The Treatment and Prognosis of Older Tuberculosis Patients with a Poor Performance Status Caused by Underlying Diseases

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Abstract:
Objective: The incidence of tuberculosis in Japan has been decreasing in the overall population but is increasing in older patients ≥90 years old. A poor performance status due to underlying diseases makes it difficult for patients with tuberculosis to receive standard oral treatment. However, there is no consensus concerning alternative treatments. This study examined the treatments and outcomes of older patients with tuberculosis and a poor performance status and determined the limitations of tuberculosis treatment for them.

Patients and Methods: We retrospectively enrolled 121 older patients with tuberculosis and a performance status of 3 or 4 due to underlying diseases during their hospitalization between April 2015 and March 2017 at National Hospital Organization Tokyo National Hospital. We classified them according to the drug administration route (oral, enteral, and injection routes) on admission and compared the characteristics and prognoses among the three groups.

Results: There were 79 patients in the oral route group, 28 (35.4%) of whom died during hospitalization. Among the 15 patients in the enteral route group, 6 (40.0%) died. Among the 27 patients in the injection route group who received non-oral agents, 22 (81.5%) died.

The prognosis of the injection route group was poor, with a median survival time of 21 days.

Conclusion: Treatment success cannot be expected with injection treatment in patients with a poor general condition because of complications. Although injection treatment may be a viable alternative treatment, its establishment as the standard treatment cannot be currently endorsed.

Key words: older patients, tuberculosis, injection treatment, performance status

Introduction
The aging of tuberculosis patients has advanced, and the number of patients ≥90 years old has been increasing in Japan (1). Many older patients have a poor performance status (PS) due to underlying diseases, such as malignancies and advanced dementia. It is therefore often difficult for them to achieve successful treatment with the standard oral therapy for tuberculosis.

When standard oral treatment is not possible, enteral or injection treatment is administered, or the treatment is discontinued depending on the overall status, and different therapeutic strategies are used.

We retrospectively investigated the treatments and outcomes of older patients with tuberculosis and a poor PS due to underlying diseases to determine the limitations of tuberculosis treatment for this patient group.

Methods

Patients
We enrolled 121 consecutive older patients with a PS of 3
or 4 ≥65 years old who were diagnosed with tuberculosis by a bacteriological examination and admitted to National Hospital Organization Tokyo National Hospital between April 2015 and March 2017. We classified the study patients into three groups according to the route of anti-tuberculosis medication administration at the onset of treatment: oral, enteral, and injection treatment. We retrospectively compared the characteristics, outcomes, and prognoses among the three groups. The route of drug administration for each patient was selected by the attending doctors who examined each patient’s status on admission.

Patient data, including the age, sex, PS, laboratory findings [albumin, hemoglobin, C-reactive protein (CRP) levels and lymphocyte count], imaging findings (presence or absence of cavity, unilateral or bilateral findings, and extensive disease), oxygen inhalation on admission, therapy regimens, and underlying diseases, were collected. The mortality rates of the three groups were calculated.

This study was approved by the ethical committees of the National Hospital Organization Tokyo National Hospital and was conducted according to the principles expressed in the Declaration of Helsinki.

Definition of terms

The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) scale is an indicator for assessing the general status and activities of daily living in patients with cancer (2).

The hazard ratios for death have been found to be significantly higher among tuberculosis patients with PS 3 and 4 than among others (3); therefore, PS 3 and 4 were considered a poor PS in this study.

Survey of outcomes

We tried to collect data on the outcomes of 65 patients who showed smear-negative results 3 times and were alive at discharge from jurisdictional public health centers. We confirmed the outcomes of 48 patients. The outcomes of the remaining 17 patients were not reported because of protection of personal information. The outcome consisted of seven categories: treatment success, died, treatment failed, transferred out, lost to follow up, still on treatment, and unclassified.

Statistical analyses

Statistical analyses were performed using EZR (4). The categorical data were compared using a chi-square test or Fisher’s exact test. The continuous variables were represented by median values with interquartile ranges (IQRs), and those of the enteral and injection groups were compared using a Mann-Whitney test, while those of the three groups were compared using the Kruskal-Wallis test. A Kaplan-Meier analysis was used to examine the survival of the three groups. A P value of <0.05 indicated statistical significance.

Table 1 shows the patient characteristics of each group. The oral administration group had 79 patients, with a median age of 87 (IQR, 82-90) years old; the enteral group had 15 patients, with a median age of 84 (IQR, 80-88.5) years old; and the injection group had 27 patients, with a median age of 87 (IQR, 84-93) years old. None of the patients had only extrapulmonary tuberculosis.

Regarding the therapeutic regimen, HRE [rifampicin (RFP), isoniazid (INH), and ethambutol hydrochloride (EB)] was the most commonly used regimen in both the oral and enteral groups. Injection treatment included a combination of non-oral agents including INH, streptomycin (SM), and levofloxacin (LVFX). INH and LVFX were administered intravenously, and SM was administered intramuscularly or intravenously. HSL combined with INH, SM and LVFX was administered to 24 patients; HL combined with INH and LVFX was administered to 2 patients; and LS combined with LVFX and SM was administered to 1 patient. Injection treatment was administered because of the presence of complications, such as difficulty in oral intake, gastrointestinal bleeding, and respiratory failure.

Both the enteral and injection groups had a high proportion of patients with PS 4, and there was no significant difference in PS 4 between the enteral and injection groups. However, the CRP level and proportion of oxygen administration were significantly higher in the injection group than in the enteral group. We found that injection treatment was administered to patients with worse general condition among the patients with a poor PS. The median survival time (MST) in the oral, enteral, and injection groups was 134, 59, and 21 days, respectively. The injection group had the highest mortality rate. There was a significant difference in the survival durations among the three groups. The injection group had more patients with a poor prognosis than the other two groups (Figure).

For some patients, the routes of drug administration were switched, or treatments were discontinued during hospitalization (Table 2). One reason for changing the administration route was the onset of complications. Nine patients in the oral group were switched to enteral administration without a change in the regimen due to difficulty in oral intake. Among them, five patients died during hospitalization. In addition, four patients in the oral group were switched to enteral administration with a change in the regimen due to difficulty in oral intake. Sixteen patients in the oral group were switched to injection administration due to the following: cardiovascular events in one patient, dysphagia in three patients, worsened respiratory status caused by pneumonia in seven patients, other infectious diseases in four patients, and organ disorder in one patient. These complications were critical, and all 16 patients died in the hospital.

Another reason for changing the administration route was switching to standard treatment. In the injection group, one
Table 1. Characteristics and Comparisons of the Three Groups Classified according to Route of Drug Administration.

<table>
<thead>
<tr>
<th></th>
<th>Oral group (n=79)</th>
<th>Enteral group (n=15)</th>
<th>Injection group (n=27)</th>
<th>*p value</th>
<th>**p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>87(82–90)</td>
<td>84(80–88.5)</td>
<td>87(84–93)</td>
<td>0.0869</td>
<td>0.0674</td>
</tr>
<tr>
<td>Male · Female</td>
<td>43 · 36</td>
<td>10 · 5</td>
<td>14 · 13</td>
<td>0.626</td>
<td>0.546</td>
</tr>
<tr>
<td>Performance status 4</td>
<td>51(64.6%)</td>
<td>14(93.3%)</td>
<td>24(88.9%)</td>
<td>0.00793</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin value (g/dL)</td>
<td>11.1(9.70–12.0)</td>
<td>9.4(8.60–11.85)</td>
<td>10.5(9.45–11.95)</td>
<td>0.321</td>
<td>0.416</td>
</tr>
<tr>
<td>Median albumin level (g/dL)</td>
<td>2.4(2.15–2.9)</td>
<td>2.1(1.90–2.6)</td>
<td>2.1(1.85–2.5)</td>
<td>0.0188</td>
<td>0.693</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>5.16(2.05–9.57)</td>
<td>4.55(1.76–9.75)</td>
<td>7.96(4.15–13.68)</td>
<td>0.0515</td>
<td>0.0481</td>
</tr>
<tr>
<td>Lymphocyte count (/μL)</td>
<td>666(448–966)</td>
<td>942(519–1096)</td>
<td>420(217–949)</td>
<td>0.0336</td>
<td>0.0274</td>
</tr>
<tr>
<td>Radiological findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>67(84.8%)</td>
<td>14(93.3%)</td>
<td>23(85.2%)</td>
<td>0.853</td>
<td>0.403</td>
</tr>
<tr>
<td>Cavity</td>
<td>21(26.6%)</td>
<td>3(20.0%)</td>
<td>6(22.2%)</td>
<td>0.858</td>
<td>1</td>
</tr>
<tr>
<td>Extensive disease</td>
<td>37(46.8%)</td>
<td>9(60.0%)</td>
<td>17(63.0%)</td>
<td>0.282</td>
<td>1</td>
</tr>
<tr>
<td>Oxygen inhalation on admission</td>
<td>32(40.5%)</td>
<td>5(33.3%)</td>
<td>20(74.1%)</td>
<td>0.00551</td>
<td>0.0245</td>
</tr>
<tr>
<td>Therapeutic regimen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HREZ</td>
<td>8</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRE</td>
<td>63</td>
<td>9</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other internal regimen</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HSL</td>
<td>0</td>
<td>0</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HL</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignant disease</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9</td>
<td>0</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>22</td>
<td>4</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>26</td>
<td>8</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopedic disease</td>
<td>18</td>
<td>2</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>11</td>
<td>0</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
<td>1</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>28(35.4%)</td>
<td>6(40.0%)</td>
<td>22(81.5%)</td>
<td>&lt;0.001</td>
<td>0.0168</td>
</tr>
</tbody>
</table>

*p value: comparison between the three groups
**p-value: comparison between enteral group and injection group

Extensive disease: total lesions exceeding one side lung field area.
HREZ: standard treatment consisted of rifampicin (RFP), isoniazid (INH), ethambutol hydrochloride (EB) and pyrazinamid (PZA).
HRE: standard treatment consisted of RFP, INH, and EB.
HSL: injection regimen consisted of INH, streptomycin (SM), and levofloxacin (LVFX).
HL: injection regimen consisted of INH and LVFX.
LS: injection regimen consisted of LVFX and SM.

Malignant disease: two patients with lung cancer and one patient with metastatic prostate cancer in the oral group. Two patients with pancreatic cancer in the injection group.

Finally, Table 3 shows the outcomes of tuberculosis treatment in 48 patients who were alive at discharge. In the injection group, we confirmed the outcomes of all survivors. The treatment in two patients who were switched to oral HRE was successful. One patient continued to receive injection treatment after discharge but died soon after. Two patients were switched to enteral HRE but died.

Discussion

The revised standard of tuberculosis treatment states that tuberculosis treatment without RFP takes 18 months after negative conversion of tuberculosis bacillus using INH, PZA, LVFX, SM, and EB (5). However, this regimen can be
The patients who received injection treatment in our study also showed a poor prognosis. To be more accurate, the patient’s characteristics forced attending doctors to select injection treatment due to their poor PS. In our study, two patients with pancreatic cancer managed by the best supportive care died during hospitalization in the injection group. The median life expectancy was 3 to 6 months for metastatic pancreatic cancer and 6 to 10 months for non-metastatic cases (13). Cancer bearing therefore impacted their prognosis. In a previous study to predict the survival of advanced dementia patients with complete dependency in all activities of daily living, the mean age of the patients dying within 6 months was 82.9±9.3 years old, and the average albumin level was 2.8±0.5 g/dL. These patients were significantly older and had lower albumin levels than the patients who survived for more than six months (14, 15). The prognosis endorsed with oral or enteral administration. Injectable antituberculosis agents were indicated for gastrointestinal tuberculosis with difficulty in absorbing oral medication as the initial treatment (6, 7) or parts of therapeutic regimens for multi-drug resistant tuberculosis (8). Injection treatment has issues of a long treatment duration and high cost (9), so the World Health Organization has recommended tuberculosis management including oral treatment regimens and a reduction of the treatment duration, regardless of susceptibility to RFP (10).

Previous studies showed that a poor PS, advanced age, and respiratory failure were poor prognostic factors for patients with tuberculosis (3, 11). In one study, the in-hospital mortality was approximately 70% in cases where injection treatment was administered to older patients with difficulty in oral intake, malnutrition, and oxygen inhalation (12).
of many patients in our study was restricted because they also had the abovementioned characteristics. The MST of the injection group was the shortest among the 3 groups, and the duration of only injection treatment took 18 months longer because it did not include RFP in Japan. Therefore, it would be difficult for older patients with tuberculosis and a poor PS to achieve treatment success with only injection treatment.

In addition, switching to injection treatment, which required a longer treatment period than standard treatment under conditions of a poor general status due to complications, would be inconsistent with the goal of treatment success. Indeed, no patient achieved treatment success with injection treatment alone. Only two patients who were switched to oral administration during the course of treatment achieved treatment success. In contrast, the two patients who were switched to enteral administration with a gastrostomy or gastric tube died during the treatment period. The prolonged survival of patients with dementia receiving enteral nutrition was not observed (16, 17), and the MST of patients with dementia who underwent gastrostomy at ≥80 years old was <6 months (18). Tuberculosis treatment with enteral administration may also not achieve treatment success in older tuberculosis patients with dementia. However, enteral administration enables standard treatment with RFP, which can lead to bacilli discharge in the two patients in the injection group who survived to discharge while receiving injection treatment.

In conclusion, it may be appropriate to consider injection treatment for older tuberculosis patients with a poor PS unlikely to achieve treatment success. However, despite this lack of an endorsement, injection treatment may be a viable alternative treatment until standard treatment with oral or enteral administration can be received and for controlling bacilli discharge.

The authors state that they have no Conflict of Interest (COI).

**Table 3. Treatment Outcome of Each Group.**

<table>
<thead>
<tr>
<th></th>
<th>oral group</th>
<th>enteral group</th>
<th>injection group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment success</td>
<td>18</td>
<td>2</td>
<td>*2</td>
</tr>
<tr>
<td>Died</td>
<td>14</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Treatment failed</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Transfer out</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lost to follow up</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Still on treatment</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Unclassified</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

The outcomes of 48 patients (37 in oral group, 6 in enteral, and 5 in injection) were confirmed. Those of 14 patients in oral and 3 patients in enteral were not reported.

Still on treatment: It took more than twelve months to treat tuberculosis.

*: one patient switched to receive HRE orally during hospitalization and the other switched to receive HRE orally after discharge.

References


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