

Effective Chemotherapy Based on a Chemosensitivity Test for Malignant Pleural Mesothelioma

Yoshimasa Maniwa, MD,¹ Masahiro Yoshimura, MD,⁴ Masahiko Takata, MD,¹
Yoshihiro Nishimura, MD,² and Yoshiharu Ohno, MD³

Malignant pleural mesothelioma (MPM) is an aggressive and fatal tumor of the pleura and its incidence has been increasing as a result of the widespread use of asbestos worldwide. Numerous chemotherapeutic agents have been tested in many clinical trials, but the response rate does not exceed 20% for most of the investigated regimens. Here we report a case of MPM in which the chemotherapy based on the chemosensitivity test was very effective on palliation with stable disease for a long time. (Ann Thorac Cardiovasc Surg 2008; 14: 319–321)

Key words: chemosensitivity test, chemotherapy, malignant pleural mesothelioma

Case Report

A 63-year-old woman was admitted to our hospital with progressive dyspnea caused by the left pleural effusion. Diffuse pleural thickening of the whole left hemithorax was detected with a chest CT scan and MRI, suggesting malignant pleural mesothelioma (MPM). To confirm the diagnosis and the accurate stage of progression, the patient was scheduled for thoracoscopy and laparoscopy after the approval of further examination, including the chemosensitivity test of a pleural tumor. A histochemical study of the biopsy specimen of pleural tumor revealed a diffuse malignant epithelioid mesothelioma of the pleura with high-grade lymphatic invasion. A small peritoneal nodule, which was detected on the left diaphragmatic dome during the laparoscopy, revealed similar findings of the pleural tumor, and she was diag-

nosed as T4 and stage IV.

Immediately after the diagnosis and staging of MPM, she underwent practical chemotherapy (weekly methotrexate 100 mg/m² plus irinotecan 40 mg/m² on days 1 and 8; doxorubicin 30 mg/m² on days 2 and 9). However, a follow-up CT after two cycles of chemotherapy revealed progressive disease (Figs. 1A and 1B). While the chemotherapy was being done, a collagen gel droplet embedded culture-drug sensitivity test (CD-DST) for the biopsy specimen of the pleural tumor was being performed with a CD-DST kit (Nitta Gelatin Inc., Osaka, Japan). The result showed that two drugs, gemcitabine (GEM) and vinorelbine (VNR) had a significantly higher inhibitory rate than cisplatin (CDDP), docetaxel (TXT), and 5-fluorouracil (5-FU). At the moment when the progression of the MPM was confirmed, we could finally obtain the patient's approval to use VNR and GEM based on the result of a chemosensitivity test. She could receive a regimen of combined VNR 25 mg/m² and GEM 1,000 mg/m² on days 1 and 8 of a 21-day cycle for the first two cycles during her hospitalization and the following eight cycles in the outpatient setting. During these seven months of ten cycles of the chemotherapy, a follow-up CT scan revealed stable disease (Figs. 1C and 2), and she tolerated this regimen well with performance status 0-1; no serious adverse effects were observed. But before the

From Divisions of ¹Thoracic Surgery, ²Respiratory Medicine, and ³Radiology, Kobe University Graduate School of Medicine, Kobe; ⁴Department of Respiratory Surgery, Hyogo Cancer Center, Akashi, Japan

Received July 2, 2007; accepted for publication November 5, 2007

Address reprint requests to Yoshimasa Maniwa, MD: Division of Thoracic Surgery, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan.

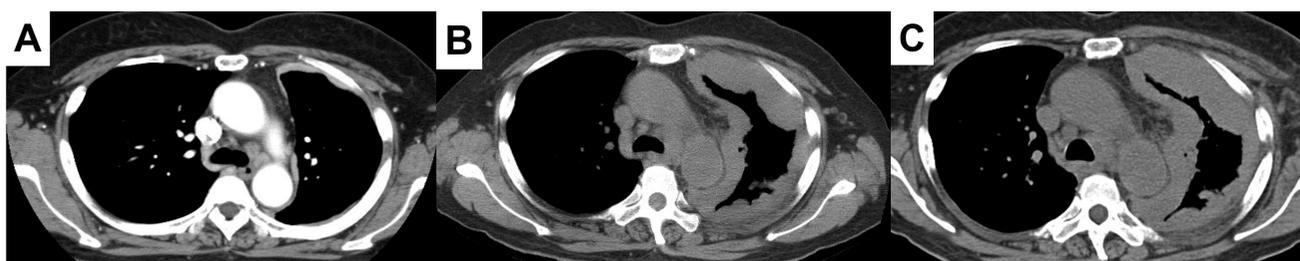


Fig. 1. Chest CT scans in the present case.
A: On admission.
B: After two cycles of initial chemotherapy.
C: After nine cycles of chemotherapy based on the chemosensitivity test.

eleventh cycle of chemotherapy, she noticed a gradual onset of dyspnea, and a chest roentgenogram demonstrated bilateral pleural effusion. Administration of the additional chemotherapy was difficult and, unfortunately, she died two months later.

Discussion

Efforts for clinical trials are being made to get the evidence convincing enough to support the standard use of chemotherapy in malignant diseases, including MPM, although individual response to an anticancer drug is unpredictable. A wide range of chemotherapeutic agents used singly or in combination have been evaluated in the treatment of mesothelioma, but no drugs have consistently induced a response rate of greater than 20%.¹⁻³⁾ Several chemotherapy regimes for MPM are valuable for palliation, but no regimen has proven curative. The phase III trial demonstrated that the survival benefit was achieved with the combination of pemetrexed and CDDP compared with CDDP alone.⁴⁾ The result of median survival time of 12.1 months by the combination chemotherapy is promising, but MPM still remains as a fatal disease; also, unfortunately, the practical use of pemetrexed is not now permitted in Japan. At the present time, it is important for the selection of anticancer drugs not only to achieve the state of partial response or stable disease, but also to improve the symptoms of MPM.

In vitro anticancer drug sensitivity tests have been performed for various types of cancers, and a good relationship with clinical response has been observed.⁵⁾ To select the most appropriate anticancer drugs for different patients with cancer, we have been studying the chemosensitivity of cancer tissues using the CD-DST.^{6,7)} In CD-DST procedures, extracted cancer cells

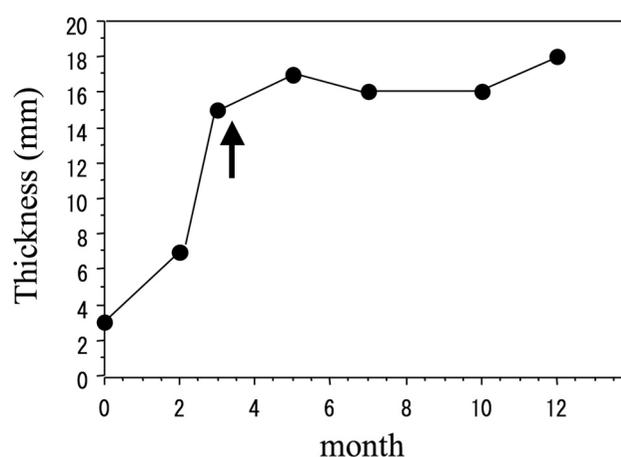


Fig. 2. The pleural thickness at the fifth intercostal space on the middle axillary line was measured with the chest CT films, and the variations in the thickness against time was plotted. Zero (0) of the horizontal axis indicates the period just before the initial chemotherapy. The arrow in the graph indicates the period when chemotherapy based on collagen gel droplet embedded culture-drug sensitivity test (CD-DST) was started.

are cultured 3-dimensionally in collagen gel droplet. Three-dimensional culture with collagen matrix is preferable for establishing cell culture from human cancer tissue.⁸⁾ This characteristic has made it possible to measure chemosensitivity with as little as 1×10^5 cancer cells, which would be present in small biopsy specimens.⁹⁾ The results show that CD-DST is capable of selecting the responders and the respective optimal regimens, and also delineating the patients less likely benefit from treatment.¹⁰⁾ We believe that the in vitro chemosensitivity assay is a good indicator of cellular response to chemotherapy, and it may provide reliable information for the basis of the selection of anticancer drugs to be used for the treatment of patients with malignant disease rather than having them rely on stan-

dard protocols.

In this report, we demonstrated a case of MPM in which the chemotherapy regimen based on a chemosensitivity test was very effective on palliation under the stable disease for seven months, and the patient was doing well in outpatient setting (she could recuperate at home) with good performance status. To our knowledge, this is the first case report of clinically effective chemotherapy for MPM based on a chemosensitivity test.

References

1. Ong ST, Vogelzang NJ. Chemotherapy in malignant pleural mesothelioma: A review. *J Clin Oncol* 1996; **14**: 1007–17.
2. Ryan CW, Herndon J, Vogelzang NJ. A review of chemotherapy trials for malignant mesothelioma. *Chest* 1998; **113** (1 Suppl): 66–73S.
3. Steele JP, Klabatsa A. Chemotherapy options and new advances in malignant pleural mesothelioma. *Ann Oncol* 2005; **16**: 345–51.
4. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003; **21**: 2636–44.
5. Takamura Y, Kobayashi H, Taguchi T, Motomura K, Inaji H, et al. Prediction of chemotherapeutic response by collagen gel droplet embedded culture-drug sensitivity test in human breast cancers. *Int J Cancer* 2002; **98**: 450–5.
6. Takata M, Yoshimura M, Maniwa Y, Tanaka Y, Okita Y. Chemo-sensitivity of lung cancer, difference between primary tumor and metastatic lymph node. *Chest* 2006; **130**: 234s.
7. Nakajima K, Okita Y, Matsuda S. Sensitivity of scirrhous gastric cancer to 5-fluorouracil and the role of cancer cell-stromal fibroblast interaction. *Oncol Rep* 2004; **12**: 85–90.
8. Kobayashi H. Development of a new in vitro chemosensitivity test using collagen gel droplet embedded culture and image analysis for clinical usefulness. *Recent Results Cancer Res* 2003; **161**: 48–61.
9. Cortazar P, Johnson BE. Review of the efficacy of individualized chemotherapy selected by in vitro drug sensitivity testing for patients with cancer. *J Clin Oncol* 1999; **17**: 1625–31.
10. Kawamura M, Gika M, Abiko T, Inoue Y, Oyama T, et al. Clinical evaluation of chemosensitivity testing for patients with unresectable non-small cell lung cancer (NSCLC) using collagen gel droplet embedded culture drug sensitivity test (CD-DST). *Cancer Chemother Pharmacol* 2007; **59**: 507–13.