Clinical Trial Note

A Feasibility Study of Induction Pemetrexed Plus Cisplatin Followed by Pleurectomy/Decortication Aimed at Macroscopic Complete Resection for Malignant Pleural Mesothelioma

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A prospective multi-institutional study has been initiated in Japan to evaluate the feasibility of induction chemotherapy using pemetrexed plus cisplatin, followed by pleurectomy/decortication aimed at macroscopic complete resection in patients with resectable malignant pleural mesothelioma. The study was initiated on September 2012, for which 24 patients will be recruited over a period of 2 years. The primary endpoint is the macroscopic complete resection rate, regardless of the surgical technique employed (i.e. pleurectomy/decortication or extrapleural pneumonectomy). The secondary endpoints are the pleurectomy/decortication rate, macroscopic complete resection rate by pleurectomy/decortication, pulmonary function at 3 months after surgery, adverse events, treatment-related mortality, response rate to chemotherapy and 3-year overall survival rate.

Key words: extrapleural pneumonectomy – induction chemotherapy – malignant pleural mesothelioma – macroscopic complete resection

INTRODUCTION

Malignant pleural mesothelioma (MPM) is an extremely poor-prognosis malignant tumor caused by asbestos exposure. The number of cases of this tumor in Japan is expected to rise in the future (1–3). MPM is very difficult to cure. While extrapleural pneumonectomy (EPP) is performed with radical intent, the outcome is not very good in patients treated with surgery alone (4). The current standard for possible cures for this disease has shifted to a multidisciplinary approach combining induction chemotherapy with cisplatin and pemetrexed followed by EPP and radiation therapy (trimodality therapy).

In recent years, another operative method, known as pleurectomy/decortication (P/D), has come into the spotlight. EPP is a very invasive surgery and shows cardiorespiratory depression and high rates of mortality and complications. P/D is less invasive than EPP. As of yet, it is not apparent which risk-benefit ratio of P/D and EPP is better as a part of multimodality therapy. It has been reported that the survival rate of P/D is higher than or equal to that of EPP (5–8). The possible reasons for this are as follows:
(1) The perioperative mortality rate of P/D is lower than that of EPP.
(2) Patients who had P/D receive better treatment than those who received EPP at the time of recurrence.

Postoperative quality of life is maintained to a larger extent in those patients who have undergone P/D rather than EPP (9). The results of major clinical trials for trimodality therapy, including EPP, have been reported by cancer study groups in North America, the University of Toronto and Europe (10–12). In all clinical trials, only around 50% of patients completed trimodality therapy, thus suggesting that trimodality therapy, including EPP, poses major difficulties even at some of the world’s most experienced and top-ranking facilities. In addition, both a high complication rate and a number of treatment-related deaths were reported in a Japanese multi-institutional clinical trial for trimodality therapy conducted in 2008. Considering this, the survival benefits of this therapy reported from clinical trials in Europe and the USA are not high. Therefore, the risk-benefit ratio of this treatment is not satisfiable.

There is no good evidence of multimodality therapy involving P/D. However, the benefit of adding induction chemotherapy to P/D may be speculated in the light of that for EPP (13–15). The study protocol is a clinical trial to evaluate induction chemotherapy with pemetrexed plus cisplatin followed by P/D aimed at macroscopic complete resection (MCR) for resectable MPM (16). The study protocol was approved by the protocol review committee and activated on 12 October 2012. The study has been registered at the UMIN Clinical Trials Registry as UMIN000009092 (http://www.umin.ac.jp/ctr/index.htm).

**PROTOCOL DIGEST OF THE STUDY**

**PURPOSE**

The aim of this study is to evaluate the feasibility of multimodality therapy for resectable MPM, comprised induction chemotherapy using pemetrexed plus cisplatin (PC) followed by P/D aimed at MCR.

**STUDY SETTING**

This is a multi-institutional, single-arm study.

**STUDY METHOD**

Figure 1 shows a flow chart of the study.

**ENDPOINTS**

The primary endpoint is MCR rate regardless of the surgical technique employed (i.e., P/D or extrapleural pneumonectomy). MCR is defined as the surgical removal of all gross tumor tissue (16,17). Secondary endpoints are as follows: (i) P/D rate, (ii) MCR rate by P/D, (iii) pulmonary function

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**Figure 1.** Flow chart of the study.
at 3 months after surgery, (iv) incidence of treatment-related adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 guidelines (18), (v) treatment-related mortality, (vi) response rate for induction chemotherapy evaluated by a modified version of the Response Evaluation Criteria in Solid Tumors [modified RECIST (19)], (vii) 3-year overall survival rate in all eligible patients with MCR.

ELIGIBILITY/INCLUSION CRITERIA

Patients are eligible for the trial if they have a histologically confirmed diagnosis of MPM, including all subtypes and clinical T1–3, N0–2, M0 disease considered to be resectable. Other requirements are as follows: no prior treatment with chemotherapy, surgery or radiation therapy (RT) for the disease; age between 20 and 75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; a predicted postoperative forced expiratory volume of >1000 ml in 1 s; adequate bone marrow, hepatic, renal, cardiac and respiratory functions; a life expectancy of >12 weeks; and written informed consent.

EXCLUSION CRITERIA

Patients are excluded if they meet any of the following criteria: serious systemic complications including poorly controlled diabetes or hypertension, active infectious diseases, interstitial pneumonia or lung fibrosis; simultaneous or metachronous (within 5 years) double cancers; serious drug allergy or hypersensitivity to any drugs; pregnancy or breast-feeding; Grade 2 or greater peripheral neuropathy at registration; or considered as clinically inappropriate for registration.

TREATMENT METHODS

INDUCTION CHEMOTHERAPY

Induction chemotherapy consists of three cycles of pemetrexed at 500 mg/m² followed by cisplatin 75 mg/m² on Day 1, given every 21 days. Folic acid (0.5 mg per daily oral administration) and vitamin B12 (1 mg intramuscularly every 9 weeks) are administered a week before the first dose of chemotherapy and continue to be administered throughout the induction chemotherapy. Dose adjustments of chemotherapy are required for renal and nonhematologic toxicity as well as hematologic effects. Dose delays of up to 42 days are permitted for recovery from drug toxicity. Tumor response is assessed through computed tomography (CT) following the completion of induction chemotherapy using unidimensional measurement of the pleural thickness perpendicular to the chest wall or mediastinum and modified RECIST criteria.

PLEURECTOMY/DECORTICATION AND EXTRAPELVxbbL PNEUMONECTOMY

All patients undergo P/D or EPP within 42 days of the last dose of induction chemotherapy unless there is deterioration of organ functions that would make the surgery intolerable. P/D complies with the definition of the International Association for the Study of Lung Cancer (IASLC) staging committee and the International Mesothelioma Interest Group (IMIG). The above report does not prescribe whether P/D mandates the removal of a part of the pleura without macroscopic disease. Therefore, in this study, it is stipulated that P/D requires mandatory removal of all the parietal pleura and removal of all the area of the visceral pleura with macroscopic disease. If it is necessary to achieve MCR, P/D permits resecting either of the diaphragm, pericardium, chest wall and lung parenchyma. EPP is defined as an en-bloc resection of the entire pleura, lung, ipsilateral diaphragm and pericardium (20). Also, while it is impossible to achieve MCR through P/D, EPP is performed in cases where operators deem that MCR can be achieved through EPP. If lymph node metastasis is confirmed by pathological examination, excision of this is also a prerequisite for MCR. Mediastinal nodal dissection is recommended in all patients having either P/D or EPP.

STUDY DESIGN AND STATISTICAL METHODS

The primary analysis of this study was to estimate the MCR rate and 95% confidence interval (CI). If the lower limit of the 95% CI exceeds 0.5, the protocol treatment will be considered feasible. Thus, 24 patients were planned to be enrolled onto this study, with planned accrual of 2 years and follow-up of 3 years after the accrual completion. This sample size was considered sufficient to estimate 95% confidence intervals for the true MCR rate within a width of ±0.2, when the true MCR rate is expected to be 70%.

STUDY MONITORING

The Data and Safety Monitoring Committee (DSMC) will make independent recommendations to investigators regarding the continuation, termination or modification of the trial. Protocol compliance, safety and study progress will also be monitored by the DSMC.

PARTICIPATING INSTITUTIONS

A total of 24 institutions in Japan with certified specialists in oncology and surgery will participate in this trial.

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Conflict of interest statement

None declared.

References