Outcomes of Patients With Multidrug-Resistant Pulmonary Tuberculosis Treated With Ofloxacin/Levofloxacin-Containing Regimens*

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Objective: To analyze outcomes of patients with multidrug-resistant tuberculosis (MDR-TB) treated with ofloxacin/levofloxacin-containing regimens.

Materials and methods: From February 1990 through June 1997, 63 MDR-TB patients (with bacillary resistance to at least isoniazid and rifampin in vitro) were analyzed retrospectively. Twenty-two patients (34.9%) had had no previous antituberculosis chemotherapy. Each patient received either ofloxacin (53) or levofloxacin (10) even though 13 patients had bacilli resistant to ofloxacin in vitro. The other accompanying drugs mainly included aminoglycosides, cycloserine, ethionamide/prothionamide, and pyrazinamide. Sputum smear and culture examinations for acid-fast bacilli (AFB) were performed monthly for the initial 6 months and then at 2- to 3-month intervals until the end of treatment. Comparison was made between clinical successes and failures using univariate and multiple logistic regression analyses for the following variables: age, sex, presence of cavitation, extent of disease, sputum smear positivity, in vitro resistance to ofloxacin, in vitro resistance to streptomycin and/or ethambutol, treatment adherence, and the number of drugs per regimen.

Results: Fifty-one patients (81.0%) were cured, nine patients (14.3%) failed, and three patients (4.7%) died. For the entire group, the mean duration of treatment was 14.0 months, and the mean number of drugs was 4.7. Mean durations of chemotherapy in successful and failed patients were 14.5 and 14.2 months, respectively. Mean time for sputum smear and culture conversions were 1.7 and 2.1 months, respectively. Only cavitation, resistance to ofloxacin, and poor adherence were found to be variables independently associated with adverse outcomes (p < 0.05; odds ratios = 15.9, 13.5, 12.8, respectively). Negative sputum cultures after 2 and 3 months of therapy were 100% predictive of cure. Positive sputum cultures after 2 and 3 months were 52.3% and 84.6% predictive of failure, respectively. One patient (2.1%) relapsed after apparent cure. Twenty-five patients experienced adverse drug reactions, but only 12 of them needed drug modifications.

Conclusion: Most MDR-TB patients can be treated effectively with ofloxacin/levofloxacin-containing regimens. Presence of cavitation, resistance to ofloxacin in vitro, and poor adherence to therapy portend treatment failure. Monitoring monthly sputum culture for AFB in the initial months of chemotherapy helps predict clinical outcomes.

Key words: multidrug resistance; ofloxacin/levofloxacin; tuberculosis

Abbreviations: AFB = acid-fast bacilli; MDR-TB = multidrug-resistant tuberculosis; MIC = minimum inhibitory concentration; TB = tuberculosis

The fluoroquinolones were found to have good in vitro activity against Mycobacterium tuberculosis in the 1980s.1–5 Subsequent observations have suggested in vivo efficacy.6–11 Thus, incorporation of fluoroquinolones in second-line regimens for the management of multidrug-resistant tuberculosis (MDR-TB) has been recommended by many authorities, including the World Health Organization.12–14 Despite this, there is still a dearth of evidence on the role of fluoroquinolones in the management of MDR-TB.13 Randomized, controlled clinical trials on MDR-TB are difficult to conduct and have additional ethical constraints. We therefore performed a retrospective analysis of a cohort of MDR-TB patients treated with fluoroquinolone-containing regimens in the 1990s. We
hoped to evaluate the overall contribution of fluoroquinolones to the therapy of MDR-TB and the optimal duration of such treatment.

The fluoroquinolones studied were ofloxacin and levofloxacin. The former has been used by us for treatment of MDR-TB since the late 1980s. More recent observations suggest in vitro activity of levofloxacin (active S(-) enantiomer of ofloxacin) against *M tuberculosis*, although cross-resistance has also been demonstrated. This superior in vitro activity, in addition to clinical data suggesting that levofloxacin causes less neurotoxicity, resulted in a preference for levofloxacin in the later part of this study.

**Materials and Methods**

**Data Collection**

The inpatient and outpatient medical records of 79 patients with MDR-TB were reviewed. These patients had been admitted to Grantham Hospital, a tertiary referral center for tuberculosis (TB), from chest clinics under the administration of the Department of Health in Hong Kong between February 1990 and June 1997. All 79 patients were seronegative for the HIV antibody by the enzyme-linked immunosorbent assay. The inpatient and outpatient medical records of 79 patients were reviewed. Patients had been admitted to Grantham Hospital, a tertiary referral center for tuberculosis (TB), from chest clinics under the administration of the Department of Health in Hong Kong between February 1990 and June 1997. All 79 patients were seronegative for the HIV antibody by the enzyme-linked immunosorbent assay. *M tuberculosis*, although cross-resistance has also been demonstrated. This superior in vitro activity, in addition to clinical data suggesting that levofloxacin causes less neurotoxicity, resulted in a preference for levofloxacin in the later part of this study.

**Drug Susceptibility Tests**

The drug susceptibility tests were performed using the absolute minimum inhibitory concentration (MIC) method for isoniazid and the resistance-ratio method for all other drugs. The lute minimum inhibitory concentration (MIC) method for isoniazid, an isomer of isonicotinic, streptomycin and amikacin, ethionamide/prothionamide, cycloserine, pyrazinamide, ethambutol, p-aminosalicylic acid, amoxicillin-clavulanic acid, and chloramphenicol; these were largely selected on the basis of results of *in vitro* susceptibility tests. After discharge from the hospital, patients continued to receive directly observed treatment, by clinic staff in most cases and by family members in a small number.

**Monitoring of Sputum Bacteriology and Definitions of Outcomes**

After the pretreatment sputum smear and culture, each patient had sputum evaluated monthly for 6 months. After that, the sputum was evaluated every 2 or 3 months, at the discretion of the attending physician. Success or cure was defined as sustained bacteriologic conversion of sputum culture of AFB from positive to negative for at least 6 consecutive months during therapy and after its cessation. Temporary conversion of sputum culture to negative not meeting the above was labeled as failure; so was the absence of sputum culture conversion to negative throughout treatment.

**Statistical Analysis**

Data were expressed in means ± SD and ranges. In identification of variables that might affect treatment outcomes, namely, age, male sex, presence of cavitation, extensive disease, sputum smear positivity, *in vitro* resistance to ofloxacin, *in vitro* resistance to streptomycin and/or ethambutol, poor adherence, and the number of drugs used, comparison of the success and failure or death groups was made using Student’s independent samples *t* tests for numeric variables and *χ*² test for categoric variables. Where an expected value in a certain cell in a contingency table was < 5, the Fisher’s Exact Test was used. A *p* value < 0.05 was considered significant. A multiple logistic regression analysis was then performed to identify the variables that were independently associated with adverse outcomes of chemotherapy.

**Results**

**Patients Excluded**

Sixteen patients were excluded because they received treatment for < 6 months. Two patients left against medical advice and did not receive any chemotherapy. Another two patients succumbed before chemotherapy could be initiated; they had severe COPD and carcinomatosis. Three patients died of diseases other than TB: the first was a 72-year-old man who died of chronic renal failure after 5 months of drug treatment. Sputum smear and culture for AFB had converted from positive to negative after 1 month of treatment. The second was a 66-year-old man who died of acute myocardial infarction. Sputum smear and culture for AFB had become negative after 2 months of therapy. The third was a 61-year-old man who died suddenly of cerebrovascular accident after he had received 4 months of chemotherapy. Sputum smear and culture for AFB were still positive. Three more patients who
did not receive fluoroquinolone-containing drug regimens were also excluded. Each of these three patients had bacilli resistant to ofloxacin. They received a mean of 4.3 ± 0.6 drugs (range, 4 to 5 drugs), and only one of them achieved treatment success. Finally, six more patients abandoned treatment after they had received chemotherapy for < 6 months (2.8 ± 1.6 months; range, 1 to 5 months).

**Demographic and Clinical Characteristics**

Sixty-three patients were included in the final analysis. Sixty-two were Chinese and one was British. Forty-seven (74.6%) were male, and 16 (25.4%) were female. Mean age was 45.2 ± 16.0 years (range, 12 to 77 years). Mean body weight was 51.4 ± 8.8 kg (range, 29 to 73 kg). All had radiographic and bacteriologic evidence of pulmonary TB. Two patients had extrapulmonary involvement: meningitis and spondylitis. Concomitant medical diseases were present in 23 patients (36.5%). These included COPD, hypertension, diabetes mellitus, hyperlipidemia, and chronic viral or alcoholic liver diseases. Forty-one patients (65.1%) had previous therapy. The mean number of previous treatment courses was 2.0 ± 1.4 (range, 1 to 5). Each treatment course lasted > 4 weeks. Thus, 34.9% of patients had initial resistance to isoniazid and rifampin (with or without associated resistance to streptomycin and/or ethambutol), whereas 65.1% of patients may have acquired resistance to the aforementioned drugs. A comparison of the various characteristics of the patients included in and those excluded from the final analysis is presented in Table 1. There are no significant differences, except that the excluded patients were older.

**Drug Regimens and Durations**

As a group, all patients included in the final analysis received a mean of 4.7 ± 0.7 drugs (range, 3 to 6 drugs) on commencement of therapy. Ofloxacin was used in 53 patients and levofloxacin in 10 patients. The other common drugs in the regimens included aminoglycosides, ethionamide/prothionamide, cycloserine, pyrazinamide, and ethambutol (Table 2). The fluoroquinolone was administered until cessation of chemotherapy in all 63 patients. Aminoglycosides were usually administered for 3 to 6 months depending on tolerance. The duration of therapy with other agents was tailored to patient tolerance and individual physician judgment. The minimum duration of therapy for patients who responded microbiologically was 1 year. The variables considered at discontinuation of treatment included time of sputum smear and culture conversion, extent of radiographic disease and rapidity of improvement, rapidity and completeness of closure of cavities, extent of drug resistance in vitro, presence of diabetes mellitus or silicosis, and extrapulmonary disease. Presence of unfavorable variables prompted the decision to prolong therapy beyond 1 year. Patients who had not responded microbiologically after 9 to 12 months of chemotherapy would have treatment reviewed. Treatment was stopped then or continued for a few more months. The mean number of drugs received by patients at the seventh month was 3.6 ± 0.6 drugs (range, 3 to 5 drugs). Dosages of the second-line drugs are depicted in Table 3. The mean duration of chemotherapy in 63 patients was 14.0 ± 3.7 months (range, 0.5 to 24 months). Three patients died of TB after 0.5, 7, and 7 months of chemotherapy. Excluding those three patients, the mean duration of chemotherapy was 14.4 ± 3.1 months (range, 9 to 24 months).

**Adherence to Therapy**

Fourteen patients (22.2%) had poor adherence to chemotherapy, which was defined as missing ≥ 20% of the designated number of drug doses. The rest received ≥ 80% of the designated treatment doses.

**Outcomes**

Fifty-one patients were cured. These included the two patients with extrapulmonary disease. Their sputum smear for AFB converted from positive to negative at a mean of 1.7 ± 1.0 months (range, 1 to 5 months) after chemotherapy commencement. Their sputum culture converted from positive to negative at a mean of 2.1 ± 1.2 months (range, 1 to

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**Table 1—Comparison of Demographic, Clinical, and Bacteriologic Characteristics Between Patients Included in and Excluded From Analysis**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients Included (N = 63)</th>
<th>Patients Excluded (N = 16)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>47:16</td>
<td>13:3</td>
<td>NS</td>
</tr>
<tr>
<td>Age, yr</td>
<td>45.2</td>
<td>61.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>51.4</td>
<td>48.4</td>
<td>NS</td>
</tr>
<tr>
<td>Previous treatment (lots)</td>
<td>1.3</td>
<td>1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>22 (34.9%)</td>
<td>6 (37.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Extensive disease†</td>
<td>34 (54.0%)</td>
<td>10 (62.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cavity</td>
<td>32 (50.8%)</td>
<td>11 (68.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Positive sputum smear</td>
<td>57 (90.5%)</td>
<td>15 (93.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Resistance to first-line drugs, n‡</td>
<td>3.3</td>
<td>3.2</td>
<td>NS</td>
</tr>
<tr>
<td>Resistance to ofloxacin</td>
<td>13 (20.6%)</td>
<td>4 (25.0%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*NS = not significant.
†Total radiographic extent greater than one lung.
‡With reference to (isoniazid and rifampin) ± (streptomycin and/or ethambutol).
5 months) after starting chemotherapy. The bacteriologic conversion of the successful patients was sustained. Nine patients failed and three died of TB. The mean duration of chemotherapy in the 51 successful patients was 14.5 ± 3.0 months (range, 9 to 24 months). Four patients in this group discontinued chemotherapy at their own will after receiving 9 to 24 months). Four patients in this group discontinuated chemotherapy at their own will after receiving 9 to 11 months of drug treatment. However, all of them had sputum culture converted to negative at a mean of 2.3 ± 1.3 months (range, 1 to 4 months) after initiation of chemotherapy. One patient with extensive drug resistance received 24 months of chemotherapy. The mean duration of chemotherapy in the 51 successful patients was 14.5 ± 3.0 months (range, 9 to 24 months). Four patients in this group discontinued chemotherapy at their own will after receiving 9 to 11 months of drug treatment. However, all of them had sputum culture converted to negative at a mean of 2.3 ± 1.3 months (range, 1 to 4 months) after initiation of chemotherapy. One patient with extensive drug resistance received 24 months of chemotherapy. The mean duration of chemotherapy in the 51 successful patients was 14.5 ± 3.0 months (range, 9 to 24 months). Four patients in this group discontinued chemotherapy at their own will after receiving 9 to 11 months of drug treatment. However, all of them had sputum culture converted to negative at a mean of 2.3 ± 1.3 months (range, 1 to 4 months) after initiation of chemotherapy. One patient with extensive drug resistance received 24 months of chemotherapy. The mean duration of chemotherapy in the 51 successful patients was 14.5 ± 3.0 months (range, 9 to 24 months). Four patients in this group discontinued chemotherapy at their own will after receiving 9 to 11 months of drug treatment. However, all of them had sputum culture converted to negative at a mean of 2.3 ± 1.3 months (range, 1 to 4 months) after initiation of chemotherapy. One patient with extensive drug resistance received 24 months of chemotherapy. The mean duration of chemotherapy in the 51 successful patients was 14.5 ± 3.0 months (range, 9 to 24 months). Four patients in this group discontinued chemotherapy at their own will after receiving 9 to 11 months of drug treatment. However, all of them had sputum culture converted to negative at a mean of 2.3 ± 1.3 months (range, 1 to 4 months) after initiation of chemotherapy. One patient with extensive drug resistance received 24 months of chemotherapy. The mean duration of chemotherapy in the 51 successful patients was 14.5 ± 3.0 months (range, 9 to 24 months). Four patients in this group discontinued chemotherapy at their own will after receiving 9 to 11 months of drug treatment. However, all of them had sputum culture converted to negative at a mean of 2.3 ± 1.3 months (range, 1 to 4 months) after initiation of chemotherapy. One patient with extensive drug resistance received 24 months of chemotherapy. The mean duration of chemotherapy in the 51 successful patients was 14.5 ± 3.0 months (range, 9 to 24 months). Four patients in this group discontinued chemotherapy at their own will after receiving 9 to 11 months of drug treatment. However, all of them had sputum culture converted to negative at a mean of 2.3 ± 1.3 months (range, 1 to 4 months) after initiation of chemotherapy. One patient with extensive drug resistance received 24 months of chemotherapy. The mean duration of chemotherapy in the 51 successful patients was 14.5 ± 3.0 months (range, 9 to 24 months). Four patients in this group discontinued chemotherapy at their own will after receiving 9 to 11 months of drug treatment. However, all of them had sputum culture converted to negative at a mean of 2.3 ± 1.3 months (range, 1 to 4 months) after initiation of chemotherapy. One patient with extensive drug resistance received 24 months of chemotherapy. The mean duration of chemotherapy in the 51 successful patients was 14.5 ± 3.0 months (range, 9 to 24 months). Four patients in this group discontinued chemotherapy at their own will after receiving 9 to 11 months of drug treatment. However, all of them had sputum culture converted to negative at a mean of 2.3 ± 1.3 months (range, 1 to 4 months) after initiation of chemotherapy. One patient with extensive drug resistance received 24 months of chemotherapy. The mean duration of chemotherapy in

Table 2—Profile of Susceptibility Patterns to Conventional Short-Course Chemotherapeutic Drugs and Treatment Regimens for 63 Patients With MDR-TB

<table>
<thead>
<tr>
<th>First-Line Drugs</th>
<th>Number of Patients Resistant</th>
<th>Number of Patients on Second-Line Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>12‡</td>
<td>12 O/L K/S/A Et/Pt Cye Z M PAS Ang Clo</td>
</tr>
<tr>
<td>HRM</td>
<td>9†</td>
<td>9 6 5 7 12 0 0 0 0</td>
</tr>
<tr>
<td>SHR</td>
<td>17§</td>
<td>17 6 5 9 3 2 1 0 0</td>
</tr>
<tr>
<td>SHRM</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>63</td>
<td>63 6 57 57 34 29 7 4 3</td>
</tr>
</tbody>
</table>

*A = amikacin; Ang = amoxicillin-clavulanic acid; Clo = clofazimine; Cye = cycloserine; Et/Pt = ethionamide/prothionamide; H = isoniazid; K = kanamycin; L = levofloxacin; M = ethambutol; O = ofloxacin; PAS = p-aminosalicylic acid; R = rifampin; S = streptomycin; Z = pyrazinamide.

‡8 patients received 5 drugs; 4 patients received 4 drugs.

†1 patients received 5 drugs; 7 patients received 4 drugs; 1 patient received 3 drugs.

§3 patients received 6 drugs; 12 patients received 5 drugs; 2 patients received 4 drugs.

||2 patients received 6 drugs; 19 patients received 5 drugs; 4 patients received 4 drugs.

the nine living patients with treatment failure was 14.2 ± 3.4 months (range, 10 to 18 months). Thus, there was no difference in the durations of chemotherapy between the treatment success and failure groups (p > 0.05).

Of the variables that might be associated with the treatment outcome, only the presence of cavitation, resistance to ofloxacin in vitro, and poor adherence emerged as variables significantly associated with adverse outcomes (Table 4). When the total number of drugs used, as well as the number of active drugs at different junctures of treatment, namely, at commencement, seventh month, and cessation of treatment, was compared by univariate analysis between the success and failure or death groups, no significant difference was noted. Active drugs referred to those drugs with activity demonstrated by susceptibility tests in vitro. Further analysis was made after stratification of patients receiving fluoroquinolones into those who received ofloxacin (n = 53) and levofloxacin (n = 10). Forty-three of 53 patients in the ofloxacin group had bacilli susceptible to ofloxacin, and 37 achieved treatment success. Among the remaining 10 patients with bacillary resistance to ofloxacin, only 5 were cured. In the levofloxacin group, 7 of 10 patients had bacilli susceptible to ofloxacin, and all had treatment success with levofloxacin-containing regimens. Of the remaining three patients with bacillary resistance to ofloxacin, two were successfully treated with levofloxacin-containing regimens. The three variables independently associated with adverse outcomes persisted when multiple logistic regression analysis was applied to the 53 patients given ofloxacin only (p = 0.01 [cavitation], p = 0.004 [resistance to ofloxacin], p = 0.01 [poor adherence]; odds ratios, 17.5, 18.2, and 10.8, respectively).

Table 3—Dosages of Second-Line Antituberculosis Drugs Used in 63 Patients With MDR-TB

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofloxacin</td>
<td>645.3 ± 84.5 mg (600–800 mg)</td>
<td>once daily</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>640 ± 84.4 mg (600–800 mg)</td>
<td>once daily</td>
</tr>
<tr>
<td>Kanamycin/streptomycin/amikacin</td>
<td>735.8 ± 66.7 mg (500–750 mg)</td>
<td>5 times per week</td>
</tr>
<tr>
<td>Kanamycin/streptomycin/amikacin</td>
<td>800.0 ± 111.8 mg (750–1000 mg)</td>
<td>3 times per week</td>
</tr>
<tr>
<td>Ethionamide/prothionamide</td>
<td>728.1 ± 64.8 mg (500–750 mg)</td>
<td>once daily</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>720.0 ± 82.1 mg (500–750 mg)</td>
<td>once daily</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>1.8 ± 0.3 g (1–2 g)</td>
<td>once daily</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>956 ± 339.2 mg (600–1700 mg)</td>
<td>once daily</td>
</tr>
<tr>
<td>p-Aminosalicylic acid</td>
<td>5 g bid</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td>750 mg–375 mg bid</td>
<td></td>
</tr>
<tr>
<td>Clofazimine</td>
<td>100 mg once daily</td>
<td></td>
</tr>
</tbody>
</table>

*Dosage is reported as mean ± SD, with range in parentheses.
Adverse Drug Reactions

Twenty-five of the treated patients (39.7%) experienced adverse drug reactions of varying severity. The most common ones were related to the otoves-tibular and gastrointestinal systems and the CNS. Some patients had multiple adverse reactions (Table 5). However, modification of drug regimens was needed in only 12 patients. Nine of them required termination of aminoglycoside treatment after a mean of 3.0 ± 1.6 months (range, 1 to 5 months) because of otovestibular toxicity or nephrotoxicity. Five patients had CNS dysfunction, namely, depression (n = 3) and seizures (n = 2), which necessitated withdrawal of cycloserine at a mean of 4.0 ± 3.6 months (range, 1 to 9 months). Four patients had intolerable bloating, nausea, and vomiting that required withdrawal of ethionamide/prothionamide from the regimen after a mean of 4.0 ± 3.6 months (range, 1 to 9 months). Two patients had pyrazinamide withdrawn after 3 months of therapy because of severe clinical gout and drug-induced hepatitis. Two patients had ethambutol withdrawn because of blurring of vision after 4 months of treatment. Finally, one patient had persistent dizziness despite withdrawal of cycloserine. This necessitated change of the fluoroquinolone from ofloxacin 600 mg daily to levofloxacin 300 mg daily 4 months from commencement of therapy. There was no significant difference in the incidence of adverse effects from the drugs between the success and failure groups (p > 0.05).

Follow-up Assessment

Four of the 51 patients cured were lost to follow-up. The remaining 47 were followed up for a mean of 24.5 ± 16.5 months (range, 3 to 75 months). Only one patient (2.1%) was found to have radiographic and bacteriologic relapse 6 months after treatment cessation. This patient had 24 months of treatment and initial bacillary resistance to ofloxacin in vitro. She eventually had a right upper lobectomy performed 6 months after retreatment with drugs. Three of the nine patients with treatment failure were lost to follow-up on completion of chemotherapy. The remaining six patients with treatment failure were followed up for a mean of 28.0 ± 21.9 months (range, 3 to 66 months). Two subsequently died of TB 48 and 52 months after discontinuation of chemotherapy. None of the failed patients was suitable for surgical treatment, largely because of the presence of bilateral disease.

Monitoring of Sputum Bacteriology

The relationship between sputum culture after 2 and 3 months of chemotherapy and final outcomes was also assessed. Information was available in all patients except one who died of TB within the first month of chemotherapy. All 41 patients with nega-
tive sputum cultures after 2 months of chemotherapy and all 49 patients with negative sputum cultures after 3 months of chemotherapy eventually achieved success. Thus, the predictive values of negative sputum cultures after 2 and 3 months of treatment for success were both 100%. Eleven of 21 patients with positive sputum cultures after 2 months of chemotherapy and 11 of 13 patients with positive sputum cultures after 3 months of chemotherapy eventually failed or died. Thus, the predictive values of positive sputum cultures after 2 and 3 months of treatment for failure were 52.4% and 84.6%, respectively.

**Discussion**

In this community, the initial MDR-TB prevalence rates ranged from 0.4 to 0.7%, and the combined MDR-TB prevalence rates ranged from 0.9 to 1.0% in the study period (unpublished data, Department of Health, Hong Kong). The demographic and clinical characteristics of MDR-TB patients in our analyzed cohort were similar to other series, with a predominance of male patients. Approximately 40% of our patients did not receive any previous antituberculosis drugs. Our high initial MDR-TB proportion concurred with data from some series but not others. The overall success rate of approximately 80% corroborates the best results of published studies or analyses.

Among the three variables that were found to be independently associated with adverse outcomes of patients, the presence of cavitation might impede drug penetration and thus attenuate the therapeutic efficacy of antimicrobial agents. In a study on retreatment cases, it was found that cavitary disease per se, irrespective of drug-resistance status, was associated with poor treatment outcomes. Poor adherence linked with adverse treatment outcomes is not unexpected and emphasizes the importance of directly observed therapy in the treatment of TB, which should be mandatory for all patients with MDR-TB. Contrary to one important study undertaken in the United States, male sex was not found to be an important determinant for adverse outcomes. This might be related to particular factors linked to the male population in that study but not in ours. As the details of previous history of chemotherapy were generally incomplete for our patients, we could not study the relationship between the number of previously used drugs and the likelihood of adverse treatment outcomes. Some investigators have found this relationship significant.

Previous studies on the outcomes of chemotherapy in patients with MDR-TB have stressed the negative impact of extensiveness of drug resistance and the positive impact of the number of appropriate drugs (≥2) administered in accordance to drug susceptibility tests. However, it has also been shown that some patients who received drugs to which their organisms were susceptible in vitro did not respond microbiologically. At least one possible explanation for this discrepancy between in vitro activity and in vivo efficacy is that susceptibility testing for second-line agents needs greater standardization. For practical purposes, it would be useful to find a single drug resistance that could help predict the outcome of therapy. We focused our attention on ofloxacin resistance as such a potential marker for several reasons. First, the MICs of ofloxacin against strains of *M tuberculosis* have been consistent irrespective of the methodology or culture medium used, with MICs against 90% of ofloxacin-susceptible strains ≤1.25 mg/L. Many other fluoroquinolones behave similarly. Second, ofloxacin or other fluoroquinolones are very commonly included in second-line drug regimens for MDR-TB. Third, preliminary data have suggested a good correlation between activity in vitro and efficacy in vivo for ofloxacin. In our analysis, bacillary resistance to ofloxacin was indeed found to be an important variable significantly associated with adverse treatment outcomes. This finding implicates the likely pivotal role of ofloxacin/levofloxacin in multidrug regimens used for treatment of patients with MDR-TB. The six patients with bacillary resistance to ofloxacin in vitro who failed ofloxacin/levofloxacin-containing regimens still received a mean of 2.7 active drugs (range, 2 to 3 drugs).

Aside from in vivo efficacy, ofloxacin/levofloxacin has the favorable therapeutic characteristics of high peak serum drug concentration: MIC ratio, good tissue penetration, particularly into lungs, and good tolerance by patients on long-term administration. Our patients tolerated the fluoroquinolones even at high doses, corroborating the experience of others. Fluoroquinolones must be used carefully to prevent the emergence of cross-resistance among other members of this class of drugs. This has been experienced in certain communities.

In our present cohort of patients, only one of the six failed patients who had ofloxacin-susceptible *M tuberculosis* strains developed acquired resistance to ofloxacin with treatment. This patient also had poor adherence to therapy. Further, our data suggest that levofloxacin, when used at a dose of 600 to 500 mg daily, is more effective than ofloxacin at a similar dose. However, the difference in efficacy of the two fluoroquinolones for patients with ofloxacin-susceptible and ofloxacin-resistant bacilli did not reach
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statistical significance ($p > 0.05$). Evaluation with a larger sample size might allow a more definitive conclusion.

The optimal duration of therapy for patients with MDR-TB is unknown. A number of authorities including the World Health Organization have recommended a total duration of $\geq 18$ months after culture conversion, even for non-HIV-infected subjects.$^{12,13}$ However, our data suggest that at least some non-HIV-infected patients who managed to achieve sustained sputum culture conversion to negative status could be adequately treated with 12 months of fluoroquinolone-containing second-line chemotherapy regimens. In our patients, only those at risk because of diabetes mellitus, silicosis, extensive radiographic disease with or without cavities, extensive drug resistance in vitro, delayed sputum culture conversion (ie, after $> 3$ months of chemotherapy), and extrapulmonary involvement were treated for $> 12$ months, often for 15 to 18 months in toto. Although our relapse rate of 2.1% is gratifying, it is important to note that approximately 50% of our patients were followed up for $< 24$ months; some of these may have relapsed subsequently. We believe that in formulating the optimal duration of therapy for MDR-TB, multiple factors must be considered, particularly the bactericidal capacity and dosage of the drugs used, cost, and drug toxicity as well as anticipated patient adherence.

In this retrospective analysis of MDR-TB patients, those who responded achieved sputum culture negativity during the early months of treatment, usually within 3 months. This concurs with a study of HIV-negative subjects with MDR-TB.$^{20}$ Negative sputum culture at 2 and 3 months was predictive of eventual cure in 100% of patients. The predictive value for failure of positive sputum cultures at 2 and 3 months was 52.4% and 84.6%, respectively. The predictive values of negative and positive sputum cultures for failure or success both reached 100% after 6 months. Thus, monitoring monthly sputum culture for AFB in the initial 6 months of treatment helps greatly in predicting outcome. Such monitoring has been our practice since 1990 and currently is recommended by the World Health Organization.$^{13}$

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