Treatment of Malignant Pleural Effusion*

Khaled Reshad, M. D.; Kenji Inui; Yoshiaki Takeuchi; Yutaka Takahashi; and Shigeki Hitomi, M. D., F.C.C.P.

Two hundred consecutive patients with malignant pleural effusion were reviewed. The pathologic etiology of malignant pleurisy was: primary lung cancer in 123 cases; five, mesothelioma; and 72 cases secondary to metastatic tumors. Adenocarcinoma of the lung and mammary cancer were the most frequent tumors causing malignant pleural effusion. The modalities employed in local treatment consisted of thoracocentesis in 62 patients, tube thoracotomy in 111 cases with local instillation of Adriamycin, MMC, CQ, 5FU, OK432 or talc. Surgical procedures including pleuroperoneumonectomy or reduction surgery of the tumor with decortications were performed in ten patients. Tube drainage with local instillation of drugs was more effective than thoracocentesis with or without local therapy. Excellent initial results were obtained in patients who received reduction surgery with decortications and pleurodesis. Results of cytologic investigation were positive in 157 cases (78.5 percent). The tumor cells disappeared in 79.4 percent of primary cancer pleurisy cases and 81.1 percent of patients with metastases while disappearance or significant decrease in pleural effusion following treatment was obtained in 75.2 and 77.8 percent respectively. The median survival was 11.3 months in primary cases, and 11.7 months in patients with metastases.

Carcinomatous pleurisy is not uncommon as a manifestation of cancer, and often results in significant pulmonary and cardiac insufficiency threatening the life of the patient. The ideal treatment is to remove the fluid, and also to prevent the reaccumulation of effusion. Despite the many methods tried in the past and in use today, no single method of treatment is entirely satisfactory. Various methods have been advocated to prevent recurrent fluid, including multiple thoracocentesis or tube pleural drainage with or without injection of antineoplastic agents, radioactive isotopes and sclerosing materials such as talc, quinacrine and tetracycline. Radiation to the chest wall, open thoracotomy with decortications, and pleurectomy have also been described.

This report presents a review of our experience since 1975 with a series of 200 consecutive patients with carcinomatous pleurisy. The results were analyzed to determine the effect of therapy and its significance in prognosis.

CLINICAL MATERIAL AND METHODS

Diagnosis of Malignant Pleurisy

The diagnosis of malignant pleurisy was provided by chest x-ray film, chest computed tomography, and cytologic examinations of the pleural fluid obtained by initial thoracocentesis. More invasive diagnostic procedures such as needle biopsy, pleuroscopy or pleural biopsy during open drainage and decortications were performed in patients with several negative cytologic investigations of pleural effusions.

The results of 200 consecutive patients treated at Kansai Denryoku Hospital, Tenri Hospital and Shima Municipal Hospital for malignant pleural effusion between January, 1975 and December, 1983 were reviewed in this series.

There were 123 malignant pleural effusions due to primary lung cancer with an average patient 67.8 years of age, ranging from 32 to 85 years. Seventy-six patients were men and 47 were women. Nine patients had bilateral malignant pleural effusion, 65 had right sided, and 49 had left sided hemithorax.

The histologic distribution of primary lung cancer causing malignant pleural effusion is listed in Table 1. Malignant pleurisy secondary to metastatic tumors and mesothelioma involved 52 women and 25 men, of which 29 were right-sided, 32 left-sided and 16 bilateral pleurisy. Their average age was 53 years, with the range 13 to 84 years. The pathologic etiology of metastatic malignant pleurisy is listed in Table 2.

A variety of modalities was employed in local treatment of malignant pleural effusion. They included thoracocentesis or tube intercostal drainage with or without instillation of antineoplastic drugs, sclerosing agents, and surgical procedures such as pleuroperoneumonectomy (Table 3). Thoracocentesis was applied in 62 patients, four times per patient on average, and tube intercostal drainage was performed in 111 cases with an average of 16 days of therapy. Ten patients were subjected to surgical procedures which included pleuroperoneumonectomy in four cases, and lobectomy or partial resection of the primary site of the tumor with decortications and pleurodesis in six patients with malignant pleural effusion. Palliative therapy with a systemic chemotherapy without local instillation was performed in 16 patients because of rejection of the local therapy.

The drugs instilled into the pleural cavity during tube drainage were adriamycin (20 mg), mitomycin C (10 to 20 mg), 5FU (500 mg) and carboxazidoline (10 mg) as antineoplastic drugs; OK432 (10 to 20 KE) as an immunotherapeutic agent and talc or tetracycline as sclerosing materials. These agents were selected randomly and used singly or in combination, dissolved in 20 ml of saline solution and injected into the pleural cavity through a chest tube which was then

Table 1—Histology of Carcinomatous Pleurisy

<table>
<thead>
<tr>
<th>(Primary Lung Cancer, 123 Cases)</th>
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<tbody>
<tr>
<td>Adeno car</td>
<td>71</td>
</tr>
<tr>
<td>Sq cell car</td>
<td>24</td>
</tr>
<tr>
<td>Large cell car</td>
<td>7</td>
</tr>
</tbody>
</table>

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Table 2—Histology of Carcinomatous Pleurisy

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Number</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammary c</td>
<td>25</td>
<td>Thyroid t</td>
</tr>
<tr>
<td>Gastroint t</td>
<td>22</td>
<td>Sarcomas</td>
</tr>
<tr>
<td>Utero-ovar t</td>
<td>6</td>
<td>Kidney t</td>
</tr>
<tr>
<td>Mal Lymph</td>
<td>5</td>
<td>Others</td>
</tr>
<tr>
<td>Mal Thym</td>
<td>5</td>
<td>Mesoth</td>
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</tbody>
</table>

Table 3—Treatment of Carcinomatous Pleurisy

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palliative therapy</td>
<td>17 Cases</td>
</tr>
<tr>
<td>Thoracenteses</td>
<td>62 Cases</td>
</tr>
<tr>
<td>Tube thoracostomy</td>
<td>111 Cases</td>
</tr>
<tr>
<td>Surgical operation</td>
<td>10 Cases</td>
</tr>
</tbody>
</table>

Results of Cytologic Investigations

Results of cytologic investigation of the pleural effusion showed that 157 of the 200 effusions were positive for tumor cells (78.5 percent). Needle biopsy of the pleura was performed 22 times in 18 patients with 12 positive results (55.5 percent). When the results of cytologic investigations and needle biopsy failed, pleuroscopy was performed in nine cases with eight positive pleural biopsies; open biopsy during surgical procedures was performed in ten cases with 100 percent positive results.

Disappearance of Tumor Cells and Control of Pleural Effusion with Survival Time in Relation to Treatment

The results of treatment in 183 patients who received local instillation of antineoplastic drugs, immunotherapeutic agent or sclerosing materials are listed in Table 4.

Disappearance or significant decrease of pleural fluid stable for more than four weeks was evaluated as effective treatment according to the Japan Lung Cancer Society. In our protocol, significant decrease constitutes a 75 percent decrement in treated pleural effusion. One hundred thirty-seven of 183 primary lung cancer, mesothelioma and metastatic pleural effusions responded to therapy.

In contrast, the effectiveness of systemic chemotherapy in patients who did not receive local instillation of the drugs was 50 percent in both primary and metastatic pleural patients.

The survival time of those responding to local therapy was 11.3 months on average in primary cancer patients, and 11.7 months in patients with secondary pleurises due to metastatic lesions (p<0.01).

Table 5—Treatment Effectiveness and Survival Time (Chemotherapy)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>in Primary LC Pleurisy (%)</th>
<th>Survival Time (Months)</th>
<th>in Metastatic Pleurisy (%)</th>
<th>Survival Time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>(n = 85)</td>
<td></td>
<td>Number</td>
<td>(n = 55)</td>
</tr>
<tr>
<td>Systemic Chemo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMC Only</td>
<td>9</td>
<td>50.0</td>
<td>7</td>
<td>50.0</td>
</tr>
<tr>
<td>MMC + ADM</td>
<td>28</td>
<td>79.0</td>
<td>15</td>
<td>90.0</td>
</tr>
<tr>
<td>MMC + ADM + 5FU</td>
<td>4</td>
<td>85.0</td>
<td>14.8</td>
<td>10</td>
</tr>
<tr>
<td>CO + 5FU</td>
<td>19</td>
<td>85.0</td>
<td>14.0</td>
<td>8</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>80.0</td>
<td>12.0</td>
<td>6</td>
</tr>
</tbody>
</table>

Treatment of Malignant Pleural Effusion (Reshad et al)
Table 6—Treatment Effectiveness and Survival Time (Chemotherapy + Immunotherapy)

| in Primary LC Pleurisy (%) | Survival Time (Months) | Number | \( (n = 38) \) | | in Metastatic Pleurisy (%) | Survival Time (Months) | Number | \( (n = 21) \) |
|-----------------------------|------------------------|--------|----------------|-----------------------------|------------------------|--------|----------------|
| MMC + OK432                 | 16                     | 83.4   | 12.2           | 9                           | 71.5                   | 12.0   |                |
| ADM + OK432                 | 10                     | 55.0   | 6.2            | 5                           | 75.0                   | 7.0    |                |
| MMC + ADM + OK432           | 2                      | 75.0   | 7.5            | 3                           | 67.0                   | 8.0    |                |
| Others                      | 4                      | 90.0   | 9.8            | 1                           | 88.0                   | 11.3   |                |
| OK432                       | 6                      | 67.7   | 4.5            | 3                           | 67.7                   | 5.0    |                |

Table 5 shows the treatment effectiveness and survival time of 140 patients, who received antineoplastic drugs by local instillation (124 cases), compared with those who received systemic chemotherapy without local instillation of the drugs (16 cases).

Improvement in 67 to 85 percent of primary cancer patients and in 75 to 100 percent of metastatic pleurisy was obtained by intrapleural instillation of antineoplastic agents. More successful therapeutic response with intrapleural instillation of MMC singly and CQ plus 5FU therapy in combination was obtained in 79 to 90 percent and 85 to 100 percent of primary lung cancers and metastatic pleural effusions, respectively (\( p < 0.01 \)).

The median survival period ranged from 7.8 to 14.8 months in pleurisy of primary cancer and 5.0 to 13.5 months in cases with metastases.

In contrast, the treatment effectiveness was 50 percent with 3.9 and 4.0 months median survival periods in patients who received systemic chemotherapy only. The difference in survival time between local treated pleurisy and those who received only a systemic chemotherapy was significant (\( p < 0.001 \)).

The response to treatment according to intrapleurally instilled chemoimmunotherapeutic agents is shown in Table 6. The effectiveness of these agents in 38 primary lung cancer patients varied from 55 to 90 percent and 67 to 88 percent in 21 patients whose pleural effusion was secondary to metastatic tumor. Although all combinations showed better improvement rates than OK432 instilled alone, there was also a significant difference in survival time between these two groups (\( p < 0.01 \)).

Treatment Effectiveness and Survival Time in Relation to Tumor Type

The response to local treatment according to tumor type in primary lung cancer and methothelioma is shown in Figure 1. Sixty seven patients with primary adenocarcinoma treated with local instillation of chemotherapeutics, immunotherapeutic or sclerosing agents showed tumor cells in the pleural fluid becoming negative in 49 patients (73.5 percent) and pleural effusion disappearing in 48 patients (72 percent). The

<table>
<thead>
<tr>
<th>Histology</th>
<th>No of Cases</th>
<th>Decrease 1st Line (%)</th>
<th>Decrease 2nd Line (%)</th>
<th>Decrease 3rd Line (%)</th>
<th>Decrease 4th Line (%)</th>
<th>Survival Time (Months)</th>
<th>No of Cases</th>
<th>Decrease 1st Line (%)</th>
<th>Decrease 2nd Line (%)</th>
<th>Decrease 3rd Line (%)</th>
<th>Decrease 4th Line (%)</th>
<th>Survival Time (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>67</td>
<td>38</td>
<td>29</td>
<td>73.5</td>
<td>72.0</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td></td>
<td></td>
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<tr>
<td>Squamous Cell Car</td>
<td>24</td>
<td>13</td>
<td>5</td>
<td>77.0</td>
<td>74.0</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
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<tr>
<td>Large Cell Car</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>83.0</td>
<td>83.0</td>
<td>5</td>
<td>10</td>
<td>15</td>
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<tr>
<td>Small Cell Car</td>
<td>6</td>
<td>5</td>
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<td>Acinar Cell Car</td>
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<tr>
<td>Others</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>67.7</td>
<td>67.7</td>
<td>5</td>
<td>10</td>
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<tr>
<td>Mesothelioma</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>100.0</td>
<td>80.0</td>
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<td>10</td>
<td>15</td>
<td>20</td>
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<tr>
<td>Total</td>
<td>118</td>
<td>72</td>
<td>43</td>
<td>79.4</td>
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Figure 1. Effectiveness of local treatment and survival time (primary lung cancer, 113 cases; mesothelioma, five cases).

Figure 2. Effectiveness of local treatment and survival time (metastatic tumors, 65 patients).
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Pleuro-pneumonectomy has been shown to be highly effective in patients with malignant pleural effusion who experienced recurrences after other methods of treatment. However, persistent air leakage, bleeding, pneumonia, empyema and decreased pulmonary function or secondary heart failure complicated more than 20 percent of the cases postoperatively, and mortality from this procedure is also high. Four patients with malignant pleural effusion, three with primary lung cancer and one with malignant mesothelioma underwent pleuro-pneumonectomy. One patient died suddenly one month after surgery, and two patients two to three months after the operation. The last patient survived for eight months. Because of this high mortality rate after pleuro-pneumonectomy, two patients were subjected to lobectomy and pleurectomy after decortication of the pleura, and four patients to partial resection of the tumor with pleurodesis. Two patients who received partial resection with pleurodesis died ten and 24 months after surgery. Four patients are alive six, ten, 18, 36 months after this procedure with no recurrence of malignant effusion (Fig 3).

Mitomycin C and OK432 insufflation over the pleural surface was performed during open thoracotomy to prevent the recurrence of malignant pleural effusion.

**Discussion**

Malignant pleural effusion is a common complication of malignant diseases, occurring in 50 to 70 percent of all cancers in the course of the illness. Although the exact pathogenesis of malignant pleural effusion is often obscure, direct invasion of the pleura by tumor cells and obstruction of lymphatic and venous channels are probably the usual mechanisms. Some malignant pleural effusion may respond to effective systemic chemotherapy, but too often malignant effusion remains intractable.

There continue to be various therapies advocated for the treatment of malignant effusion. Each therapy has some level of morbidity and mortality, so it is difficult to determine which therapy is most beneficial to the patient. It is now generally accepted that repeated thoracocentesis is inferior to other forms of therapy because it leads to protein depletion, high risk of infection, trapped lung, etc. Tube thoracotomy with continued evacuation, especially with instillation of different types of agents, is a much more effective method.

Adler and Sayenk reported that talc powder controlled malignant pleural effusion when intruded at the time of open thoracotomy. Also, insufflation of talc powder over the pleural surface through a tube thoracotomy has been described by Jones with initial success in 90 percent of patients. Other sclerosing agents such as quinacrine and tetracycline have been administered for treatment of malignant pleural effusion with good to excellent results. Rocklin et al. Borja and Pugh, and Hickman and Jones reported successful treatment with quinacrine instillation intrapleurally.

Nitrogen mustard has been used most frequently in the treatment of malignant effusion. Kinsey et al. reported complete control of pleural effusion from various metastatic tumors, and Leininger et al. achieved successful results in 90 percent of patients.
with the instillation of nitrogen mustard into the pleural space through a tube thoracotomy, but Anderson and coworkers obtained poor response with intracavitary administration of this drug in lymphomatous pleurisy.

Adriamycin, carbazilquinone, mitomycin C, bleomycin and 5FU were instilled into the pleural cavity by several authors with results varying from good to excellent. Immunotherapeutic agents such as Norcadia CWS or OK432 were instilled via the intracavitary route by Saito et al, Naga, Ohta et al and Egawa and Meguro. Successful initial results obtained in 15 out of 18 patients (83 percent), who received Norcadia CWS instilled intrapleurally have been reported by Saito. The median survival period was six months and the most effective case survived for 27 months when OK432 was locally instilled in patients as reported by Naga. Successful treatment results were obtained in up to 90 percent of the patients in our series, with a longer median survival period than in these reports.

Instillation of radioactive isotopes into the pleural cavity has been reported to give improvement in 30 to 90 percent of cases. Sixty percent of patients with malignant pleural effusion were controlled with pleural drainage and 32P given intrapleurally in the study by Izbricki et al. However, the use of radioactive isotopes is not available in ordinary hospitals and may constitute a radiation hazard to hospital staff.

Pleuroneuromectomy has been shown to be a highly effective treatment for patients with malignant pleural effusion in properly selected patients. Martini et al performed this procedure in patients who had recur rent pleural effusion after other methods of treatment, and obtained successful results in 90 percent, but the mortality from this method is about 10 to 20 percent for the high incidence of postoperative complications.

In our series, successful treatment results were obtained in up to 90 percent of primary cancer pleurisy and up to 100 percent in metastatic tumors, who received chest tube drainage with local therapy. Multiple drug instillation into pleural space was more effective in obliterating pleural fluid than single agent instillation. There was a high response rate obtained with intrapleural instillation of MMC combined with any other agent and CQ plus 5FU. Also, we achieved successful results in most of the patients who had a short interval between diagnosis and local therapy. In contrast, in most of the patients who failed to have obliteration the pleural effusion, trapped lung due to therapy delay was frequently the responsible reason.

We obtained excellent initial results in definite lung resection with pleurodesis in malignant pleural effusion patients in whom other treatment methods were ineffective, but when this procedure is too radical and definitive for a majority of patients with malignant pleural effusion, it should be kept for situations where conservative approaches have failed.

We conclude that, since the general approach to treatment of malignant pleural effusion is mostly palliative for alleviation of the symptoms, the method selected for treatment should be highly effective with low morbidity and mortality. Consequently, we recommend aggressive and immediate action consisting of chest tube drainage and local instillation of antineoplastic or immunotherapeutic agents in treatment of malignant pleural effusion, which may possibly prevent trapped lung in subacute cases. Also, a careful search for factors contributing to effusion or treatment of effusion such as decreasing pulmonary function, secondary heart failure, protein depletion or infection should be performed.

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