

UFT plus gemcitabine combination chemotherapy in patients with advanced non-small-cell lung cancer: a multi-institutional phase II trial

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A multi-institutional phase II trial was conducted to evaluate the efficacy and toxicity of combination chemotherapy consisting of gemcitabine and UFT, which is composed of tegafur and uracil, for non-small-cell lung cancer (NSCLC) patients. Patients with advanced NSCLC received an oral administration of UFT (tegafur 200 mg m⁻²) b.i.d. from days 1 to 14 and intravenous injection of gemcitabine 900 mg m⁻² on days 8 and 15. This treatment was repeated every 4 weeks. A total of 44 patients were enrolled into this trial. The median age of all patients was 74 years, with 23 patients younger than 75 years and 21 patients with 75 years of age or older. A total of 18 patients (41%) achieved a partial response. The median survival time was 13.2 months and the 1-year survival rate was 59%. The most common grade 3–4 toxicity was neutropenia (57%). The frequency of grade 3 nonhaematologic toxicities was less than 5%. In addition, no significant difference in the response, survival or toxicities was observed between the patients younger than and those older than 75 years of age. This combination chemotherapy demonstrated a promising effectiveness and acceptable toxicity in patients with advanced NSCLC, even in patients older than 75 years.

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UFT is an oral anticancer agent composed of tegafur and uracil at a 1:4 fixed molar ratio (Fujii *et al*, 1979). Although the clinical effectiveness of the single agent against advanced non-small-cell lung cancer (NSCLC) has not been evaluated in adequate sample size (Keicho *et al*, 1986), a recent randomised phase III trial in 984 patients with completely resected stage I adenocarcinoma demonstrated that postoperative adjuvant chemotherapy with UFT significantly prolonged the survival of patients in comparison to observation alone (Kato *et al*, 2004). The combination chemotherapy of UFT plus cisplatin has also been reported to be an effective treatment for advanced NSCLC. The combination chemotherapy consisting of a daily administration of UFT for 2 or 3 weeks and a bolus injection of cisplatin at the mid-cycle of the administration of UFT yields a response rate of 29–38%, and a median survival time of 10–13 months (Ichinose *et al*, 1995, 2000; Saito *et al*, 2001).

Gemcitabine is an active anticancer agent for the treatment of NSCLC. The objective response rates of patients with advanced NSCLC treated with gemcitabine alone and the combination chemotherapy of platinum plus gemcitabine range from 20 to 26%

and from 25 to 61%, respectively (Harper, 2003). A median survival time of 8–16 months in patients treated with the combination chemotherapy has been reported (Harper, 2003).

Both 5-FU generated from tegafur in UFT and gemcitabine are antimetabolites but inhibit DNA synthesis via a different pathway. The main mechanism of inhibiting DNA synthesis by 5-FU is due to 5-FU-derived fluorodeoxy monophosphate binding to thymidylate synthase (Madajewicz *et al*, 1984). The incorporation of gemcitabine triphosphate, which is generated from the phosphorylation of gemcitabine by deoxycytidine kinase, into DNA is most likely the major mechanism by which gemcitabine exerts its cytotoxic action (Huang *et al*, 1991). Such different antitumour mechanisms suggest a potential synergism between 5-FU and gemcitabine. This potential synergism has been indeed observed in *in vitro* studies using various cancer cell lines (Schulz *et al*, 1998; Peters *et al*, 2000).

In our prior phase I trial, the combination chemotherapy of UFT plus gemcitabine was found to be feasible (Seto *et al*, 2002). The most appropriate schedule and dosing was 200 mg m⁻² of UFT b.i.d. for 14 consecutive days with 900 mg m⁻² gemcitabine on days 8 and 15. The main toxicity was haematologic. The overall response rate was 33%, while the rate was 45% in the 13 patients without any prior chemotherapy. With these backgrounds, we conducted a phase II trial of combination chemotherapy using

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UFT plus gemcitabine. In the present multi-institutional phase II trial, we found the proportion of elderly, especially patients older than 75 years of age, to be high. Therefore, the results of all patients in the phase II trial and the differences between patients younger than 75 years and those 75 years of age or older were evaluated.

MATERIALS AND METHODS

Patient eligibility

The patients were eligible for this phase II trial if they had been either cytologically or histologically confirmed to have NSCLC; stage IIIB without any indications for radiotherapy or stage IV; measurable disease; no prior chemotherapy; an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1 or 2; a projected life expectancy of at least 3 months. Other eligibility criteria regarding organ functions were as follows: a leucocyte count of $4000-12\,000\ \mu\text{l}^{-1}$; platelet count of $100\,000\ \mu\text{l}^{-1}$ or greater; haemoglobin level of $9\ \text{g dl}^{-1}$ or greater; a serum bilirubin level less than $1.5\ \text{mg dl}^{-1}$; serum aspartate aminotransferase and alanine aminotransferase levels of twice the upper limit or less; a serum creatinine level of $1.5\ \text{mg dl}^{-1}$ or less. For staging, all patients underwent a computed tomography (CT) scan of the thorax, including the upper abdomen, and either brain CT or magnetic resonance images of the brain, and a radioisotopic bone scan were performed for almost all patients.

Any patients who were pregnant or had concomitant serious diseases, a concomitant malignancy, pleural effusion necessitating treatment or symptomatic cerebral involvement were excluded from the study. However, patients whose malignant pleural effusion was controlled by intrapleural hypotonic cisplatin treatment (Ichinose *et al*, 2003) were eligible. Written informed consent was required from all patients and the protocol was approved by the institutional ethics committee of each of the participating institutions. On entrance to the study, the eligibility of patients was checked via facsimile by the central administration office of the Kyushu Yamaguchi Thoracic Oncology Group (Fukuoka).

Treatment schedule

UFT (tegafur $400\ \text{mg m}^{-2}\ \text{day}^{-1}$) in the form of a 100-mg capsule (100 mg of tegafur plus 224 mg of uracil) was given orally in two separate doses, before meals, from days 1 to 14. The dose was rounded up or down to the nearest 100 mg. Most patients received UFT three capsules (tegafur 300 mg and uracil 672 mg) b.i.d. Gemcitabine ($900\ \text{mg m}^{-2}$) was dissolved in 20 ml of physical saline and then diluted further with physical saline or 5% glucose to a volume of 250 ml. The gemcitabine solution was administered by intravenous drip infusion over 30 min on days 8 and 15. On the day gemcitabine was administered, a complete blood count was performed and the drug was administered only when the leucocyte count was $2000\ \mu\text{l}^{-1}$ or higher and the platelet count was $70\,000$ or higher μl^{-1} . If these requirements were not met, then drug administration was postponed for a maximum of 4 days. The treatment regimen was repeated every 4 weeks and at least two cycles were administered unless disease progression or an unacceptable toxicity occurred. A leucocyte count of $3000\ \mu\text{l}^{-1}$ or greater and the entry eligibility criteria regarding organ functions had to be satisfied to start the next cycle. The doses of gemcitabine were reduced to $800\ \text{mg m}^{-2}$ either when grade 4 haematologic toxicities occurred or when the administration of gemcitabine on day 15 was skipped in a prior cycle. The doses were increased to $1000\ \text{mg m}^{-2}$ if both nadirs of the leucocyte and platelet counts were more than 3000 and $100\,000\ \mu\text{l}^{-1}$, respectively, in a prior cycle.

Evaluation of response and toxicity

All eligible patients who received any part of the treatment were considered assessable for response and toxicity. The complete blood count, and blood chemistry studies were repeated weekly. The response was assessed based on the chest X-ray or CT scan findings that initially had been used to define tumour extent. The response was evaluated according to the criteria of the World Health Organization (Miller *et al*, 1981). A central radiologic review was performed to determine the eligibility of patients and the response of treatment. Any adverse events were graded according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 2.0.

Statistical analysis

The primary end point of this study was to determine the tumour response rate produced with this treatment protocol. Based on the assumption that a response rate of higher than 40% would warrant a further investigation of this combination chemotherapy, and that a rate of below 20% would make such an investigation unnecessary, a sample size of 36 patients was required with an alpha error of 0.05 and a beta error of 0.2. Therefore, the accrual of 40 patients was planned for a 2-year period since several ineligible patients might be identified in the course of the study.

The overall survival of the eligible patients was defined as the time from the start of the treatment until death from any cause and it was estimated by the Kaplan-Meier method. Differences between the proportions were evaluated by the chi-square test. The data were considered to be significant when the *P*-value was 0.05 or less.

RESULTS

Patient characteristics

From July 2000 to September 2002, 44 patients were entered into this phase II trial. Since no upper age limit for the eligibility criteria was established, in contrast to other Japanese trials, many elderly patients were included in this trial. The patient characteristics classified by an age of less than 75 years of age or 75 years of age and older are shown in Table 1. There were no statistically significant differences in the proportions regarding gender, performance status, stage, histology or previous treatment between the two (<75 vs ≥ 75 years) groups. There were 33 patients who were 70 years of age or older.

Treatment delivery

The median number of treatment cycles for all patients was three as shown in Table 2. In all, 39 (89%) patients received at least two cycles of the treatment. The reasons for terminating the chemotherapy before the second treatment cycle were adverse events in three patients, a progression of dementia in one and patient refusal in one. Although the proportions of the cycles administered between the two-age groups showed no significant difference, 10 (48%) patients in the older age group received five or more cycles of the treatment.

The administration of gemcitabine on day 15 was skipped in 10 (5%) of a total of 196 cycles. A dose decrease to $800\ \text{mg m}^{-2}$ and the increase to $1000\ \text{mg m}^{-2}$ were reported in four and five patients, respectively.

Adverse events

The main adverse events were haematologic toxicities as shown in Table 3. Grade 3 and 4 neutropenia was reported in 57% of the patients and grade 4 in 20%, while no grade 4 anemia or

Table 1 Patient characteristics

	<75 years (n=23)	≥75 years (n=21)	Total (n=44)
Age			
Median (range)	70 (58–74)	78 (75–89)	74 (58–89)
Gender			
Male/female	7/16	11/10	18/26
Performance status (ECOG)			
0/1/2	8/13/2	8/13/0	16/26/2
Stage			
III/IV	5/18	7/14	12/32
Histology			
Adenoca/others	17/6	15/6	32/12
Previous treatment			
None	11	11	22
HPT ^a	6	8	14
Operation	5	2	7
Radiotherapy	1	0	1

^aHypotonic cisplatin treatment. ECOG = Eastern Cooperative Oncology Group.

Table 2 Treatment delivery

Cycle of treatment	<75 years (n=23)	≥75 years (n=21)	Total (n=44)
1	23 (100%)	21 (100%)	44 (100%)
2	21 (91%)	18 (86%)	39 (89%)
3	12 (52%)	14 (67%)	26 (59%)
4	9 (39%)	11 (52%)	20 (45%)
≥5	6 (26%)	10 (48%)	16 (36%)
No. of cycles			
Median	3	4	3
Range	1–18	1–16	1–18

thrombocytopenia was observed. The frequency of grade 3 and 4 haematologic toxicities was 57% in the younger-age group and 62% in the older-age group. The frequency of grade 3 or greater nonhaematologic toxicities was 5% or less. No grade 4 non-haematologic toxicity was observed.

Response

Among the 44 patients, 18 patients showed a partial response (41%; 95% confidence interval, 26–55%). There were 24 patients (55%) with no change and two patients (5%) with progressive disease. There were no differences in the response rate according to age (<75 vs ≥75 years, 44 vs 38%), gender (male vs female, 46 vs 33%), stage (III vs IV, 42 vs 41%) and histology (adenocarcinoma vs others, 44 vs 33%). Median duration of response was 6.9 months.

Survival

The overall median follow-up time for all patients was 38 months (range from 23 to 50 months). As shown in Figure 1, the median survival time of all 44 patients was 13.2 months, and the survival rates at 1 and 2 years were 59% (95% confidence interval, 45–74%) and 34% (95% confidence interval, 20–48%), respectively. There were no statistically significant differences in survival between the patients under 75 and those over 75 years ($P=0.4948$). The median survival time was 13.2 and 13.3 months, respectively.

Table 3 Haematologic and nonhaematologic toxicities (n=44)

Toxicity	Grade				Frequency of Grade 3 or 4 (%)
	1	2	3	4	
Leukopenia	4	19	13	1	32
Neutropenia	5	8	16	9	57
Anemia	22	13	4	0	9
Thrombocytopenia	15	9	8	0	18
GOT	8	1	0	0	
GPT	10	1	0	0	
Creatinine	1	0	0	0	
Anorexia	4	1	2	0	5
Vomiting	2	2	0	0	
Diarrhoea	0	1	2	0	5
ALP	0	0	1	0	2
Febrile neutropenia	0	0	1	0	2

GOT = glutamic oxaloacetic transaminase; GPT = glutamic pyruvic transaminase; ALP = alkaline phosphatase.

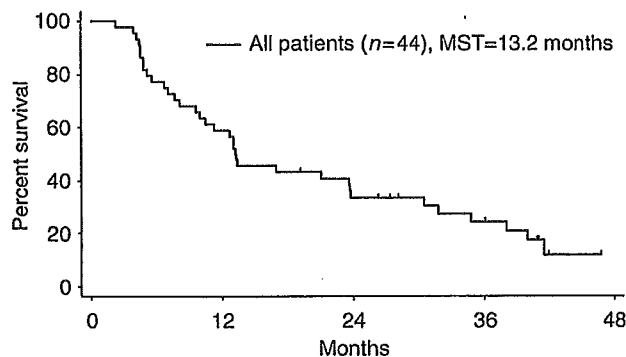


Figure 1 Overall survival. Each tick represents a patient who is alive.

DISCUSSION

Platinum-based combination chemotherapy is recommended for the treatment of advanced NSCLC patients with a good performance status (Pfister et al, 2004). However, the incidence of severe adverse effects induced by this combination chemotherapy is indeed more frequently observed in elderly patients than younger patients even if the subjects have good performance status (Langer et al, 2002). Therefore, a single agent such as vinorelbine, whose effect on prolonging survival in advanced NSCLC with elderly has been demonstrated in comparison to the best supportive care (Anonymous, 1999), is sometimes selected to treat such patients in practice. In addition, the combination of vinorelbine plus gemcitabine has been reported to be not more effective than single-agent vinorelbine or gemcitabine in the treatment of elderly patients with advanced NSCLC (Gridelli et al, 2003).

Lung cancer is primarily a disease of the elderly. More than one half of new diagnoses and more than two-thirds of annual deaths occur in patients over 65 years (Havlik et al, 1994; Gridelli et al, 1997). Although the aim of the present study was not to develop a treatment for only the elderly, the median age of the patients in this study was 74 years and 48% of the patients were 75 years or older. The reasons for this age distribution were thought to be partly due to the followings: First, the subjects of almost all previous clinical trials for chemotherapy against advanced NSCLC conducted in Japan were limited to patients under 75 years of age. Second, both UFT and gemcitabine were considered to be relatively safe anticancer agents. Third, they could be administered on an outpatient basis with no need for premedication and rehydration.

The overall response rate of the present trial using UFT and gemcitabine was 41%. In a phase I trial of this combination chemotherapy, the response rate of patients without prior chemotherapy was also reported to be 45% (Seto *et al*, 2002). This high antitumour effect may lend support to the sequence of administration of UFT and gemcitabine. In fact, an *in vitro* study has shown the sequence-dependent antitumour effects of the combination of 5-FU and gemcitabine to be seen with a maximum effect when 5-FU preceded gemcitabine (Rauchwerger *et al*, 2000). Since the 5-FU concentration in blood reaches a steady state 5 days after the start of UFT administration (Ho *et al*, 1998), the administration of gemcitabine on days 8 and 15 is considered to be most appropriate.

Since the recent randomised trial demonstrated that gemcitabine plus carboplatin produced a significantly higher response rate and survival rate than gemcitabine alone in advanced NSCLC patients including a substantial proportion of elderly patients (37% of patients >70 years old), the combination chemotherapy using gemcitabine and carboplatin (Sederholm, 2002) may also be considered to be a suitable chemotherapy regimen for the treatment of elderly patients. The response rate and median

survival time in the combination chemotherapy group has been reported to be 30% and 10 months, respectively. Grade 3 or 4 nonhaematologic toxicity was observed in 26% of the patients, while grade 3 and 4 thrombocytopenia was reported in 24% each of patients, respectively. A toxicity profile in the elderly has not yet been reported.

In the present phase II trial of 44 patients with a median age of 74 years, including 21 patients who were 75 years or older, the response rate was 41% and the median survival time was 13.4 months. These observations suggest that this combination chemotherapy is also worthy of further investigation for the treatment of all NSCLC patients including the elderly. In addition, it should be confirmed whether or not this combination regimen is equally effective in ethnic groups other than Japanese.

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Intrathoracic Omental Herniation through the Esophageal Hiatus in a Young Patient

We herein present a case of intrathoracic omental herniation through the esophageal hiatus in a young patient. A 21-year-old obese man was asymptomatic, and his chest X-ray demonstrated a large, sharply defined mass. A computed tomography scan of the thorax indicated a large retrocardial mediastinal mass in which the density indicated the presence of fatty tissue judging from the Hounsfield unit range. A thoracotomy was performed under a diagnosis of either mediastinal lipoma or liposarcoma with an encapsulated fatty mass, measuring 17×12×8 cm in size. The mass, however, proved to be an omental herniation through the esophageal hiatus. It is generally assumed that the major contributing factors leading an individual to develop an omental herniation through the esophageal hiatus include aging and obesity. This is the first report of omental herniation through the esophageal hiatus in a patient still in his twenties. (*Jpn J Thorac Cardiovasc Surg* 2005; 53: 452–454)

Key words: omentum, hernia, esophageal hiatus, young patient

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Omental herniation through the esophageal hiatus, without stomach involvement, is rare. Omental herniation has been previously misdiagnosed as a lipomatous tumor.¹ To the best of our knowledge, there have been only eight reports on omental herniation through the esophageal hiatus in the Japanese and English literatures within last three decades.^{1–8} In addition, there have also been no reports on young patients with this problem up to now.

Case

A 21-year-old obese man (height: 174 cm, weight: 90 kg, body mass index: 29.7) was admitted to our department for an investigation of a chest roentgenographic abnormality. He was asymptomatic, and his physical examination and laboratory data were all within the normal limits. A postero-anterior view of his chest X-ray demonstrated a large, sharply defined mass. The mass

measured over 15 cm in diameter with a smooth outline, it did not demonstrate either calcification or cavitation, and it extended from the retrocardial mediastinum to the diaphragm level (Fig. 1A). A computed tomography (CT) scan of the thorax showed the presence of a mass, in which the density indicated the presence of fatty tissue according to the Hounsfield unit (HU) range,⁹ in the lower thorax, located behind the heart, and beside the thoracic vertebrae (Fig. 1B). The HU of water and air in the lung parenchyma were 0 and –1,000, respectively. The HU of the fatty tissue are usually in the range of –50 to –200. Both coronal and sagittal sections of T1-weighted magnetic resonance imaging (MRI) clearly depicted a fatty mass on both sides of the diaphragm (Fig. 2). A thoracotomy was performed under an initial diagnosis of either mediastinal lipoma or liposarcoma which demonstrated an encapsulated fatty mass, measuring 17×12×8 cm in size, but which proved to be an omental herniation through the esophageal hiatus. The esophageal hiatus was repaired after the omental mass and hernia sac had first been resected. The patient had an uneventful postoperative recovery without any complications.

Discussion

The omentum sometimes herniates as a result of

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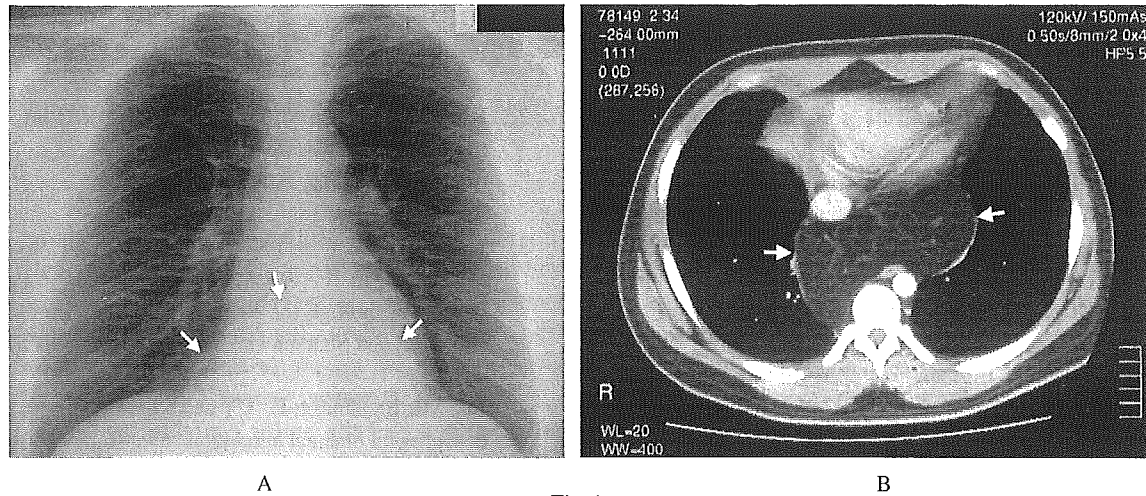


Fig. 1.

A: Postero-anterior view of a chest X-ray demonstrates a large retrocardiac mass (arrows).
B: A CT scan (axial section) demonstrates a large retrocardiac fatty mass (arrows).

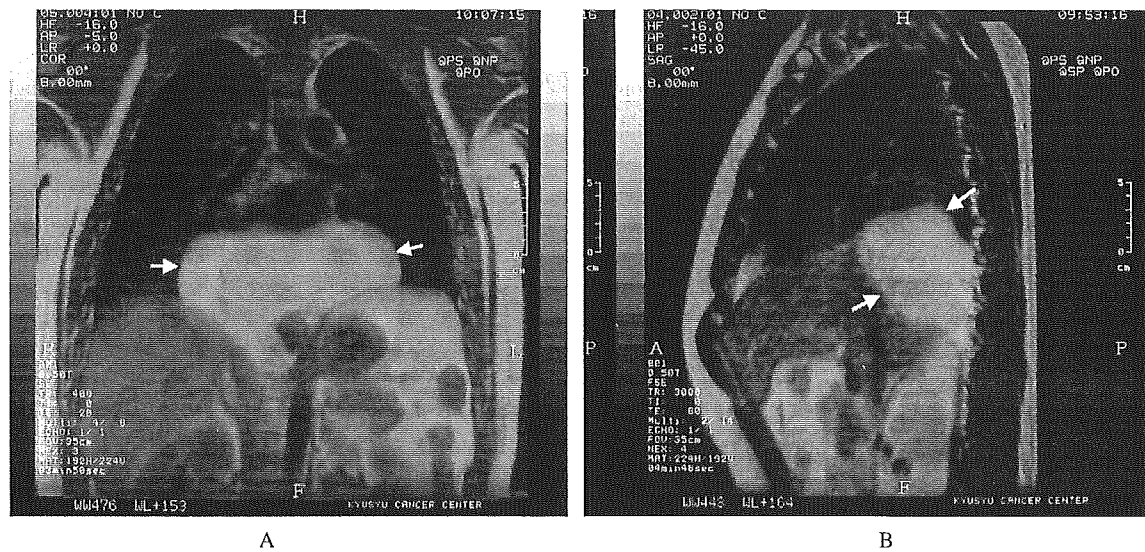


Fig. 2. Coronal (A) and sagittal (B) sections of T1-weighted MRI clearly depict a fatty mass on both sides of the diaphragm (arrows).

congenital defects of the diaphragm, such as Morgagni or Bochdalek defects. However, there have only been eight reports on omental herniation through the esophageal hiatus in the Japanese and English literatures within last three decades.¹⁻⁸ Omental herniation has previously either been misdiagnosed as intrathoracic lipomatous tumor or has been resected without a conclusive diagnosis.¹ CT and MRI are very useful modalities for establishing a differential diagnosis preoperatively.^{4,5} However, a correct diagnosis of omental herniation requires evidence

of omental fat accompanied with omental vessels passing through the esophageal hiatus. In this case, vascular structures were recognized on the CT scan. However, it is difficult to distinguish these components from areas of neovascularity due to malignant formation. Kubota et al. performed celiac arteriography to rule out the possibility of a lipomatous tumor.⁸ Since angiography is an invasive diagnostic procedure, they also recommend dynamic MRI or reconstructed 3 dimension (3D) MR angiography as alternatives to angiography.

Eliska suggested that the phreno-esophageal membrane can act as one of the main mechanisms of competence in the cardio-esophageal junction, and thus preventing reflux and hiatal hernia.¹⁰ This membrane has two limbs, one which passes through the esophageal hiatus, and then attaches itself to the esophagus in the chest, while the other limb extends downward and attaches itself to the esophagus in the abdomen. The membrane is normally rich in elastic fibers, but in people over 50 years of age, the amount of elastic tissue tends to decrease and the esophagus becomes much more mobile within the hiatus. In obese patients, the omentum may also be more prominent than usual, thus predisposing it to herniation without any significant gastroesophageal hernia. It is generally assumed that the major contributing factors leading to an omental herniation through the esophageal hiatus include aging and obesity. Therefore, previous reports about omental herniation all described either middle-aged or elderly patients.¹⁻⁸ This is the first report of intrathoracic omental herniation through the esophageal hiatus in a patient still in his twenties. The weakness of the phreno-esophageal membrane was not recognized based on an intraoperative view. In addition to obesity, these findings indicate the possibility that some congenital anomaly may thus have existed in the esophageal hiatus in our case and an omental mass thereafter formed as the patient became older.

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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.

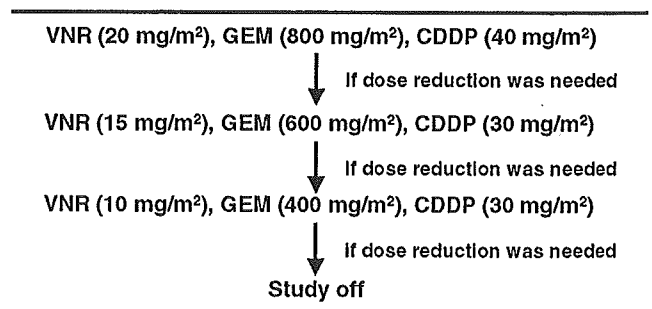


Figure 1. A schematic drawing of the dose modification in this study.

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-naive 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-naive 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

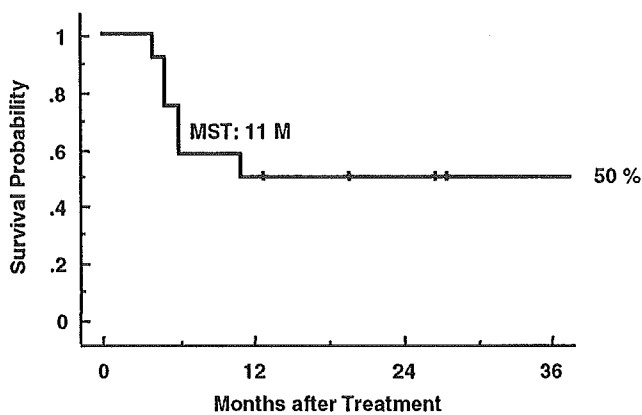


Figure 2. Overall survival in all patients.

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-naive patients with MPM as an intergroup study of the Japan Clinical Oncology Group and the West Japan Thoracic Oncology Group.

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Long-term survivors in stage IV non-small cell lung cancer

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Summary

Background and Objectives: To determine the prognostic factors for long-term survivors (LTS) with stage IV non-small cell lung cancer (NSCLC) who had undergone various treatments.

Patients and methods: From 1990 to 1999, 222 NSCLC patients with stage IV disease, who had been treated in our department, were reviewed. As the initial treatment, 135 patients (48%) were treated with chemotherapy alone, 52 patients with a combination of chemotherapy and radiotherapy, 19 patients underwent an operation with or without any other therapeutic modalities and 16 were received radiotherapy alone.

Results: Seventeen (7.7%) patients survived for more than 2 years, and all but one had adenocarcinoma. Among these LTS, eight patients received surgery as the initial therapy, and 16 (94.1%) received some type of local-control therapy, including surgery or radiotherapy, during the course of their disease. Regarding the clinical characteristics between LTS and others (non-LTS), an early N status, a single metastatic site, a good performance status, and surgery for initial therapy were all found to be significantly important factors for LTS. A multivariate analysis using a logistic regression model also showed an early N status and surgical treatment to be significantly associated with LTS.

Conclusions: Selected patients with an early N status may be appropriate candidates for aggressive multimodality treatment including surgery, in order to provide a long-term survival for stage IV NSCLC.

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1. Introduction

Approximately 80% of all lung cancer patients have non-small cell lung cancer (NSCLC) [1]. Although

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a surgical resection is the most effective therapy for an early stage NSCLC; most patients with NSCLC have advanced disease which cannot be resected at the initial presentation [2]. Many recent studies have demonstrated that platinum-based chemotherapy may have a better potential for prolonging survival than the best supportive care for these patients [3,4]. A greater than 20% reduction in the risk of death and an improvement in the median survival time of at least 6 weeks, have been reported.

Since 1990, several new agents, referred to as third generation agents, have been developed including: paclitaxel; docetaxel; vinorelbine; gemcitabine; and irinotecan. Several recent phase III trials have clearly demonstrated platinum-based combination chemotherapy with these new generation agents to be preferable to single agent chemotherapy or a combination of platinum and old generation agents, including vindesine and etoposide [5,6]. In spite of the recent advances in chemotherapy, the prognosis of patients with stage IV NSCLC is still poor and most large phase III trials have shown a median survival time of from 8 to 10 months and a 1-year survival rate of 30–35% [2].

Among many patients with stage IV NSCLC, there must be various types of patients whose clinical characteristics or clinical course differ, and we also sometimes experience a long-term survival in clinical practice. There are several reports on long-term survivors (LTS) among NSCLC patients with stage IV disease NSCLC [7–11], however, only 4 to 6% of patients with stage IV have been reported to survive for more than 2 years. In these studies, almost all the patients were initially treated with chemotherapy; however, there is still little detailed information regarding the clinical course of LTS. In the present paper, we therefore investigated the clinical characteristics of LTS among all the patients with stage IV NSCLC who were treated at our institution, and analyzed the clinical prognostic factors regarding such patients, in order to obtain a better understanding for the treatment of this metastatic disease.

2. Methods and materials

Between January 1990 and December 1999, 1251 patients with primary lung cancer were treated at the Department of Thoracic Oncology of National Kyushu Cancer Center. One thousand and one hundred fifteen patients (89.1%) had NSCLC. Among them, 284 of NSCLC (25.5%) patients had stage IV disease and 222 received some kind of

Table 1 Details of the initial treatment for patients with stage IV NSCLC

	Number of patients	Percentage
Chemotherapy alone	135	60.8
Chemotherapy + radiotherapy	52	23.4
Radiotherapy alone	16	7.2
Surgery alone	9	4.1
Surgery + chemotherapy	6	2.7
Surgery + radiotherapy	1	0.5
Surgery + chemotherapy + radiotherapy	3	1.4
Total	222	100.0

treatment. As the initial treatment, chemotherapy was performed in 135 patients (48%), a combination of chemotherapy and radiotherapy in 52, an operation with or without other therapeutic modalities in 19 and radiotherapy alone in 16 (Table 1).

The histological analysis of the tumor was based on the WHO classification for cell types [12]. A panel of pathologists reviewed the histopathologic materials. The clinical stage of these patients was determined based on the TNM classification of the Union Internationale Contre Cancer (UICC) [13]. For TNM staging, all patients underwent a computed tomography (CT) scan of the thorax and the upper part of abdomen, a bone scintigram, and a brain CT or MRI. Statistical significance for the various clinicopathological factors between LTS and non-LTS was evaluated using the χ^2 test, Fisher's exact probability test, or the Mann–Whitney test. A multivariate analysis of the clinical factors for LTS was performed by a logistic regression model. The survival curves for all patients and surgically treated patients were estimated according to the Kaplan–Meier method [14]. The terminal event was death due to any cause. Differences were considered to be statistically significant if the *P* value was below 0.05.

3. Results

3.1. Long-term survivors

The median survival time (MST) for all 222 patients who received any kind of treatment was 6.8 months, and the 1-year survival rates was 27.5%.

Among the 222 patients, 17 (7.7%) patients survived for more than 2 years. On the other hand, the MST, 1- and 2-year survival rates for patients who did not receive any treatment was 3.5 months, 8 and 0%. The details of the individual characteristics and the clinical course of LTS are presented in Table 2. Fifteen patients received chemotherapy during the course of their disease. Eight patients received surgery as the initial therapy, and 16 (94.1%) received some type of local-control therapy, including surgery or radiotherapy, during the course of their disease. All but one had adenocarcinoma and 16 were classified as having an ECOG performance status 0 or 1. Eight patients survived for more than 3 years, and three of them have been alive for more than 8 years. These three had single metastasis at the initial treatment and underwent a resection of the primary site.

3.2. Three cases who survived for more than 8 years

Patient 1 had squamous cell carcinoma in segment 3 (S3) of the left upper lobe, which was diagnosed based on a transbronchial biopsy. Two small metastases in segment 6 (S6) of the left lower lobe were demonstrated by a chest CT scan. A left upper lobectomy and a segmentectomy of S6 were performed and pulmonary metastases were also confirmed by a pathological examination. Patient 2 had adenocarcinoma in the left upper lobe and bone metastasis in the left sacrum. A pathological diagnosis of the metastasis was performed by a bone needle biopsy. He underwent concurrent chemoradiotherapy for preoperative therapy, with uracil-tegafur and cisplatin plus radiotherapy (45 gray) for bone metastasis. A left upper lobectomy and an intra-operative radiation (25 gray) were performed. Jejunal metastasis was detected 7 months later, which was again removed by operation. These two patients have so far shown no recurrence. Patient 3 had a huge mass shadow in the right middle and lower lobe with a nodular shadow in segment 6 of the left lower lobe. Brushing cytology under bronchoscopy was performed for each lesion and adenocarcinoma was detected from both specimens. A bilobectomy of the right middle and lower was performed. After surgery, five cycles of trans-bronchial interferon-gamma therapy using nebulizar was given in accordance with his request for more than a year. In addition, 2 years later, a total of 10 cycles of chemotherapy with four regimens were given over a 4-year period. He is alive with multiple pulmonary metastases.

3.3. Factors associated with LTS

A comparison of clinical characteristics between LTS and the others (non-LTS) are shown in Table 3. An early N status, a single metastatic site, a good performance status, and surgery as the initial therapy were significantly predominant in the LTS. The multivariate analysis using a logistic regression model showed an early N status and surgical treatment to be significantly associated with LTS (Table 4).

3.4. Surgery as the initial treatment

Among 19 patients who underwent surgical treatment, 17 patients had a single metastatic site; four brain, four bone, four lung, two cervical lymph nodes (LN), one axillary LN, one adrenal, and one subcutaneous metastasis. Two patients had two metastatic sites; one had adrenal gland and bone metastasis, while the other had adrenal gland and brain metastasis. All of the surgically treated patients had a controlled metastatic site and a good performance status (0 or 1). Fifteen patients were males and four were females, and the average age was 57.6 years (46–75). Thirteen had adenocarcinoma, two large cell carcinoma, two adenosquamous cell carcinoma, and two squamous cell carcinoma.

A lobectomy was performed for 10 patients, a bilobectomy for three patients, a pneumonectomy for five patients, and a wedge resection for one patient. The site where metastasis exists had no statistical impact on survival among surgical patients. When these surgical patients were divided into two categories according to the pathological N status, the 2- and 5-year survivals of the nine patients with N0 and N1 disease were 70 and 47%, respectively, while only one out of nine with N2 and N3 disease survived more than 2 years.

4. Discussion

Many randomized trials and several recent meta-analyses have demonstrated platinum-based chemotherapy to have a greater potential of prolonging survival than the best supportive care, and chemotherapy for patients with a good performance status is thus recommended [3,4]. However, the prognosis of patients with stage IV NSCLC is still poor; most large phase III trials have shown a median survival time of from 8 to 10 months and a 1-year survival rate of 30–35% [2]. We have hardly experienced that patient with metastatic NSCLC

Table 2 Individual characteristics of the 17 patients with >2 years survival

Patients	Age	Gender	PS	Survival (months)	Cell type	Alive/dead	Metastatic sites	Clinical stage	Initial therapy	CT regimen (initial treatment)	Response to CT	Further treatment
1	60	Male	0	120.3	sq	Alive	Lung (s)	T2N1	S (primary + pulmonary meta)			—
2	47	Male	1	108.9	ad	Alive	Bone (s)	T3N0	CT + RT (bone) → S (primary)	CDDP + UFT	NC	S (small intestine)
3	46	Male	1	102.8	ad	Alive	Lung (s)	T2N0	S (primary)			CT
4	58	Male	0	56.2	ad	Dead	Adrenal gland (d)	T2N3	CT + RT (primary + adrenal)	CDDP + UFT	PR	CT, RT (abdominal LN)
5	49	Male	0	53.9	ad	Alive	Axillary LN (m)	T2N3	CT → S (primary)	CDDP + DOC	PR	—
6	71	Female	1	41.3	ad	Dead	Lung (m)	T2N2	CT	S-1	NC	CT, RT (bone)
7	53	Male	1	38.0	ad	Dead	Lung (m), cervical LN	T4N0	CT	CDDP + VP16	NC	CT, RT (whole brain)
8	73	Male	1	36.5	ad	Dead	Adrenal gland (s)	T2N0	CT	CDDP + VDS	NC	—
9	54	Male	0	34.3	ad	Dead	Bone (s)	T2N1	S (bone) → CT → S (primary)	CDDP + UFT	NC	RT (bone), RT (radiosurgery), S (inguinal LN)
10	55	Female	0	32.1	ad	Dead	Lung (m)	T2N0	CT	DOC	PR	CT, RT (whole brain)
11	53	Male	1	31.9	ad	Dead	Brain (d)	T1N2	CT + RT (whole brain)	CDDP + DOC	NC	CT + RT (primary)
12	73	Female	0	30.0	ad	Alive	Bone (m)	T2N0	S (primary) + RT (bone)			CT
13	65	Male	0	28.2	ad	Dead	Lung (m)	T2N0	CT	CDDP + VDS + MMC	PR	CT, RT (bone), RT (whole brain)
14	67	Male	0	26.8	ad	Dead	Brain (m), lung (m)	T4N3	CT	CDDP + DOC	PR	CT, RT (whole brain)
15	68	Female	2	26.3	ad	Dead	Bone (d)	T4N0	CT + RT (primary)	CDDP + UFT	PR	—
16	50	Female	0	25.1	ad	Dead	Brain (s)	T2N0	S (brain) → S (primary) → RT (whole brain)			CT, CT + RT (adrenal)
17	70	Male	1	24.9	ad	Alive	Brain (s)	T2N0	S (brain) → S (primary) → RT (whole brain)			—

PS: performance status; s: single; d: double; m: multiple; LN: lymph node; CT: chemotherapy; RT: radiotherapy; S: surgery; CDDP: cisplatin; DOC: docetaxel; VDS: vindesine; MMC: mitomycin.

Table 3 Differences between the clinical characteristics of long-term survivors (LTS) and non-LTS

Characteristics		Non-LTS (n)	LTS (n)	P value
Age	<65/≥65	84/121	10/7	>0.999
Gender	Male/Female	152/53	12/5	0.973
Histologic type	Adenocarcinoma	156	16	—
	Squamous cell	35	1	
	Large cell	10	0	
	Adeno-squamous cell	4	0	
T stage	T1/T2/T3/T4/Tx	20/82/21/79/3	1/12/1/3/0	0.108
N stage	N0/N1/N2/N3/Nx	26/20/74/82/3	10/2/2/3/0	0.0003
Performance status	0/1/2/3/4	56/91/36/15/7	9/7/1/0/0	0.010
Number of metastatic sites	1/≥2	120/85	15/2	0.031
Metastatic sites				
Brain	Yes/no	61/144	4/13	0.791
Lung	Yes/no	82/123	7/10	>0.999
Bone	Yes/no	96/109	4/13	0.109
Liver	Yes/no	24/181	0/17	0.277
Adrenal gland	Yes/no	28/176	2/15	>0.999
Initial therapy	Surgery +/-	11/194	8/9	<0.0001

Table 4 Multivariate analysis using a logistic regression model for LTS in all patients with stage IV NSCLC

Variable	Category	n	OR	95%CI	P value
T stage	T1,2/T3,4	115/104	1.49	0.38–5.43	0.560
N stage	N0,1/N2,3	58/161	4.31	1.25–14.9	0.021
Performance status	0,1/2,3	162/60	3.75	0.39–30.30	0.266
Number of metastatic sites	1/≥2	135/87	3.21	0.63–16.13	0.159
Initial therapy	Surgery +/-	19/203	6.54	1.71–25.0	0.006

OR: odds ratio; CI: confidence interval.

could be successfully cured by chemotherapy alone in clinical practice.

Some studies in the literature have reported LTS among unresectable cases of NSCLC [7–11]. Patients with stages III and IV disease were included in these studies, and they were mainly treated with initial chemotherapy followed by other treatments. Only 4–6 % of stage IV patients have been reported to have survived for more than two years. A similar number of patients (7.7%) survived more than two years in the present series. There are two different groups among LTS regarding the clinical course; first are those who have chemotherapy-sensitive tumors; and thus, underwent long-term chemotherapy alone, while the second group received multimodality therapy including systemic chemotherapy plus any local-control therapy as surgery or radiotherapy during the clinical course. The majority of LTS with NSCLC belong to the latter group. In the study of European Lung Cancer Working Party, 79% of the patients with unresectable NSCLC who survived more than 4 years were treated

after chemotherapy by other therapeutic modalities [9]. Satoh and coworkers [10] reported that nine out of the 14 survivors of more than 2 years underwent chest irradiation or surgery after initial chemotherapy, and other studies also reported similar data. In the present study, all but one LTS of more than 2 years received multimodality therapies, and two potential cured patients, who survived for more than 8 years, received surgery for the primary site.

There have been many studies about local treatment for metastatic NSCLC, and among them, treatment for brain metastasis have been most frequently reported. Local-control therapy using surgery or stereotactic radiosurgery (SRS) for the patients with solitary brain metastasis have a positive impact on prolonging survival [15,16]. The ASCO treatment guidelines state that in patients with controlled disease outside of the brain who have an isolated cerebral metastasis in a resectable area, a resection followed by whole brain radiotherapy is superior to whole brain radiotherapy alone

[17]. Concerning other metastatic sites, while no sufficient evidence to support a routine resection of the metastasis exists, there have been small series indicating an improvement in the long-term survival rates of patients after a surgical resection of solitary metastases of the adrenal gland and other sites [18,19]. In the present paper, the specific site of the metastasis had no significant influence on the LTS; however, an early N status, good performance status, single site of distant metastasis, and surgical treatment as initial treatment were all found to be significant factors in the long-term survival. When surgery is considered for stage IV patients, those with a good performance status and a controlled metastatic site are selected in clinical practice. Therefore, it is compatible that, in a multivariate analysis, surgical treatment, and an early N status proved to be significant prognostic factors for LTS.

Among the surgically treated patients in our series, patients with $N \leq 1$ disease had a better survival than those with $N \geq 2$ diseases. Two studies demonstrated that an NO status was an important prognostic factor for the surgical treatment of primary lung cancer with synchronous brain metastases [20,21]. These data suggest that patients with an early N status may have an advantage for surgical treatment of stage IV NSCLC.

5. Conclusion

Adequate treatment including multimodality strategies, therefore, plays an important role in the long-term survival of stage IV NSCLC, and an aggressive treatment strategy including surgery might thus be considered for selected patients with an early N status.

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