedures included lobectomy (14 patients), lobectomy plus segmentectomy or wedge resection (four patients), and pneumonectomy (one patient). There were no significant postoperative complications such as bleeding, empyema, and bronchopleural fistula. Ten patients (52.6\%) had preoperative sputum AFB smear and/or culture positivity; for these individuals, the median time to sputum smear and culture conversion was 2 days (range 1—3 days for smear and 1—23 days for culture), and each remained serially smear-negative after surgery.

Fifteen (78.9\%) patients had durable cures (mean follow-up period 53.2 months). One of these subjects died from an unknown cause other than pulmonary tuberculosis one and a half years after treatment completion. One patient failed to convert her sputum smear and culture even after seven months of treatment postoperatively. Drug sensitivity testing revealed her isolate to be resistant to isoniazid, rifampin, ethambutol, para-aminosalicylic acid, and streptomycin. Her drug regimen was changed to second-line drug therapy consisting of prothionamide, pyrazinamide, ofloxacin, cycloserine, and kanamycin and sputum conversion was achieved four months later. Another patient relapsed during the follow-up period, 68 months after cure. He was retreated with second-line drugs and achieved a second cure after an additional 24 months of chemotherapy. The remaining two patients interrupted their medications and were lost during the follow-up period (Table 3).

**Discussion**

The successful treatment of any infectious disease involves a delicate balance of host and pathogen processes. Surgery for MDR-TB and XDR-TB can best be considered as a neo-adjuvant ‘debulking’ procedure to remove a major, focal burden of tubercle bacilli contained within necrotic and non-viable lung tissue. In one study, resected tissue culture demonstrated mycobacterial growth even from patients who were sputum AFB smear-negative preoperatively.\(^{24}\) In the present study, we also performed tissue culture for nine subjects with sputum culture-negativity before surgery, and all of them had tissue that was both smear- and culture-positive. Incomplete resection of tuberculous lesions, especially cavities, but also nodules, bullae, microcavities, or fibrotic areas, is one of the risk factors for disease relapse.\(^{25}\) These prior studies and the excellent outcome in our study exemplify the benefit of complete or radical removal of all tuberculous lesions for cure in both MDR- and XDR-TB patients.

In the human lung, selection of drug-resistance mutations in M. tuberculosis occurs predominantly within lung cavities in which high bacterial loads, active mycobacterial replication, and reduced exposure to host defense mechanisms have
been reported. It may also be that surgical removal of heavily-diseased lung segments results in partial restoration of immunologic responses or some change in immunologic milieu in the host, which can allow the host to more efficiently contain and eradicate the tuberculous infection, even in the presence of chemotherapeutic agents that do not have sufficient eradication activity in vitro against multidrug-resistant 

It seems likely that the 78.9% long-term cure rate seen in our series may have been determined, at least in part, by the varying degrees of susceptibility of 

Table 3 Clinical profiles and outcomes for 19 multidrug-resistant or extensively drug-resistant TB subjects who received radical surgical resection and a regimen composed of first-line anti-tuberculous drugs

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Sex/age (years)</th>
<th>Date of diagnosis</th>
<th>Resistant drugs</th>
<th>Date of surgery</th>
<th>Type of surgery</th>
<th>Outcome</th>
</tr>
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<tr>
<td>1</td>
<td>M/32</td>
<td>1997-09-30</td>
<td>HERO</td>
<td>1998-02-11</td>
<td>RUL</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>M/37</td>
<td>1997-03-07</td>
<td>HERZ</td>
<td>1998-06-02</td>
<td>RUL</td>
<td>D</td>
</tr>
<tr>
<td>3</td>
<td>F/36</td>
<td>1997-11-11</td>
<td>HERPS</td>
<td>1998-07-01</td>
<td>LUL + Wedge</td>
<td>F</td>
</tr>
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<td>4</td>
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<td>HERPSK</td>
<td>2000-01-12</td>
<td>RUL</td>
<td>C</td>
</tr>
<tr>
<td>5</td>
<td>M/30</td>
<td>1999-10-17</td>
<td>HR</td>
<td>2000-02-15</td>
<td>RUL</td>
<td>C</td>
</tr>
<tr>
<td>6</td>
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<td>HERPSK</td>
<td>2001-02-13</td>
<td>RUL</td>
<td>C</td>
</tr>
<tr>
<td>7</td>
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<td>HERPSK</td>
<td>2001-05-29</td>
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<td>C</td>
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<td>8</td>
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<td>HERZD</td>
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<tr>
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<td>HER</td>
<td>2002-03-19</td>
<td>LUL</td>
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<tr>
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<td>HRS</td>
<td>2002-11-12</td>
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<td>C</td>
</tr>
<tr>
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<td>HRPSK</td>
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<tr>
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<td>HER</td>
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<tr>
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<td>2004-01-07</td>
<td>RUL + Seg</td>
<td>C</td>
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<td>2003-08-09</td>
<td>HRO</td>
<td>2004-02-10</td>
<td>RUL + Wedge</td>
<td>C</td>
</tr>
</tbody>
</table>

*a* H, isoniazid; E, ethambutol; R, rifampin; Z, pyrazinamide; P, para-aminosalicylic acid; C, cycloserine; Th, prothionamide; O, ofloxacin; S, streptomycin; K, kanamycin.

*b* RUL, right upper lobectomy; LUL, left upper lobectomy; LP, left pneumonectomy; Wedge, wedge resection; Seg, segmentectomy.

*c* R, relapse; D, default; F, failed; C, cure.
were resistant to at least one of the first-line agents other than isoniazid and rifampin, and 52.6% were resistant to at least two drugs. This suggests that surgery rather than antimicrobial drug effect, may have been the most crucial factor leading to clinical cure in these patients, as does the short mean time of 2 days to sputum conversion following operation.

Our study could not identify possible risk factors for treatment failure or relapse among the participants due to its small numbers. In one patient who developed active tuberculosis 68 months later after completion of treatment, the different antibiograms of his pre- and post-chemotherapy isolates strongly suggested exogenous re-infection with a new strain of M. tuberculosis rather than late disease relapse, although genetic fingerprinting of these isolates was not performed.31 A cautionary note is that patients whose primary infection is clearly from a source patient with known resistant disease are likely to have clonal expansion of the resistant clone and may, therefore, be less likely to benefit from the rationale employed in this isoniazid- and rifampin-based drug regimen.

In using isoniazid and rifampin to treat MDR-TB, we had to confront several ethical issues. Theoretically, in removing portions of the lung that contained the entire burden of disease according to chest CT imaging and manual palpation of the lung during operation, it is possible that no further chemotherapy was needed in order to cure infection in these patients. Analogously, from historical experience during the pre-antibiotic era we know that adequate drainage of bacterial abscesses can sometimes lead to complete cure of infection without the concomitant use of antimicrobial drugs. Understandably, however, we did not feel ethically comfortable in this option. But we do believe, however, that for individuals with well-demarcated pulmonary tuberculosis that can be radically removed by surgical intervention, the effective use of first-line drugs with bactericidal efficacy can be ethically justified.

In conclusion, resectional lung surgery combined with isoniazid- and rifampin-based first-line anti-tuberculous chemotherapy can be an effective treatment strategy for patients with well-localized, cavitary pulmonary MDR-TB and XDR-TB.

Conflict of interest: No conflict of interest to declare.

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