

Triplet Chemotherapy with Cisplatin, Gemcitabine and Vinorelbine for Malignant Pleural Mesothelioma

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Background: The incidence of malignant pleural mesothelioma (MPM) is expected to increase due to delayed control of occupational exposure to asbestos in Japan. We investigated the use of triplet combination chemotherapy with cisplatin (CDDP), gemcitabine (GEM) and vinorelbine (VNR) for the treatment of Japanese patients with MPM.

Methods: From December 2000 to August 2003, 12 patients received the following regimen: CDDP 40 mg/m², GEM 800 mg/m² and VNR 20 mg/m² on days 1 and 8 every 4 weeks. Among the 12 patients, six selected patients underwent an extrapleural pneumonectomy (EP) after a median of three cycles of triplet chemotherapy.

Results: The overall response rate for all patients and the response rate for chemotherapy-naïve cases were 58 and 67%, respectively. The median survival time and survival rate at 2 years for all patients were 11 months and 50%, respectively. The 2-year survival rates for the patients with and without EP were 83.3 and 16.7%, respectively.

Conclusions: Triplet chemotherapy with CDDP, GEM and VNR was thus found to be highly effective for patients with MPM and its toxicity was manageable. A multi-institutional phase II trial is now being planned to establish the effectiveness of this new regimen in chemotherapy-naïve patients with MPM.

Key words: malignant pleural mesothelioma – triplet chemotherapy – extrapleural pneumonectomy

INTRODUCTION

Malignant pleural mesothelioma (MPM) is a relatively rare neoplasm in Japan. The number of deaths and the proportional mortality rates from this disease in 2001 were 722 and 0.26%, respectively (1). Epidemiological studies have shown that the incidence of malignant mesothelioma is increasing worldwide, due to the occupational exposure to asbestos (2,3). While this disease may have already peaked in the USA because of the earlier control of asbestos use (4), a continuing increase of malignant mesothelioma has been shown in Japan based on the analysis of registered autopsy cases (5). The natural history is characterized by a median survival of 9–14 months, with <5% 5-year survivors. The objective response rates of 16–48% and median survivals of 9.4–11.2 months have been reported with the combination of cisplatin (CDDP) and gemcitabine (GEM) in malignant mesothelioma (6–8). GEM has shown a synergistic effect with such drugs as CDDP, vinorelbine (VNR), ifosfamide and mitomycin (9). VNR is a semi-synthetic derivative of vinblastine which is structurally modified in the catharanthine nucleus. Recently, an objective response rate of

24% has been reported with the single agent VNR in a single institution study (10). Therefore, the triplet combination chemotherapy using CDDP, GEM and VNR seems to have a potential anti-tumor activity against MPM. The Southern Italy Cooperative Oncology Group has already investigated the combination of CDDP, GEM and VNR in patients with advanced non-small cell lung carcinoma (NSCLC) as a three-armed randomized phase III trial comparing this triplet regimen with either CDDP and VNR or CDDP and GEM (11). The CDDP–GEM–VNR triplet combination produced a highly significant survival gain when compared with the CDDP–VNR doublet treatment. According to their schedule, the patients received CDDP 50 mg/m², GEM 1000 mg/m² and VNR 25 mg/m² intravenously on days 1 and 8 every 3 weeks. Under this regimen, however, Hesketh and associates observed a high rate of severe hematological toxicity, especially febrile neutropenia, despite a low delivered dose intensity of CDDP–GEM–VNR (12). Therefore, the initial doses of each drug were reduced to 80% of their planned dose in this study.

PATIENTS AND METHODS

PATIENTS

From December 2000 to August 2003, 12 patients with histologically proven MPM were enrolled into a single-center

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study of CDDP–GEM–VNR triplet combination. The study had appropriate institutional ethical review board approval, and all patients provided their written, informed consent according to institutional guidelines. All patients were required to be age ≤ 75 years old, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1 and with no uncontrolled cardiac or hepatic diseases. All patients had an adequate bone marrow function [defined as total leukocyte count $\geq 4 \times 10^9/l$, absolute neutrophil count (ANC) $\geq 2 \times 10^9/l$, platelet count $\geq 100 \times 10^9/l$ and hemoglobin level ≥ 9.5 g/dl]; adequate renal function (defined as serum creatinine level \leq upper normal limit for the laboratory, or creatinine clearance ≥ 60 ml/min); and an adequate hepatic function (defined as total bilirubin level ≤ 1.5 times the upper limit of normal and serum AST and/or ALT and alkaline phosphatase levels ≤ 2 times the upper normal limit for the laboratory). The clinical or pathological stage of the disease was based on the International Mesothelioma Interest Group (IMIG) staging system (13). The histological analysis of the tumor was based on the WHO classification for cell types (14). The toxicity criteria were based on the National Cancer Institute–Common Toxicity Criteria (NCI–CTC), version 2.0 (<http://ctep.info.nih.gov/>). The clinico-pathological characteristics of the patients are shown in Table 1. The doublet regimens (CDDP plus GEM or carboplatin plus etoposide) were performed in two patients as first-line chemotherapy.

TREATMENT SCHEDULE

The patients received the following regimen: CDDP 40 mg/m², GEM 800 mg/m² and VNR 20 mg/m² on days 1 and 8 every 4 weeks. In the absence of either disease progression or unacceptable toxicity levels, the patients were scheduled to receive the treatment for three cycles (maximum of six cycles). If grade 3 or more leukopenia and neutropenia, grade 2 or more thrombocytopenia, or grade 2 or more non-hematological toxicities occurred on day 8, the treatment on that day was skipped. If the total leukocyte count and ANC were $\geq 3 \times 10^9/l$ and $\geq 1.5 \times 10^9/l$, respectively and if the other eligibility criteria were satisfied, then the patients could receive the next cycle. If these toxicities persisted after 6 weeks from day 1 of the previous cycle, then the treatment regimen was discontinued. The blood counts and chemistries were examined at least once a week. Patients should not receive prophylactic granulocyte colony-stimulating factor (G-CSF) during any cycle. G-CSF may be used only for patients who have ANC $< 0.5 \times 10^9/l$, neutropenic fever or documented infections while neutropenic.

DOSE ADJUSTMENTS

As shown in Fig. 1, the doses of each drug were reduced by 25% in patients in whom grade 4 hematological toxicities or grade 3 or greater non-hematological toxicities (excluding nausea and vomiting) occurred, or in whom the scheduled treatment was skipped on day 8 in the previous cycle.

Table 1. Clinico-pathological characteristics of the patients

| Parameter | No. | % |
|---------------------------|------------|----|
| Median age, years (range) | 53 (34–67) | |
| Gender | | |
| Male | 11 | 92 |
| Female | 1 | 8 |
| Performance status (ECOG) | | |
| 0 | 8 | 67 |
| 1 | 4 | 33 |
| Histological type | | |
| Epithelioid | 7 | 58 |
| Sarcomatoid | 1 | 8 |
| Biphasic | 3 | 25 |
| Unknown | 1 | 8 |
| IMIG stage | | |
| I | 6 | 50 |
| II | 1 | 8 |
| III | 3 | 25 |
| IV | 2 | 17 |
| Prior treatments | | |
| Chemotherapy | 2 | 17 |
| Radiotherapy | 1 | 8 |
| None | 9 | 75 |
| Exposure to asbestos | | |
| Yes | 7 | 58 |
| No | 5 | 42 |

ECOG, Eastern Cooperative Oncology Group.
IMIG, International Mesothelioma Interest Group.

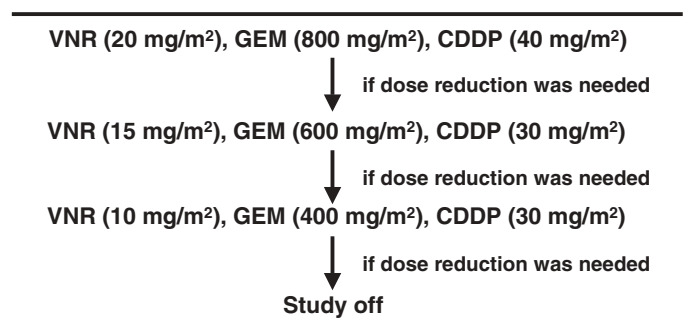


Figure 1. A schematic drawing of the dose modification in this study.

TUMOR ASSESSMENT DURING AND AFTER TREATMENT

The change in disease was assessed by measuring the thickness of the circumferential pleural tumor at three separate levels on transverse sections on the computed tomography (CT) findings of the chest, at baseline and at every other cycle (6). The sum of the measurements of tumor thickness at the three levels defined the unidimensional size. The measurability of target lesions at

baseline and the response criteria were based on the Response Evaluation Criteria in Solid Tumours (RECIST) (15). In brief, lesions that can be accurately measured in at least one dimension ≥ 20 mm with conventional techniques or as ≥ 10 mm with a spiral CT scan were defined as measurable lesions. The response criteria will be categorized as follows: complete response (CR), the disappearance of all target lesions; a partial response (PR), at least a 30% decrease in the sum of the pleural thickness at three separate levels; progressive disease (PD), at least a 20% increase in the sum of the pleural thickness at three separate levels or the appearance of one or more new lesions; and stable disease (SD), neither sufficient shrinkage to qualify for PR nor a sufficient increase to qualify for PD.

EXTRAPLEURAL PNEUMONECTOMY AFTER CHEMOTHERAPY

In addition to the chemotherapy inclusion criteria as mentioned above, patients were also candidates to undergo an extrapleural pneumonectomy (EP) if the following conditions were all satisfied: (i) age of 65 years or younger; (ii) tumor confined to stage I or II or with part of the tumor at stage III according to the IMIG staging system (13); (iii) EP would allow a complete resection of all gross disease; (iv) the room air oxygen partial pressure was >70 mmHg; and (v) a post-resection forced expiratory volume of 1 s (FEV_{1.0}) >600 ml per body surface area was predicted.

END-POINTS AND SAMPLE SIZE CONSIDERATION

The primary end-point of this study was the response rate of MPM of those who underwent this treatment. The secondary end-points were overall survival, toxicity, morbidity and mortality after surgery in the patients who underwent EP. The sample size was calculated based on an expected response rate of 54% and an acceptable lowest rate of 20%, with α and β errors of 0.05 and 0.2, respectively; a total of 11 patients were required using the one-sample multiple testing procedure of Fleming (16). In this design, when the number of responses exceeds four of 11 cases, it leads to the rejection of the hypothesis that the true response rate is $<20\%$. The accrual period and follow-up after accrual closure were 3 and 2 years, respectively.

STATISTICAL ANALYSIS

The duration of response was measured from the first day of a PR to the first date of progression or death due to any causes. The survival was calculated from the date of first chemotherapy dose until death due to any cause or the last follow-up (censored). The survival curve was produced using the Kaplan–Meier method (17). All data were analyzed using Abacus Concepts, Survival Tools for StatView (Abacus Concepts, Inc., Berkeley, CA).

RESULTS

TREATMENT TOXICITY AND RESPONSE

A total of 35 cycles of treatment (28 cycles with full dose and seven cycles with one level dose reduction) were delivered to the 12 patients. All cycles with a dose reduction were due to myelosuppression. The median number of cycles per patient was three. Out of 35 cycles, the frequency of treatment skipping on day 8 was only three cycles (myelotoxicity in one cycle and patient's refusal in two). As a consequence of delay and/or dose reductions, the median relative dose intensity (actually delivered $\text{mg}/\text{m}^2/\text{week}$ divided by the planned $\text{mg}/\text{m}^2/\text{week}$) of all drugs was 91%. Except for six candidates who were indicated to undergo EP, the reasons for discontinuing the chemotherapy were progression after SD in two patients, progression after PR, PD, patient's refusal and transition to other treatments in one case each. This regimen was associated with a manageable toxicity. No toxic deaths occurred. Grade 3–4 leukopenia, neutropenia, anemia and thrombocytopenia occurred in 50, 92, 33 and 17%, respectively (Table 2). According to the G-CSF dose criteria, eight patients received G-CSF out of 12 patients during 10 cycles out of 35. The median duration of grade 4 neutropenia was 3 days (range: 2–7 days). Severe non-hematological toxicity was uncommon. The overall response rate for all patients and that only for chemotherapy-naïve cases were 58 and 67%, respectively (Table 3). The median duration of response was 6 months (range, 2–19 months). Among the 12 patients, six patients were eligible for EP after a median of three cycles of triplet chemotherapy (one CR, four PR and one SD). All six were

Table 2. Hematological and non-hematological toxicity

| NCI-CTC grade | 0 (%) | 1 (%) | 2 (%) | 3 (%) | 4 (%) | 3/4 (%) |
|----------------|--------|--------|--------|--------|--------|---------|
| Leukopenia | 0 | 1 (8) | 5 (42) | 3 (25) | 3 (25) | 6 (50) |
| Neutropenia | 0 | 1 (8) | 0 | 5 (42) | 6 (50) | 11 (92) |
| Hb | 0 | 2 (17) | 6 (50) | 3 (25) | 1 (8) | 4 (33) |
| PLT | 4 (33) | 4 (33) | 2 (17) | 2 (17) | 0 | 2 (17) |
| AST or/and ALT | 9 (75) | 1 (8) | 2 (17) | 0 | 0 | 0 |

NCI-CTC, National Cancer Institute Common Toxicity Criteria; Hb, hemoglobin; PLT, platelets; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 3. Objective tumor response

| | All cases ($n = 12$) | Chemotherapy-naïve cases ($n = 9$) |
|-------------------------|------------------------|--------------------------------------|
| Complete response | 1 | 1 |
| Partial response | 6 | 5 |
| Stable disease | 4 | 2 |
| Progressive disease | 1 | 1 |
| Response rate (%) | 58 | 67 |
| 95% confidence interval | 30–86 | 36–98 |

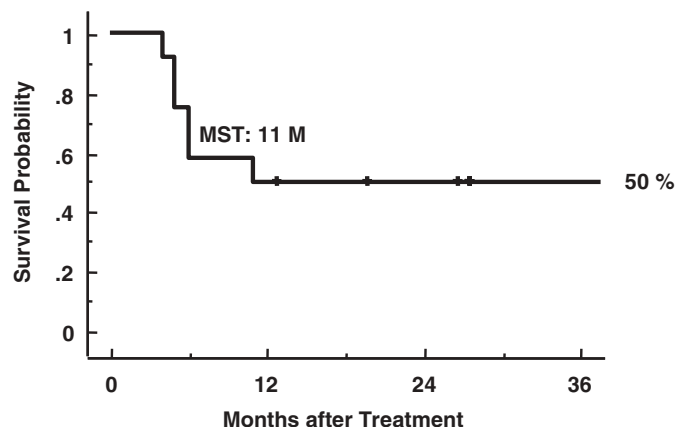


Figure 2. Overall survival in all patients.

males with a median age of 50 years (range 34–54). Three patients had stage I, one stage II and two stage III disease. The histological types were epithelioid type in four and biphasic type in two. The median duration of hospitalization after EP was 33 days (range 19–63). There were neither deaths nor major morbidity during the perioperative period except thoracic empyema in one patient. Although there were no pathological CRs (Ef3: no viable tumor cells in resected specimens), some pathological response was recognized in all six patients (Ef1a, $\geq 2/3$ viable tumor cells, in two patients; Ef1b, $1/3 \leq$ viable tumor cells $< 2/3$, in two; and Ef2, $< 1/3$ viable tumor cells, in two).

SURVIVAL

The median follow-up duration of the patients was 13 months (range 4–43). The median survival time was 11 months for all patients and 6 months for the patients who did not undergo EP. The survival of the patients who underwent EP has not yet achieved a median value. The overall survival rate at 2 years was 50% (Fig. 2). The 2-year survival rates for the patients with and without EP were 83.3 and 16.7%, respectively. Among the six patients who underwent EP, the sites of first recurrence were local in three and liver metastasis in one.

DISCUSSION

Triplet chemotherapy with CDDP, GEM and VNR used in this trial produced a 58% objective response rate in patients with MPM. Selected patients underwent EP after a median of three cycles of chemotherapy without any perioperative deaths; this triplet chemotherapy was thus found to be feasible for the induction setting. Ichinose et al. presented a multicenter phase II trial using 80% of the dose of the previous CDDP–GEM–VNR triplet regimen in 80 patients with advanced NSCLC (18). The predominant toxicity was hematological: grade 3–4 neutropenia and thrombocytopenia occurred in 84 and 44% of the patients, respectively. The frequency of grade 3–4 non-hematological toxicity was low ($< 5\%$). Sixty-three percent of the enrolled patients completed > 4 cycles in this

trial. As a consequence of delay and/or dose reductions, the median relative dose intensity (actually delivered $\text{mg}/\text{m}^2/\text{week}$ divided by the planned $\text{mg}/\text{m}^2/\text{week}$) of all drugs was $> 82\%$. The triplet chemotherapy administered at a lower dose demonstrated a sufficiently effective activity with feasibility and tolerable toxicity in Japanese patients. In this study, the response rate only for chemotherapy-naïve cases was 67%. The median survival time and survival rate at 2 years for all patients were 11 months and 50%, respectively. Our results indicate that a CDDP–GEM–VNR triplet regimen is a promising treatment for MPM.

EP involves the removal of the complete pleural envelope and all of its contents, including the ipsilateral lung, diaphragm and a portion of the pericardium. The peri-operative mortality and morbidity rates of this procedure were high because of the operative invasiveness, but with more experience and better pre-operative management, the peri-operative mortality is decreasing. In the largest series of EP for MPM reported by Sugarbaker et al., the peri-operative mortality rate and some morbidity, including atrial and ventricular arrhythmias, the most common minor morbidity, were 3.8 and 50%, respectively (19). A recent publication from a Swiss group demonstrated that neoadjuvant chemotherapy consisting of CDDP and GEM followed by EP in MPM had no peri-operative mortality (20). EP can therefore be safely performed after neoadjuvant chemotherapy in an experienced center. Rusch and associates reported that hemithoracic radiation after a complete surgical resection dramatically reduced local recurrence and was associated with a prolonged survival for early-stage MPM (21). Adjuvant radiation administered to 57 patients (54 undergoing EP and three undergoing pleurectomy/decortication) at a median dose of 54 Gy was well tolerated (grade 0–2 fatigue, esophagitis), except for one late esophageal fistula. In our trial, local recurrence was the most common form of relapse in the six patients who underwent EP. Therefore, hemithoracic radiation after EP may be considered for local control with acceptable toxicities. In their report, the initial site of relapse in the patients, especially in those with stage III disease, who underwent EP with post-operative radiation was mainly distant metastases (21). However, previous experience with post-operative chemotherapy after EP does not suggest a marked survival benefit in the patients with stage III tumors (19). Combination chemotherapies in series with > 15 patients since 1990 are shown in Table 4. Reported combinations do not consistently appear to provide satisfactory results. A treatment regimen with pemetrexed (Alimta) plus CDDP and vitamin supplementation was recently reported to result in a superior survival time, time to progression and response rate in comparison with treatment with CDDP alone in patients with MPM in a randomized phase III trial (22). The response rates were 41.3% in the pemetrexed plus CDDP arm versus 16.7% in the CDDP alone arm. The median survival time for patients treated with pemetrexed plus CDDP was longer than that for patients receiving CDDP alone: 12.1 versus 9.3 months, thus indicating a highly statistically significant difference ($P = 0.020$, two-sided log-rank test).

Table 4. Reported combinations in series with more than 15 patients

| Regimen | n | RR (%) | MST (months) |
|--|-------|--------|--------------|
| Doxorubicin/CDDP (23,24) | 24-35 | 14-25 | 9-10 |
| Doxorubicin/ifosfamide (25) | 22 | 32 | 7 |
| Cyclophosphamide/doxorubicin/CDDP (26) | 23 | 30 | 14 |
| CDDP/mitomycin (24) | 35 | 26 | 8 |
| CDDP/methotrexate/vinblastine (27) | 17 | 53 | 14 |
| CDDP/irinotecan (28) | 15 | 27 | 7 |
| CDDP/GEM (6-8) | 21-52 | 16-48 | 9-11 |
| CBDCA/pemetrexed (29) | 25 | 32 | 15 |
| CBDCA/GEM (30) | 50 | 26 | 15 |
| Oxaliplatin/GEM (31) | 25 | 40 | 13 |
| Mitomycin/methotrexate/mitoxantrone (32) | 22 | 32 | 14 |

RR, response rate; MST, median survival time; CDDP, cisplatin; GEM, gemcitabine; CBDCA, carboplatin.

A phase I/II trial is now underway using this doublet regimen in Japan; therefore, the effectiveness and toxicity for Japanese patients with MPM is uncertain. In addition to local therapy, induction systemic chemotherapy using so-called new drugs, including CDDP-GEM-VNR triplet combination or CDDP plus the pemetrexed doublet, might produce a prolonged survival in patients with MPM, a disease for which standard treatment remains to be established.

In conclusion, CDDP-GEM-VNR combination is feasible at doses which, for the respective drugs, have a proven therapeutic effect in MPM patients. This combination is selectively manageable for induction chemotherapy followed by EP. A multi-institutional phase II trial is now being planned to establish the effectiveness of this new triplet regimen in chemotherapy-naïve patients with MPM as an intergroup study of the Japan Clinical Oncology Group and the West Japan Thoracic Oncology Group.

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