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Serum carcinoembryonic antigen as a predictive marker for sensitivity to gefitinib in advanced non-small cell lung cancer

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Abstract

Gefitinib is an inhibitor of epidermal growth factor receptor tyrosine kinase, which has a tumour reducing effect in non-small cell lung cancer (NSCLC). In this study, we retrospectively reviewed the clinical data from 105 patients with advanced NSCLC treated with gefitinib at our department between May 2002 and April 2004. The overall response rate was 27.8% and the median survival time was 9.3 months. Pretreatment characteristics suggested that those with no history of smoking or an elevated serum carcinoembryonic antigen (CEA) level were more likely to be sensitive to gefitinib ($P = 0.009$). A multivariate analysis indicated good PS ($P < 0.0001$) and elevated serum CEA level ($P = 0.0027$) to be independent prognostic factors. These data show that the serum CEA level can be a predictive factor for the efficacy of gefitinib treatment while it is also a prognostic factor for advanced NSCLC patients undergoing this treatment.

Keywords: Gefitinib; CEA; NSCLC; EGFR; Tyrosine kinase inhibitor

1. Introduction

The majority of patients with non-small cell lung cancer (NSCLC) have such advanced disease that it can not be resected at initial treatment. Although chemotherapy can potentially prolong survival of patients with advanced cancer, the advantages are relatively small [1].

A molecular target drug, gefitinib (Iressa, AstraZeneca, London, UK), has recently been developed as a tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR), which was found to be a potential anti-cancer agent [2]. Two large phase II studies conducted in pretreated non-small lung cancer patients have demonstrated a response rate of 18% and 11.8% with symptomatic improvement in 40% and 43% of patients [3,4]. Based on these results, gefitinib has been approved for treating patients with NSCLC upon the failure of other chemotherapies. Although gefitinib was developed as a specific molecular target drug for EGFR, the clinical target of the drug in human tumours is not fully understood. Both basic and clinical research has not been able to show that the expression level of EGFR correlates with sensitivity of NSCLC to gefitinib. Analysis of clinical data from phase II clinical trials have suggested that gefitinib shows greater activity in patients of Japanese origin, females and those who had adenocarcinoma. Another report showed that patients with bronchioloalveolar carcinoma and no history of smoking were associated with a higher sensitivity to the drug [5].

Recently, two studies from different groups have shown that mutations in the tyrosine kinase domain of EGFR are associated with sensitivity of NSCLC to gefitinib [6,7]. Small in-frame deletions and missense substi-

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tutions were detected within the adenosine triphosphate (ATP) binding pocket of the EGFR catalytic domain in 10–28% of NSCLC tumours. Clinical observations demonstrated that almost all tumours sensitive to gefitinib had one of these mutations, while the tumours showing no response did not have them. Moreover, a recent study showed that such downstream molecules as Akt and STAT3/5 played a crucial role in the anti-apoptotic pathway of the mutant EGFR protein in tumour cells [8]. Another group found that activated Akt was associated with higher efficacy of gefitinib when investigating clinical specimens by immunohistochemical approaches [9].

In spite of these remarkable observations, the true mechanism of the tumour response to gefitinib is still not fully understood. In addition, the detection of mutations in EGFR is still not generally established in practice. We therefore investigated the clinical data of consecutive patients treated by gefitinib monotherapy in our department to detect or confirm specific characteristics in gefitinib sensitive patients, in order to better understand the molecular targets of this drug. We were particularly interested in patient serum carcinoembryonic antigen (CEA) levels prior to cancer treatment, since NSCLC patients with high CEA levels often showed good clinical response to gefitinib therapy.

2. Patients and methods

Between May 2002 and April 2004, 105 patients with advanced NSCLC were treated at the Department of Thoracic Oncology at the National Kyushu Cancer Center, Japan. All patients had unresectable lesions and 90% of patients received one or more regimens of chemotherapy before receiving gefitinib treatment. Generally, gefitinib was administered orally at a dose of 250 mg/day until disease progression, the appearance of unacceptable toxicity or patients' withdrawal from the treatment. The pretreatment variables analysed were: age, gender, clinical stage, ECOG performance status (PS), cell type, smoking history, number of prior chemotherapy regimens and CEA serum concentration. Histological analysis of tumours were based on WHO classification for cell types [10]. The clinical stage of these patients was determined based on the TNM classification of the Union Internationale Contre le Cancer (UICC) [11]. 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 magnetic resonance imaging (MRI). Serum CEA was measured by an enzyme immunoassay (SRL, Fukuoka, Japan) within six weeks before starting the gefitinib treatment. According to the manufacturer, the normal range of serum CEA level is below 5.0 ng/ml. The clinical responses to the drug were defined according to the response evaluation criteria of WHO for patients with measurable disease [12]. For patients whose tumour burden could not be quantified using these criteria, two physicians assessed each patient. Written informed consent was obtained from each patient before treatment start.

Statistical significance for the various clinicopathological factors among compared categories was evaluated using the χ^2 test, Fisher's exact probability test or the Mann–Whitney test. Overall survival was defined as the period from the starting date of the gefitinib treatment to the date of death. Patients alive at data cutoff were censored at the last date the patient was known to be alive, and the terminal event was death due to any cause. A survival analysis for each categorical variable regarding overall survival was estimated according to the Kaplan–Meier method. The statistical significance of the differences between the survival curves was evaluated by the log-rank test. A univariate analysis of several prognostic factors was carried out using the Cox proportional hazards model. In multivariate survival analysis, all variables investigated were further analysed in a stepwise manner. Statistical difference was considered to be significant if the P value was below 0.05.

3. Results

3.1. Clinical characteristics of patients treated by gefitinib

The clinical characteristics of the 105 patients are summarised in Table 1. Ninety-one percent of patients had stage IV diseases, 83.8% had adenocarcinoma and 90% had received one or more regimens of prior chemotherapy (mainly platina-based). The serum CEA level was positive (CEA $\geqslant$ 5 ng/ml) for 62.9% of the patients. A complete response (CR) and partial response (PR) were observed in 2 and 26 patients, respectively, and overall response rate was 27.8%. We compared the clinical characteristics of responders (CR + PR) with those with stable disease (SD) and progressive disease (PD) by the Mann–Whitney test (Table 2). Patients with no history of smoking and those with an elevated serum CEA level were more likely to be sensitive to gefitinib ($P = 0.009$). Thirty-five percent of the patients with elevated CEA levels experienced objective regressions compared to 16% of those with normal CEA levels. All responders with elevated CEA achieved a reduction in the serum CEA levels and 6 of 22 (27%) showed a reduction which reached normal levels.

3.2. Survival

The overall follow-up time ranged from 5.6 to 28.7 months with a median follow-up of 18.4 months. The one- and two-year overall survival rates were 44% and 23%, respectively, and the median survival time was

Table 1
Clinicopathological characteristics of the 105 patients treated by gefitinib

Category	*n*	%
Age		
Median (range)	61.9 (37–86)	
Gender		
Male	61	58.1
Female	44	41.9
Clinical stage		
IIIA	2	1.9
IIIB	7	6.7
IV	96	91.4
Performance status		
0	31	29.5
1	51	48.6
2	18	17.1
3–4	5	4.8
Histologic type		
Adenocarcinoma	88	83.8
Squamous	6	5.7
Large	3	2.9
Adenosquamous	3	2.9
Undefined	5	4.8
Smoking history		
None	62	59.0
Current + former	43	41.0
Serum CEA level		
<5 ng/ml	39	37.1
⩾5 ng/ml	66	62.9
No. of prior chemotherapy regimens		
0	11	10.5
1	38	36.2
2	26	24.8
3 or more	30	28.6
Response to gefitinib		
Complete response	2	1.9
Partial response	26	24.8
Stable disease	36	34.2
Progressive disease	36	34.3
Not evaluable	5	4.8

9.3 months. We analysed the effect of pretreatment serum CEA level on the survival of patients treated by gefitinib. Table 3 shows a comparison of the pretreatment clinicopathological characteristics between the patients with an elevated CEA level and normal CEA level. Although the adenocarcinoma patients tended to have a more elevated CEA level than other cell types, there was no significant difference between the two groups with respect to the analysed categories. The survival curve of the two levels of serum CEA showed that survival of patients with higher pretreatment CEA level to be significantly better (Fig. 1). A univariate analysis of several prognostic factors using Cox proportional hazards model indicated that younger age, presence of adenocarcinoma, good PS and elevated serum CEA levels to be positive prognostic factors for gefitinib treatment (Table 4). A multivariate analysis using a stepwise method also confirmed that a good PS and elevated serum CEA levels to be independent prognostic factors (Table 5).

Table 2
Comparison of pretreatment clinicopathological characteristics among patients with response, stable disease and progressive disease by gefitinib treatment

Category	CR + PR (*n* = 28)	SD (*n* = 36)	PD (*n* = 36)	*P* value
	n	*n*	*n*	
Age				
<65	17	22	16	0.17
⩾65	11	14	20	
Gender				
Male	13	19	24	0.10
Female	15	17	12	
Histologic type				
Adenocarcinoma	26	30	28	0.11
Non-adenocarcinoma	2	6	8	
Clinical stage				
III	1	2	4	0.23
IV	27	34	32	
Performance status				
⩽1	24	29	26	0.18
⩾2	4	7	10	
Smoking history				
None	18	14	11	0.0092
Current + former	10	22	25	
No. of prior regimens				
⩽1	14	11	21	0.39
⩾2	14	25	15	
Serum CEA level				
<5 ng/ml	6	12	19	0.009
⩾5 ng/ml	22	24	17	
Total (%)	28 (28%)	36 (36%)	36 (36%)	

4. Discussion

Gefitinib is a tyrosine kinase inhibitor of EGFR, which has the potential to reduce tumour volume in NSCLC patients. Two large phase II studies conducted in pretreated non-small lung cancer patients have demonstrated a response rate of 18% and 11% [3,4]. In the analysis of the former trial, Japanese patients observed higher response rate than non-Japanese patients (27.5% *vs.* 10.4%, odds ratio = 3.27; $P = 0.0023$). In a multivariate analysis employed at 10% significance level, a good PS, female, adenocarcinoma and a history of receiving prior immuno/hormonal treatment were all found to be independent predictable factors for response. Also a retrospective study demonstrated that patients with adenocarcinoma of the bronchioloalveolar subtype and no history of smoking were more likely to

Table 3
Comparison of pretreatment clinicopathological characteristics between patients with elevated serum CEA level and those without

Category	CEA < 5 ng/ml	CEA ⩾ 5 ng/ml	P value
	n	n	
Age (<65, ⩾65)	20, 19	37, 29	0.78
Gender (Male, female)	23, 16	38, 28	>0.99
Histologic type (Adeno, non-adeno)	29, 10	59, 7	0.080
Clinical stage (III, IV)	6, 33	3, 63	0.12
Performance status (⩽1, ⩾2)	33, 6	49, 17	0.32
Smoking history (None, current + former)	14, 25	29, 37	0.54
No. of prior regimens (⩽1, ⩾2)	18, 21	31, 35	>0.99
Total (%)	39 (37.1%)	66 (62.9%)	

Table 4
Analysis of various pretreatment prognostic factors influencing survival of patients treated with gefitinib (Cox proportional hazards model)

Variables	Hazard ratio	95% CI	P value
Age (<65 *vs.* ⩾65)	1.72	1.02–2.90	0.042
Gender (Male *vs.* female)	0.69	0.40–1.17	0.17
Histologic type (Adeno *vs.* non-adeno)	1.88	1.01–3.51	0.046
Clinical stage (III *vs.* IV)	0.78	0.33–1.83	0.57
Performance status (⩽1 *vs.* ⩾2)	5.41	3.07–9.62	<0.0001
Smoking history (None *vs.* current + former)	1.56	0.90–2.68	0.11
No. of prior regimens (⩽1 *vs.* ⩾2)	1.35	0.79–2.29	0.28
CEA (<5 *vs.* ⩾5 ng/ml)	0.53	0.32–0.90	0.018

Table 5
Multivariate analysis of various pretreatment prognostic factors influencing survival of patients treated with gefitinib

Variable	Category	Hazard ratio	P value
Performance status	(⩽1 *vs.* ⩾2)	6.10	<0.0001
CEA	(<5 *vs.* ⩾5 ng/ml)	0.44	0.0027

have an objective response to gefitinib treatment (odds ratio = 13.5 and 4.2) [5]. However, no report has so far investigated the relationship between the serum CEA concentration and responses to. In this study, a similar overall response rate (26.7% of all patients treated) as that reported in the former study of Japanese patients and association of smoking history to gefitinib sensitivity was also observed. We also demonstrate for the first time, that patients with a serum CEA concentration of over 5 ng/ml were more sensitive to gefitinib treatment than those with a concentration of below 5 ng/ml. Moreover, those with an elevated serum CEA level showed a significantly better prognosis for gefitinib treatment than those with no such increased levels based on both univariate and the multivariate analyses. These data were very surprising since an elevated serum CEA level is generally considered to be a negative prognostic factor for NSCLC [13].

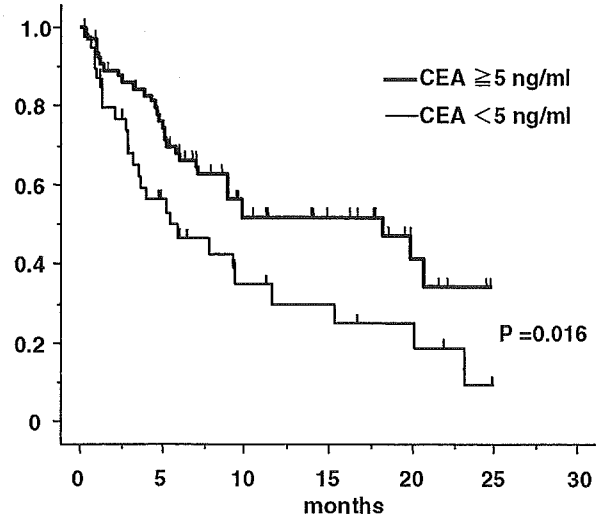

Fig. 1. The survival curves of gefitinib treated patients with elevated serum CEA (⩾5 ng/ml) and normal CEA levels (<5 ng/ml).

CEA was first described as a specific antigen that was present in both the fetal colon and colon adenocarcinoma [14]. It is a member of the immunoglobulin supergene family, which is a cell surface adhesion protein, and it is thought to play a role in cell-to-cell adhesion [15]. The overexpression of CEA has been found in many other types of carcinomas and is thought to play a role in tumourigenesis [16]. Screaton and colleagues have recently discovered that CEA has a dominant effect in blocking differentiation and it also cooperates with Myc and Bcl-2 in cellular transformation [17]. In addition, it can also inhibit cell death induced by a loss of anchorage to the extra cellular matrix (anoikis) [18]. Our data reported here suggests that NSCLC cells which produce an abundant amount of CEA protein tend to be more sensitive to the EGFR tyrosine kinase inhibitor gefitinib, and indicates that CEA proteins may play an important role in EGFR signaling in cancer cells. If this is true, then the serum CEA may be an important surrogate marker of the gefitinib treatment. In clinical practice, in the course of treating patients with gefitinib, we believe that a change in serum CEA levels seem to closely represent the burden of a CEA positive tumour.

Recently, mutations in the tyrosine kinase domain of EGFR have been found to be strongly associated with the sensitivity of NSCLC to gefitinib [6,7]. Mutations were detected within an ATP binding pocket of the catalytic domain, and the EGFR mutants also had an enhanced tyrosine kinase activity in response to the ligand. Moreover, current studies have shown that such down stream molecules as Akt and STAT3/5 play a crucial role in the anti-apoptotic pathways of the mutant EGFR in tumour cells [8,9]. Since CEA protein has been demonstrated to have an anti-apoptotic effect in cancer cells, it is possible that an anti-apoptotic signal of the mutant EGFR may elevate the expression level of CEA protein.

In conclusion, this study indicates that the serum CEA level may be a useful predictive factor for the efficacy of gefitinib treatment, while also being a prognostic factor for advanced NSCLC patients undergoing this treatment. Further basic research and clinical studies are needed to elucidate the relationship between sensitivity to gefitinib and the CEA protein.

Conflict of interest statement

None declared.

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

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Non-small cell lung cancer;
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Multimodality treatment;
Prognostic factor

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.

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 recieved some kind of 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).

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

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 bore 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 subcutanous 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), cervival 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
Nember 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
Aderenal 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 N0 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 multimodaity 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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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/m^2, GEM 800 mg/m^2 and VNR 20 mg/m^2 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-naive 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-naive 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 mitimycin (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/m^2, GEM 1000 mg/m^2 and VNR 25 mg/m^2 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 ≤ 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.

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.

Treatment Schedule

The patients received the following regimen: CDDP 40 mg/m^2, GEM 800 mg/m^2 and VNR 20 mg/m^2 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.

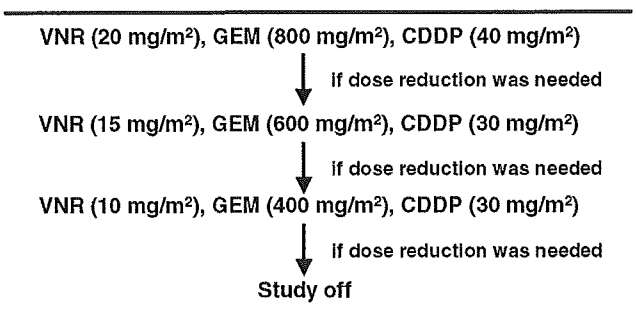

Figure 1. A schematic drawing of the dose modification in this study.

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 mg/m^2/week divided by the planned mg/m^2/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

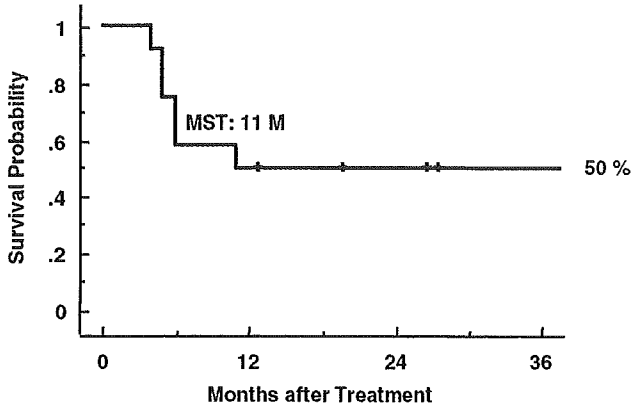

Figure 2. Overall survival in all patients.

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 mg/m^2/week divided by the planned mg/m^2/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-naive 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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CASE REPORT

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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