Table 2 Result of the univariate analyses (logrank test)

Prognostic factors	*n* (%)	*p*-value logrank test
Gender		
Female	28 (47)	0.22
Male	32 (53)	
Age		
75<	19 (32)	0.87
75≥	41 (68)	
T factor		
T2	17 (28)	0.26
T1	43 (72)	
Differentiation		
Other	31 (52)	0.43
Well	29 (48)	
VEGF		
Negative	42 (70)	0.09
Positive	18 (30)	
flt-1		
Negative	41 (68)	0.10
Positive	19 (32)	
KDR		
Negative	31 (52)	0.05
Positive	29 (48)	
VEGF and flt-1		
Other	54 (90)	0.05
Both positive	6 (10)	
VEGF and KDR		
Other	46 (77)	0.04
Both positive	14 (23)	
KDR and flt-1		
Other	48 (80)	0.002
Both positive	12 (20)	

In the present study, VEGF was expressed in the cytoplasm of tumor cells and was distributed uniformly throughout the tumor in some patients and focally within the tumor in other patients. We speculate that uniform VEGF expression may enhance the malignant potential of the tumor, whereas focal VEGF expression may be the result of ischemia or necrosis in tumor tissue. In contrast, VEGFRs were expressed uniformly throughout the tumor on cell membranes and in the cytoplasm near the cell membrane in all cases. Therefore, VEGFR expression appears to reflect the malignant potential of the tumor itself. The rates of VEGF and VEGFR expression did not differ from those in a previous report [22], which used the same antibodies of VEGF and VEGFRs used in the present study.

Table 3 Result of the multivariate analysis: final selected model by the backward Cox regression analysis with significance level of 0.01

Prognostic factors	β	*p*-value	Hazard ratio
KDR and flt-1-positive	1.57	0.002	4.79
VEGF and KDR-positive	0.82	0.095	2.26

Survival analysis in the present study showed that survival time tended to be shorter in patients with tumors expressing VEGF. However, this difference in survival did not reach the level of statistical significance, probably because only 60 patients with pathological stage I disease were analyzed. In contrast, the survival time of patients with KDR-positive tumors was significantly shorter than that of patients with KDR-negative tumors. Furthermore, KDR expression and VEGF expression were positively correlated, and the survival time of patients with tumors positive for both KDR and VEGF was shorter than that of other patients. Studies [23] of the VEGF/KDR complex in tumor vessels has shown that expression of VEGF/KDR complex activates microvessels and that the survival of patients with high VEGF/KDR complex microvessel density is significantly shorter than that of patients with low VEGF/KDR complex microvessel density. Our observations about VEGF and KDR co-expression have two meanings. One is that we observed only the VEGF/KDR complex. However, another possibility, suggested by other reports, autocrine stimulation via the VEGF–KDR pathway enhances the malignant potential of tumor cells, cannot be ruled out.

Although flt-1 has a high affinity for VEGF-A, its angiogenic effects are weak. Previous studies of the expression of flt-1 in cells, such as vascular endothelial cells, have shown that the effects of flt-1 on angiogenesis and prognosis are weaker than those of KDR. There is little information and no consensus about the correlation between flt-1 expression in tumor cells and prognosis [11]. In the present study, we found that flt-1 expression alone had no effect on survival and that flt-1 expression and VEGF expression were not correlated. However, the survival time of patients with flt-1-positive, VEGF-positive tumors was shorter than that of other patients. Recent studies have shown that flt-1 promotes the migration and invasion of cancer cell lines [24]. Although KDR expression and flt-1 expression were not correlated in the present study, simultaneous expression of both KDR and flt-1 was identified as an independent prognostic factor. This finding suggests that in tumors expressing both flt-1 and KDR, VEGF serves as an autocrine and paracrine growth factor that enhances the malignant potential of tumor cells. A challenge for future investigations will be to clarify the biological function of flt-1 in tumor cells and the interaction of flt-1 and KDR at the cellular level.

The prognosis of patients with tumors producing VEGF or expressing VEGFRs appears to be poor even in those with surgical stage I disease. Recently, therapies employing antibodies against VEGF or VEGFR or small molecules inhibiting KDR tyrosine kinase have been developed to target tumor angiogenesis [25,26]. Although, these agents are being developed mainly to treat advanced cancers, the results of the present study suggest that these angiogenesis inhibitors may also be used for preoperative induction therapy or postoperative adjuvant therapy.

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References

[1] Bikfalvi A. Significance of angiogenesis in tumour progression and metastasis. Eur J Cancer 1995;31A:1101–4.
[2] Toi M, Taniguchi T, Yamamoto Y, Kurisaki T, Suzuki H, Tominaga T. Clinical significance of the determination of angiogenic factors. Eur J Cancer 1996;32A:2513–9.
[3] Fontanini G, Vignati S, Bigini D, Mussi A, Lucchi M, Chine S, et al. Recurrence and death in non-small cell lung carcinomas: a prognostic model using pathological parameters, microvessel count, and gene protein products. Clin Cancer Res 1996;2:1067–75.
[4] Fujisawa T, Yamaguchi Y, Saitoh Y, Hiroshima K, Ohwada H. Blood and lymphatic vessel invasion as prognostic factors for patients with primary resected nonsmall cell carcinoma of the lung with intrapulmonary metastases. Cancer 1995;76:2464–70.
[5] Pezzella F, Di Bacco A, Andreola S, Nicholson AG, Pastorino U, Harris AL. Angiogenesis in primary lung cancer and lung secondaries. Eur J Cancer 1996;32A:2494–500.
[6] Angeletti CA, Lucchi M, Fontanini G, Mussi A, Chella A, Ribechini A, et al. Prognostic significance of tumoral angiogenesis in completely resected late stage lung carcinoma (stage IIIA-N2). Impact of adjuvant therapies in a subset of patients at high risk of recurrence. Cancer 1996;78:409–15.
[7] Giatromanolaki A, Koukourakis M, O'Byrne K, Fox S, Whitehouse R, Talbot DC, et al. Prognostic value of angiogenesis in operable non-small cell lung cancer. J Pathol 1996;179:80–8.
[8] Ellis LM, Fidler IJ. Angiogenesis and metastasis. Eur J Cancer 1996;32A:2451–60.
[9] Folkman J, Klagsbrun M. Angiogenic factors. Science 1987;235: 442–7.
[10] Ferrara N. Vascular endothelial growth factor. Eur J Cancer 1996;32A:2413–22.
[11] Mattern J, Koomagi R, Volm M. Association of vascular endothelial growth factor expression with intratumoral microvessel density and tumour cell proliferation in human epidermoid lung carcinoma. Br J Cancer 1996;73:931–4.
[12] Shibusa T, Shijubo N, Abe S. Tumor angiogenesis and vascular endothelial growth factor expression in stage I lung adenocarcinoma. Clin Cancer Res 1998;4:1483–7.
[13] Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22:2184–91.
[14] Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med 2003;9:669–76.
[15] Dziadziuszko R, Chyczewski L, Jassem E, Jassem J. Expression of vascular endothelial growth factor (VEGF) and its receptor FLK-1 in non-small cell lung cancer (NSCLC)—a preliminary report. Folia Histochem Cytobiol 2001;39(Suppl. 2):100–1.
[16] Zhukova LG, Zhukov NV, Lichinitser MR. Expression of flt-1 and Flk-1 receptors for vascular endothelial growth factor on tumor cells as a new prognostic criterion for locally advanced breast cancer. Bull Exp Biol Med 2003;135:478–81.
[17] Fontanini G, Vignati S, Lucchi M, Mussi A, Calcinai A, Boldrini L, et al. Neoangiogenesis and p53 protein in lung cancer: their prognostic role and their relation with vascular endothelial growth factor (VEGF) expression. Br J Cancer 1997;75:1295–301.
[18] Liu B, Earl HM, Baban D, Shoaibi M, Fabra A, Kerr DJ, et al. Melanoma cell lines express VEGF receptor KDR and respond to exogenously added VEGF. Biochem Biophys Res Commun 1995;217:721–7.
[19] Masood R, Cai J, Zheng T, Smith DL, Hinton DR, Gill PS. Vascular endothelial growth factor (VEGF) is an autocrine growth factor for VEGF receptor-positive human tumors. Blood 2001;98:1904–13.
[20] Strizzi L, Catalano A, Vianale G, Orecchia S, Casalini A, Tassi G, et al. Vascular endothelial growth factor is an autocrine growth factor in human malignant mesothelioma. J Pathol 2001;193:468–75.
[21] Volm M, Koomagi R, Mattern J. Prognostic value of vascular endothelial growth factor and its receptor flt-1 in squamous cell lung cancer. Int J Cancer 1997;74:64–8.
[22] Decaussin M, Sartelet H, Robert C, Moro D, Claraz C, Brambilla C, et al. Expression of vascular endothelial growth factor (VEGF) and its two receptors (VEGF-R1-Flt1 and VEGF-R2-Flk1/KDR) in non-small cell lung carcinomas (NSCLCs): correlation with angiogenesis and survival. J Pathol 1999;188: 369–77.
[23] Koukourakis MI, Giatromanolaki A, Thorpe PE, Brekken RA, Sivridis E, Kakolyris S, et al. Vascular endothelial growth factor/KDR activated microvessel density versus CD31 standard microvessel density in non-small cell lung cancer. Cancer Res 2000;60:3088–95.
[24] Wey JS, Fan F, Gray MJ, Bauer TW, McCarty MF, Somcio R, et al. Vascular endothelial growth factor receptor-1 promotes migration and invasion in pancreatic carcinoma cell lines. Cancer 2005;104:427–38.
[25] Kim ES, Herbst RS. Angiogenesis inhibitors in lung cancer. Curr Oncol Rep 2002;4:325–33.
[26] Kerbel RS. Clinical trials of antiangiogenic drugs: opportunities, problems, and assessment of initial results. J Clin Oncol 2001;19:45S–51S.

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Case Reports

Triplet Chemotherapy for Malignant Pericardial Mesothelioma: A Case Report

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Malignant pericardial mesothelioma (MPM) is a relatively rare neoplasm in Japan, and no standard treatment regimens have been established for this disease. A 47-year-old woman with MPM presenting with cardiac tamponade was treated using four cycles of chemotherapy consisting of cisplatin (CDDP) 40 mg/m^2, gemcitabine (GEM) 800 mg/m^2 and vinorelbine (VNR) 20 mg/m^2 on days 1 and 8 every 4 weeks after pericardial drainage alone. The diagnosis of MPM was confirmed by an immunohistochemical procedure using either positive or negative markers of malignant mesothelioma in addition to conventional cytological examinations using pericardial effusion. The patient experienced no severe non-hematological or hematological toxicities except for grade 3 neutropenia. The patient has returned to her usual activities and has remained well for 24 months after the last chemotherapy without any evidence of disease progression.

Key words: malignant pericardial mesothelioma – triplet chemotherapy – long-term survival

INTRODUCTION

Malignant mesothelioma is a relatively rare neoplasm in Japan. The number of deaths and the proportional mortality rate from this disease in 2001 were 722 and 0.26%, respectively (1). Overall, malignant mesothelioma of the pericardium accounted for ~6% of all mesotheliomas in a large study of registered autopsy cases in Japan (2). No satisfactory treatment is available, because malignant pericardial mesothelioma (MPM) tends to be diagnosed at a late presentation. As a result, the prognosis is poor. We previously reported that combination chemotherapy consisting of cisplatin (CDDP), gemcitabine (GEM) and vinorelbine (VNR) was effective for the treatment of malignant pleural mesothelioma (3). We herein report on a patient with MPM in whom triplet chemotherapy was found to result in long-term survival without any evidence of disease progression.

CASE REPORT

A 47-year-old woman, complaining of breathlessness on effort and of systemic edema, was admitted to our department. The patient was found to have a cardiac enlargement on chest X-ray and computed tomography (CT). The patient had no history of exposure to asbestos. A cytological examination of pericardial effusion revealed the findings typical of malignant mesothelioma. The malignant mesothelial cells proliferated mainly in a papillary pattern, as shown in Fig. 1A. In addition, immunohistochemical studies were performed using antibodies to CEA (prediluted, Nichirei), MOC-31 (1:50, DAKO), BerEP4 (1:100, DAKO), calretinin (1:50, Zymed), D2-40 (prediluted, Nichirei), HBME-1 (1:50, DAKO), thrombomodulin (1:50, DAKO), EMA (1:100, DAKO), CK 7 (1:100, DAKO) and CK 20 (1:25, DAKO) (4). Malignant cells stained in this case for four mesothelioma markers, namely calretinin (Fig. 1B), D2-40, HBME-1 and thrombomodulin, and other markers of EMA and CK 7. However, three adenocarcinomatous markers, namely CEA, MOC-31 (Fig. 1C) and BerEP4, and other markers of CK 20 were negative. The patient was diagnosed to have malignant mesothelioma originating from the pericardium because of the absence of effusion or any lesions in the bilateral pleural spaces. The clinical stage at diagnosis was T1N0M0, stage I according to the International Mesothelioma Interest Group (IMIG) staging system (5). After treating the cardiac tamponade by pericardial drainage, the patient received four cycles of chemotherapy consisting of CDDP 40 mg/m^2, GEM 800 mg/m^2 and VNR 20 mg/m^2

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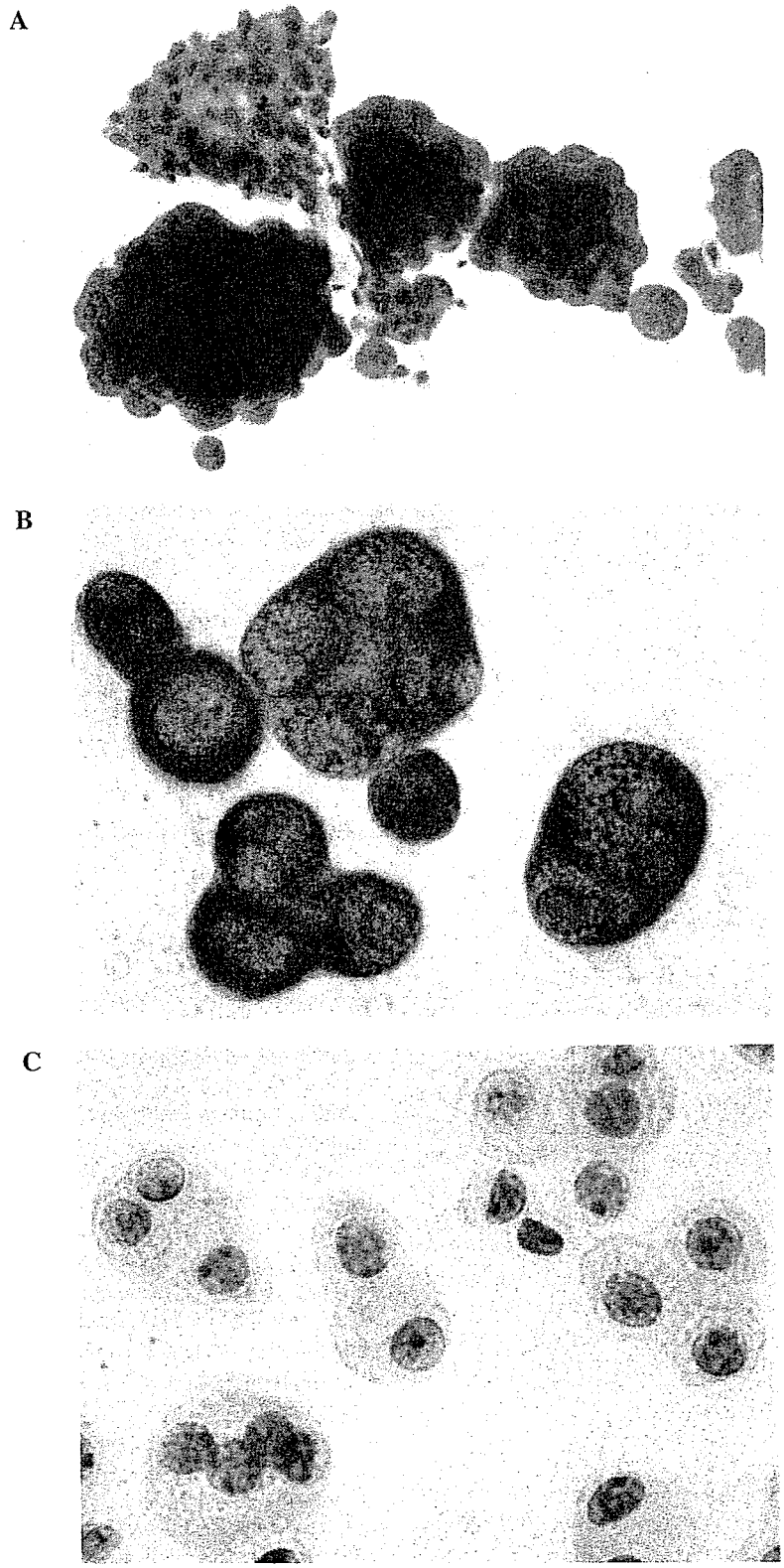

Figure 1. (A) A cytological examination of the pericardial effusion indicating the typical findings of malignant mesothelioma. (B) Immunohistochemistry using calretinin as a mesothelioma marker. Calretinin was expressed in malignant cells. (C) Immunohistochemistry using MOC-31 as an adenocarcinomatous marker. Malignant cells did not stain for MOC-31.

on days 1 and 8 every 4 weeks according to the treatment schedule described in a previous report (3). During the four cycles of chemotherapy, the patient did not experience any severe non-hematological or hematological toxicities, except grade 3 neutropenia. The patient has since returned to her usual activities and has remained well for 24 months after the last chemotherapy without any evidence of disease progression.

DISCUSSION

The onset of symptoms of MPM is usually insidious. The most common clinical manifestations of MPM are constrictive pericarditis, pericardial effusion, cardiac tamponade, and heart failure caused by myocardial infiltration. No satisfactory treatment has yet been established because MPM is commonly diagnosed at a very late stage. Fortunately, this case was diagnosed at an early stage while demonstrating cardiac tamponade due to pericardial effusion, and using a cytological and immunohistochemical examination of such effusion. Malignant cells stained in this case for four mesothelioma markers, namely calretinin, D2-40, HBME-1 and thrombomodulin, and not for three adenocarcinomatous markers, namely CEA, MOC-31 and BerEP4 (4). For distinguishing malignant mesothelioma from adenocarcinoma of the lung it is very useful to perform the immunohistochemical procedure using these markers in addition to conventional cytological examinations using the effusion.

Occupational asbestos exposure has been reported, and in a prospective study was found to be definite in 3 out of 15 cases (20%) and possible in 4 out of 15 cases (27%). In further support of this association, asbestos bodies have occasionally been identified within MPM. Treatment is usually purely palliative, and 50–60% of patients die within 6 months. The prognosis of MPM appears to be clearly worse than that of pleural or peritoneal mesotheliomas (6). Although no standard treatment has yet been established, surgery, radiotherapy, chemotherapy or the combination therapies are most frequently used in practice, and the average survival of the 140 cases reviewed by Kaul et al. was 10 months regardless of the treatment. The 2-year survival rate of the surgically treated cases, which we calculated from the literature in their review, was 14% (7). As a result, no optimal surgical therapy has yet been established regarding the extent of a pericardial resection. In addition, radiotherapy with a curative intent cannot be delivered to control the local disease, because the side effects of such radiation tend to cause primarily pericarditis or myocarditis. There is also no standard chemotherapy regimen. However, one report did describe the use of cyclical combination chemotherapy with doxorubicin, vincristine and cyclophosphamide as resulting in a 1-year event-free survival (8). We herein report, for the first time, that the triplet chemotherapy consisting of CDDP, GEM and VNR was effective for MPM. Objective response rates of 16–48% and median survivals of 9.6–11.2 months have been reported with the combination of CDDP and GEM in malignant mesothelioma (9–11). Recently, an objective response rate of 24% has been reported with the single agent of VNR in a single institution study (12). We have previously reported that triplet chemotherapy consisting of CDDP, GEM and VNR is feasible and effective for the treatment of malignant pleural mesothelioma. This regimen produced a 58% objective response rate in patients with malignant pleural mesothelioma (3). Therefore, this triplet chemotherapy seems to have potential anti-tumor activity against MPM. Recently, antifolate-based doublet chemotherapy consisting of pemetrexed and CDDP has demonstrated a high efficacy in the treatment of malignant pleural mesothelioma (13). The same regimen may be applied for the treatment of MPM. A phase I/II trial using this doublet regimen is now under way in Japan; therefore, the effectiveness and toxicity for Japanese patients is still uncertain.

In conclusion, CDDP–GEM–VNR combination chemotherapy may also be effective in patients with MPM.

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References

1. Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare of Japan. Vital Statistics of Japan 2001. Tokyo: Health and Welfare Statistics Association 2001.
2. Murai Y. Malignant mesothelioma in Japan: analysis of registered autopsy cases. *Arch Environ Health* 2001;56:84–8.
3. Maruyama R, Shoji F, Okamoto T. Miyamoto T, Miyake T, Nakamura T, et al. Triplet chemotherapy with cisplatin, gemcitabine and vinorelbine for malignant pleural mesothelioma. *Jpn J Clin Oncol* 2005;35:433–8.
4. Pier-Giacomo B. Immunohistochemistry. In: Carbone M, editor. Malignant Mesothelioma. Advances in Pathogenesis, Diagnosis, and Translational Therapies. New York: Springer Science+Business Media, Inc., 2005;490–507.
5. Rusch VW. A proposed new international TNM staging system for malignant pleural mesothelioma. From the International Mesothelioma Interest Group. *Chest* 1995;108:1122–8.
6. Chahinian AP. Clinical presentation and natural history of mesothelioma: pleural and pericardial. In: Carbone M, editor. Malignant Mesothelioma. Advances in Pathogenesis, Diagnosis, and Translational Therapies. New York: Springer Science+Business Media, Inc., 2005;380–90.
7. Kaul TK, Fields BL, Kahn DR. Primary malignant pericardial mesothelioma: a case report and review. *J Cardiovasc Surg (Torino)* 1994;35:261–7.
8. Nambiar CA, Tareif HE, Kishore KU, Ravindran J, Banerjee AK. Primary pericardial mesothelioma: one-year event-free survival. *Am Heart J* 1992;124:802–3.
9. Byrne MJ, Davidson JA, Musk AW, Dewar J, van Hazel G, Buck M, et al. Cisplatin and gemcitabine treatment for malignant mesothelioma: a phase II study. *J Clin Oncol* 1999;17:25–30.

10. Nowak AK, Byrne MJ, Williamson R, Ryan G, Segal A, Fielding D, et al. A multicentre phase II study of cisplatin and gemcitabine for malignant mesothelioma. *Br J Cancer* 2002;87:491–6.
11. van Haarst JM, Baas P, Manegold C, Schouwink JH, Burgers JA, de Bruin HG, et al. Multicentre phase II study of gemcitabine and cisplatin in malignant pleural mesothelioma. *Br J Cancer* 2002;86: 342–5.
12. Steele JP, Shamash J, Evans MT, Gower NH, Tischkowitz MD, Rudd RM. Phase II study of vinorelbine in patients with malignant pleural mesothelioma. *J Clin Oncol* 2000;18:3912–7.
13. Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *J Clin Oncol* 2003;21:2636–44.

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Prognostic value of the histological subtype in completely resected non-small cell lung cancer

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Abstract

Non-small cell lung cancer (NSCLC), which includes several different histological subtypes, is usually treated by the same strategy. However, the biological behavior of each cell type appears to be different. We retrospectively reviewed the clinical records of 1119 consecutive NSCLC patients who underwent a complete resection, in order to investigate whether a histological cell type is a powerful prognostic factor. The overall 5- and 10-year survivals of the patients with adenocarcinoma (AD), squamous cell carcinoma (SQ), large cell carcinoma (LA), and adenosquamous cell carcinoma (AS) were 54.2 and 40.2%, 51.6 and 30.3%, 40.9 and 18.7%, and 35.1 and 30.1%, respectively. The AD patients had a significantly better survival than the non-AD patients in Stage I ($P=0.0004$), whereas the SQ patients had a better survival than the non-SQ patients in Stage II ($P=0.018$). A multivariate survival analysis indicated the AD patients to have a significantly better survival than the SQ patients in Stage IA ($P=0.04$), while the SQ patients had a better survival than the AD patients in Stage II ($P=0.03$). These above observations suggest that the prognosis after complete resection is different between adenocarcinoma and squamous cell carcinoma in Stage IA and II.

Keywords: Non-small cell lung cancer; Adenocarcinoma; Squamous cell carcinoma; Prognosis

1. Introduction

Non-small cell lung cancer (NSCLC) comprises several different histological subtypes; including adenocarcinoma, squamous cell carcinoma, large cell carcinoma, adenosquamous carcinoma and others. They are usually considered to belong to the same category and are treated by the same strategy, because they have been reported to have similar results based on ordinary treatment courses. However, the biological aspects of different cell types seem to be different, and they actually show different clinical courses in some cases. Although the survival of patients with completely resected NSCLC is well known to be closely correlated to the pathological stage of the disease [1,2], the prognostic significance of different histological cell types in this setting is still controversial [3]. Some papers have demonstrated no significant survival advantages for any histological tumor type in pathological Stage I, while other groups have shown a survival advantage for patients with squamous cell carcinomas compared to adenocarcinomas [3]. In 1995, Ichinose and colleagues from our institution reported favorable outcomes of patients with squamous cell carcinomas with Stage II disease but not with Stage I [4]. In the present paper, we investigated whether the histological subtype is a powerful prognostic factor of Japanese patients with completely resected NSCLC at each pathological stage, in order to better understand the clinical behavior of each cell type and thereby better manage patients with NSCLC.

2. Patients and methods

From 1972 to 1999, 1235 patients with NSCLC underwent surgery as their initial treatment at our institution. Among them, we retrospectively reviewed the clinical records of 1119 patients who were pathologically confirmed to have a complete resection. The histological analysis of the tumor was based on the World Health Organization classification for cell types. The pathological stage of these patients was determined based on the TNM classification of the Union Internationale Contre le Cancer (UICC). Any patients who had been subjected to either pre-operative chemotherapy or radiotherapy were excluded. Generally, the patients were reexamined once every 3 months for 5 years, and thereafter at 6-month intervals after the operation. The evaluations included a physical examination and chest roentgenograms at each visit and computed tomography of the chest, magnetic resonance imaging of the brain and a bone scan. The overall follow-up time ranged from 1.6 to 120 months, with a median follow-up of 84.7 months.

The survival curves for each histological subtype were estimated according to the Kaplan–Meier method and then were compared by the log-rank test. The terminal event was death from any cause. A univariate survival analysis

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was carried out using the Cox proportional hazards model. In a multivariate survival analysis, the variables including age, gender and procedure were further analyzed in a stepwise manner. Statistical difference was considered to be significant if the *P*-value was below 0.05. All data were analyzed using Abacus Concepts, Survival Tools for StatView (Abacus Concepts, Inc., Berkeley, CA, USA).

3. Results

Six hundred and sixteen patients had adenocarcinoma (AD), 385 had squamous cell carcinoma (SQ), 55 had large cell carcinoma (LA), 37 had adeno-squamous cell carcinoma (AS), and 26 had other cell types. The patients consisted of 782 men and 337 women. The median age of the patients was 62.9 years, with a range from 24 to 90 years. A complete surgical resection consisted of 881 lobectomies, 75 bilobectomies, 144 pneumonectomies and 19 segmentectomies. The details of the clinicopathological characteristics for all patients are summarized in Table 1. Forty-four percent of the AD patients were female, where only 9.4% of the SQ patients were female. AD had a large number of Stage IA disease (32.1%), and a pneumonectomy was selected more frequently in SQ (23.6%) than for other tumors.

The overall 5- and 10-year survival rates of all patients were 52.2 and 35.1%, respectively. The 5- and 10-year survivals of the patients with AD, SQ, LA, and AS were 54.2 and 40.2%, 51.6 and 30.3%, 40.9 and 18.7%, and 35.1 and 30.1%, respectively. We divided the patients into each pathological stage and then investigated the possible prognostic factors at each stage (Table 2). Regarding the histological cell types, AD patients showed a significantly better survival than the non-AD patients in Stage I ($P=0.0004$), while the SQ patients showed a significantly better survival than the non-SQ patients in Stage II ($P=0.018$). No significant difference was shown in Stage III disease. The survival curves of the patients with each histological cell type were demonstrated for each stage in Fig. 1.

We next investigated the survival difference between AD patients and SQ patients, because the above results were mainly due to the difference of these major two cell types. In particular, Stage I patients were divided into two substages (Stage IA and IB), for which the survival curves are shown in Fig. 2A. The survival curves of patients with both cell types in Stage IB were almost the same. As a result, we focused further analyses on both Stage IA and II. A multivariate survival analysis showed that AD patients have a significantly better survival than SQ patients in Stage IA ($P=0.04$), while the opposite result was observed in Stage II ($P=0.03$) (Table 3). We then analyzed the time trends of survival for the Stage IA patients (Fig. 2B). The survival of the patients with Stage IA, AD who underwent surgery during the late period (from 1990 to 1999) was significantly better than for those who underwent surgery during the early period (from 1972 to 1989) whereas no improvement was shown in the SQ patients. Table 4 shows the tumor size of Stage IA adenocarcinoma to be significantly smaller in the late period than in the early period ($P=0.0006$), whereas no difference in age, gender or surgical procedures was observed.

Table 2
A univariate survival analysis using the Cox proportional hazard model for patients of each stage with completely resected adenocarcinoma and squamous cell carcinoma

Category	Favorable	Unfavorable	Relative risk	95% CI	*P*
Stage I					
Age	<65	≥65	2.39	1.84–3.12	<0.0001
Gender	Female	Male	1.96	1.46–2.62	<0.0001
Procedure	LO or SE	PN	1.51	0.91–2.50	0.11
Histology	AD	Non-AD	1.57	1.22–2.02	0.0004
Stage II					
Age	<65	≥65	1.41	0.99–2.02	0.056
Gender	Female	Male	1.21	0.76–1.94	0.43
Procedure	LO or SE	PN	1.02	0.65–1.60	0.93
Histology	SQ	Non-SQ	1.54	1.08–2.21	0.018
Stage III					
Age	<65	≥65	1.32	1.03–1.69	0.028
Gender	Female	Male	1.04	0.79–1.37	0.78
Procedure	LO or SE	PN	1.07	0.80–1.43	0.66
Histology	SQ	Non-SQ	1.19	0.92–1.55	0.18

AD, adenocarcinoma; SQ, squamous cell carcinoma; LO, lobectomy; SE, segmentectomy; PN, pneumonectomy.

4. Discussion

To evaluate and classify the NSCLC patients according to the prognosis is an important procedure for planning optimal treatments protocols. Although a variety of factors

Table 1
Clinicopathological characteristics of the 1119 patients with non-small cell lung cancer who underwent a complete resection

	Cell type	AD	SQ	LA	AS	Others
Age	Average (±S.D.)	62.0 (±10.6)	64.6 (±8.8)	61.7 (±9.8)	64.7 (±8.1)	64.7 (±14.1)
Gender	Male	343 (55.7%)	349 (90.6%)	45 (81.8%)	29 (78.4%)	16 (61.5%)
	Female	273 (44.3%)	36 (9.4%)	10 (18.2%)	8 (21.6%)	10 (38.5%)
p-Stage	IA	198 (32.1%)	57 (14.8%)	6 (10.9%)	3 (8.1%)	12 (46.2%)
	IB	173 (28.1%)	111 (28.8%)	19 (34.5%)	14 (37.8%)	4 (15.4%)
	IIA	25 (4.1%)	12 (3.1%)	1 (1.8%)	0 (0%)	1 (3.8%)
	IIB	60 (9.7%)	84 (21.8%)	11 (20%)	6 (16.2%)	4 (15.4%)
	IIIA	133 (21.6%)	95 (24.7%)	10 (18.2%)	13 (35.1%)	2 (7.7%)
	IIIB	27 (4.4%)	26 (6.8%)	8 (14.5%)	1 (2.7%)	3 (11.5%)
Procedure	Segmentectomy	13 (2.1%)	5 (1.3%)	0 (0%)	1 (2.7%)	0 (0%)
	Lobectomy	537 (87.2%)	253 (65.7%)	45 (81.8%)	26 (70.3%)	20 (76.9%)
	Bi-lobectomy	32 (5.2%)	36 (9.4%)	3 (5.5%)	4 (10.8%)	0 (0%)
	Pneumonectomy	34 (5.5%)	91 (23.6%)	7 (12.7%)	6 (16.2%)	6 (23.1%)

AD, adenocarcinoma; SQ, squamous cell carcinoma; LA, large cell carcinoma; AS, adeno-squamous cell carcinoma; p-Stage, pathological stage.

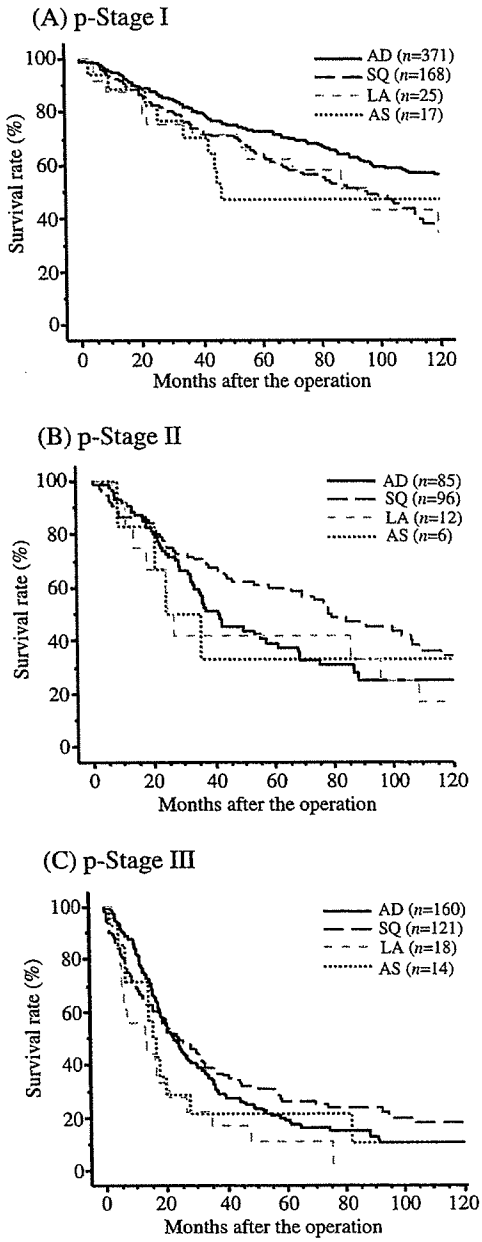

Fig. 1. Survival curves of the patients who underwent a complete resection for Stage I (A), Stage II (B) and Stage III (C) non-small lung cancer according to the histological subtypes.

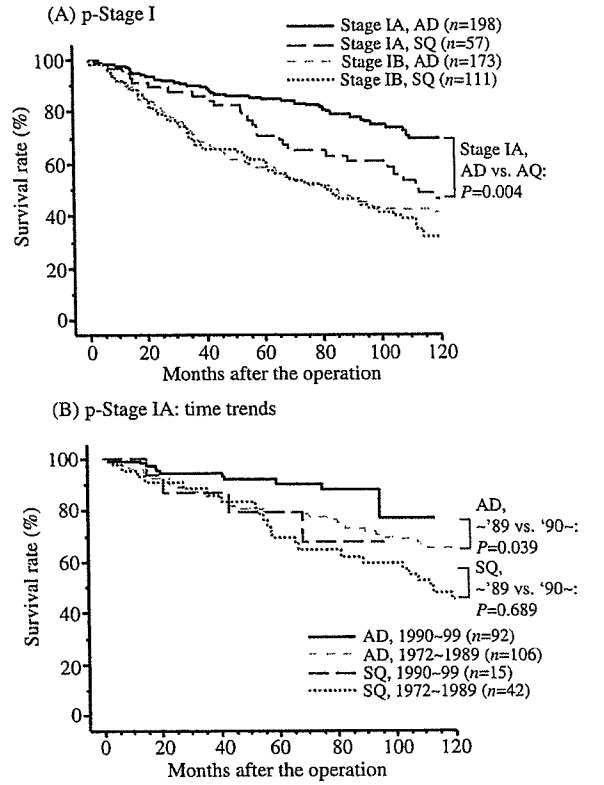

Fig. 2. (A) Survival curves of the patients with adenocarcinoma and squamous cell carcinoma in Stage IA and IB, who underwent a complete resection. (B) Survival curves of the patients who underwent a complete resection for Stage IA adenocarcinoma according to different periods.

Table 3
A multivariate survival analysis using the Cox proportional hazard model for Stage IA and II patients with completely resected adenocarcinoma and squamous cell carcinoma

Category	Favorable	Unfavorable	Relative risk	P
Stage IA				
Age	<65	≥65	3.83	<0.0001
Histological type	AD	SQ	1.65	0.04
Stage II				
Histological type	SQ	AD	1.52	0.03

AD, adenocarcinoma; SQ, squamous cell carcinoma.

have been reported to influence the patients survival in such homogenous entities as NSCLC, the TNM staging classification has consistently been reported to be closely correlated to the survival in patients who underwent a surgical resection [1,2]. A number of studies have also investigated the prognostic significance of different histological cell types in surgically resected NSCLC. However, the findings still remain controversial [3,5]. Since the distribution of patients in different stages greatly affects the overall survivals of each cell type, we compared them after stratification according to each pathological stage.

Table 4
Clinical characteristics of the 198 patients with Stage IA adenocarcinoma who underwent a complete resection during each period (time trends)

		1972~89 n=92	1990~99 n=106	P
Age	Average (±S.D.)	62.4 (±9.9)	60.3 (±11.6)	0.173
Gender	Male	39 (42.4%)	53 (50.0%)	0.354
	Female	53 (57.6%)	53 (50.0%)	
Procedure	Segmentectomy	4 (4.3%)	3 (2.8%)	0.8486
	Lobectomy	88 (95.7%)	103 (97.2%)	
Tumor size	Average (±S.D.)	2.15 (±0.55)	1.86 (±0.59)	0.0006

Regarding Stage I disease, past studies from Western countries showed that squamous cell carcinoma had a better prognosis than other cell types [3,6], whereas recent studies have shown no difference among the different cell types in this stage [4,7]. More recent studies have reported a survival advantage of adenocarcinoma patients in Stage I [2,8]. The present study also showed the patients with Stage I adenocarcinoma to have a better survival, and that the improved survival of Stage IA adenocarcinoma in the last decade affected the prognostic advantage in this early Stage (Fig. 2B). In comparisons between the patients with adenocarcinoma and squamous cell carcinoma, adenocarcinoma of Stage IA had a significantly better survival than squamous cell carcinoma of the same stage. In the 1990s, the incidence of adenocarcinoma was reported to be increasing while that of squamous cell carcinoma was decreasing in both Western and Asian countries [9]. Yoshino and colleagues demonstrated that the increasing population of female patients with adenocarcinoma was an important factor for the improved survival of surgically resected patients [10]. The recent spread of the computed tomography (CT) for screening has now made it possible to detect early-stage lung cancers, which cannot be detected by conventional chest X-rays [11]. In this study, a significant difference between the early and late periods was only shown in the tumor size (Table 4), thus suggesting that the improved technology in detecting small carcinoma at an earlier stage might have affected the improved survival of Stage IA adenocarcinoma. Bronchioloalveolar carcinoma was included with adenocarcinoma and an increased number of such non-invasive tumors may possibly influence the improvement of survival.

In Stage II diseases, many studies have shown no significant association between the survival and cell type. However, some studies have shown a survival advantage in squamous cell type [4,12,13], and the present study was consistent with them. Martini and colleagues mentioned that local recurrence was more frequent in patients with squamous carcinoma than adenocarcinoma (34 vs. 13%) whereas distant metastases were more common in adenocarcinoma (87 vs. 64%) [13]. It is possible that the widespread tendency of adenocarcinoma might result in an unsuccessful disease control even after a surgical resection in this stage.

Stage III disease also did not show any significant association between the survival and cell type in many past reports [14], although a better prognosis of squamous cell type has been mentioned in a few studies [4,15]. The current study showed no significant difference in the survival among the four cell types; however, the survival curves of adenocarcinoma and squamous carcinoma crossed in the early postoperative period. Though the meaning of this crossing is unclear, it may also be due to the biological difference of the two cell types; namely, squamous carcinoma is more likely to rapidly grow at a local site, while adenocarcinoma is likely to spread to a distant site. In the present study, local recurrence was more frequently found in Stage III patients with squamous carcinoma than in those with adenocarcinoma (36 vs. 19%) for the first recurrent site, whereas distant metastases were more common in adenocarcinoma (81 vs. 64%) ($P=0.04$). It is possible that the early deaths in squamous carcinoma patients were thus due to a failure to control local disease, while the late deaths in adenocarcinoma patients represented a failure to control distant metastasis.

In conclusion, our observations suggest that, in Stage IA, patients with adenocarcinoma may have a better prognosis after complete resection than squamous cell carcinoma, whereas patients with squamous cell carcinoma may have a better prognosis than adenocarcinoma in Stage II. Different treatment strategies, which best suit each histological subtype in each stage, should thus be considered for resectable NSCLC in order to increase the overall survival of resectable NSCLC.

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References

[1] Buccheri G, Ferrigno D. Prognostic value of stage grouping and TNM descriptors in lung cancer. Chest 2000;117:1247–1255.
[2] Naruke T, Tsuchiya R, Kondo H, Asamura H. Prognosis and survival after resection for bronchogenic carcinoma based on the 1997 TNM-staging classification: the Japanese experience. Ann Thorac Surg 2001;71:1759–1764.
[3] Nesbitt JC, Putnam JB, Jr., Walsh GL, Roth JA, Mountain CF. Survival in early-stage non-small cell lung cancer. Ann Thorac Surg 1995;60:466–472.
[4] Ichinose Y, Yano T, Asoh H, Yokoyama H, Yoshino I, Katsuda Y. Prognostic factors obtained by a pathologic examination in completely resected non-small-cell lung cancer. An analysis in each pathologic stage. J Thorac Cardiovasc Surg 1995;110:601–605.
[5] Charloux A, Hedelin G, Dietemann A, Ifoundza T, Roeslin N, Pauli G, Quoix E. Prognostic value of histology in patients with non-small cell lung cancer. Lung Cancer 1997;17:123–134.
[6] Gail MH, Eagan RT, Feld R, Ginsberg R, Goodell B, Hill L, Holmes EC, Lukeman JM, Mountain CF, Oldham RK, et al. Prognostic factors in patients with resected Stage I non-small cell lung cancer. A report from the Lung Cancer Study Group. Cancer 1984;54:1802–1813.
[7] Padilla J, Calvo V, Penalver JC, Sales G, Morcillo A. Surgical results and prognostic factors in early non-small cell lung cancer. Ann Thorac Surg 1997;63:324–326.
[8] Suzuki K, Nagai K, Yoshida J, Moriyama E, Nishimura M, Takahashi K, Nishiwaki Y. Prognostic factors in clinical Stage I non-small cell lung cancer. Ann Thorac Surg 1999;67:927–932.
[9] Charloux A, Quoix E, Wolkove N, Small D, Pauli G, Kreisman H. The increasing incidence of lung adenocarcinoma: reality or artefact? A review of the epidemiology of lung adenocarcinoma. Int J Epidemiol 1997;26:14–23.
[10] Yoshino I, Baba H, Fukuyama S, Kameyama T, Shikada Y, Tomiyasu M, Suemitsu R. A time trend of profile and surgical results in 1123 patients with non-small cell lung cancer. Surgery 2002;131:S242–248.
[11] Altorki N, Kent M, Pasmantier M. Detection of early-stage lung cancer: computed tomographic scan or chest radiograph? J Thorac Cardiovasc Surg 2001;121:1053–1057.
[12] Khan OA, Fitzgerald JJ, Field ML, Soomro I, Beggs FD, Morgan WE, Duffy JP. Histological determinants of survival in completely resected T1-2N1M0 nonsmall cell cancer of the lung. Ann Thorac Surg 2004;77:1173–1178.
[13] Martini N, Burt ME, Bains MS, McCormack PM, Rusch VW, Ginsberg RJ. Survival after resection of Stage II non-small cell lung cancer. Ann Thorac Surg 1992;54:460–465; discussion 466.
[14] Vansteenkiste JF, De Leyn PR, Deneffe GJ, Stalpaert G, Nackaerts KL,

Lerut TE, Demedts MG. Survival and prognostic factors in resected N2 non-small cell lung cancer: a study of 140 cases. Leuven Lung Cancer Group. Ann Thorac Surg 1997;63:1441–1450.

[15] Inoue M, Sawabata N, Takeda S, Ohta M, Ohno Y, Maeda H. Results of surgical intervention for p-Stage IIIA (N2) non-small cell lung cancer: acceptable prognosis predicted by complete resection in patients with single N2 disease with primary tumor in the upper lobe. J Thorac CardioVasc Surg 2004;127:1100–1106.

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A Prospective Trial of Oral Betamethason and Oral Lorazepam in the Management of Delayed Nausea and Vomiting Induced by Cisplatin-Based Chemotherapy

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ABSTRACT

Purpose: The optimal treatment modality for delayed emesis occurring later than 24 hours after the administration of cisplatin-based chemotherapy has not yet been established. *Patients and Methods*: Twenty patients received 5-hydroxytryptamine 3 receptor antagonist intravenously for the treatment of acute emesis just before cisplatin infusion in the first cycle of treatment, and the thereafter they received oral administration of betamethason (2 mg × 3/day) plus oral lorazepam (0.5 mg × 3/day) for 5 days in trial I. In trial II, 14 patients who received the other anti-emetic regimen (methylprednisolone plus metoclopramide) for delayed emesis in the first cycle of chemotherapy were treated by this regimen for the second cycle of treatment. A complete response (CR) was defined as no emetic episodes and a partial response (PR) as no vomiting episodes but some nausea. The effects of anti-emetic treatments were evaluated for 5 days from the next day after cisplatin administration. *Results*: The mean control rate (percentage of CR+PR) and CR rate for delayed emesis for the 5-day period were 97% and 84%, respectively in trial I. The mean control rate in patients undergoing the other anti-emetic regimen in the first cycle of chemotherapy was 60% compared to 96% in the same patients undergoing this regimen in the second cycle of the same chemotherapy in trial II. *Conclusions*: Oral betamethason plus lorazepam demonstrated a high control rate for delayed nausea and vomiting induced by cisplatin-based chemotherapy. *Ryukyu Med. J., 25(1,2) 17~22, 2006*

Key words: Betamethason, Chemotherapy, Cisplatin, Delayed emesis, Lorazepam, Lung Cancer

INTRODUCTION

Chemotherapy-induced emesis is one of the troublesome adverse events that impair not only the quality of life in cancer patients but also reduces their desire to receive further chemotherapy. Cisplatin, which is one of the most effective anti-cancer drugs used in the treatment of various neoplasms[1], is well known to frequently induce nausea and vomiting[2,3]. Thanks to the development of 5-hydroxytryptamine 3 (5HT3)-receptor antagonist, the occurrence of acute emesis has decreased dramatically[4-8]. However, the optimal treatment modality for delayed emesis which occurs later than 24 hours after cisplatin administration has yet to be established[9]. Adrenal cortical hormone alone or a combination of adrenal cortical hormone and metoclopramide is generally used to control emesis, but the effectiveness of these agents remains both insufficient and controversial[10-18]. Lorazepam, which is a widely used anti-anxiety drug, has been reported to prevent the acute emesis induced by

Table 1 The Patient Characteristics

	Trial I (n=20)	Trial II (n=14)
Sex		
Male	17	12
Female	3	2
Age (years)		
Mean (range)	57 (46-77)	57 (46-73)
Performance status		
0	18	13
1	2	1
Stage		
IIIA	3	1
IIIB	5	1
IV	12	12
Histology		
Adenocarcinoma	18	13
Squamous cell carcinoma	1	0
Small cell carcinoma	1	1
Chemotherapy (with concurrent radiotherapy)		
Cisplatin+UFT	10 (9)	5(5)
Cisplatin+docetaxel	9 (2)	8(2)
Cisplatin+etoposide	1 (0)	1(0)

chemotherapy[19,20]. We therefore conducted a prospective trial to determine whether or not oral betamethason plus lorazepam effectively prevents the delayed nausea and vomiting frequently induced by cisplatin-based chemotherapy.

PATIENTS and METHODS

The eligible lung cancer patients for this study were those who received cisplatin (80 mg/m^2)-based chemotherapy with/without radiotherapy, had an Eastern Cooperative Oncology Group performance status of 0, 1, or 2 and experienced neither nausea nor vomiting before starting chemotherapy. All patients gave their written informed consent before treatment. The protocol was approved by the National Kyushu Cancer Center institutional review board.

The present prospective trial of an anti-emetic regimen for delayed emesis consisted of two trials. Trial I was administered for patients who received chemotherapy for the first time. Trial II was designed for those patients who had received one cycle of chemotherapy and then underwent the experimental anti-emetic regimen in the second cycle of the same chemotherapy.

All patients in both trials received anti-emetic therapy with 5HT3 receptor antagonist intravenously to prevent acute emesis just before cisplatin infusion. From the day after the intravenous administration of cisplatin was started, betamethason (2 mg × 3/day) plus lorazepam (0.5 mg × 3/day) was given orally for 5 days (Fig. 1). In trial II, the patients received methylprednisolone sodium succinate (125 mg/day) plus metoclopramide (10 mg/day) intravenously for 5 days starting from the day after the intravenous infusion of cisplatin was given in the first cycle of chemotherapy. In the second cycle of the same chemotherapy regimen, these patients were treated with oral administration of betamethason plus lorazepam.

A complete response (CR) and partial response (PR) were defined as when patients had no emetic episodes, and no vomiting episodes but some nausea, respectively. The control rate was defined as the percentage of CR plus PR. The effects of anti-emetic treatments on delayed emesis were evaluated for 5 days beginning from the day after the cisplatin administration was given. In addition, the anti-emetic effect of 5HT3 alone on the acute phase of emesis was also evaluated in trial I.

All patients were hospitalized for their treatments. The number of episodes of vomiting and presence of nausea were monitored and recorded

Trial I

			day 1	2	3	4	5	6
5-HT3 receptor antagonist	1	ampule, i.v.	○					
Betamethasone	2.0	mg × 3, p.o.		○	○	○	○	○
Lorazepam	0.5	mg × 3, p.o.		○	○	○	○	○

Trial II

First course

			day 1	2	3	4	5	6
5-HT3 receptor antagonist	1	ampule, i.v.	○					
Methylprednisolone	125	mg, i.v.		○	○	○	○	○
Metoclopramide	10	mg, i.v.		○	○	○	○	○

Second course

			day 1	2	3	4	5	6
5-HT3 receptor antagonist	1	ampule, i.v.	○					
Betamethasone	2.0	mg × 3, p.o.		○	○	○	○	○
Lorazepam	0.5	mg × 3, p.o.		○	○	○	○	○

5-HT3: 5-hydroxytryptamine3

Fig. 1 Treatment Schema.

for each patient. The other adverse effects of the treatment were also directly monitored and recorded.

A statistical analysis was performed using Fisher's exact probability test to compare the control rate between the two groups. The results were considered significant when p values were less than 0.05.

RESULTS

From September 1999 to January 2000, 20 and 14 patients were entered into trials I and II, respectively. The patient characteristics are shown in Table 1.

The control rate of this anti-emetic treatment from days 1 to 6 in trial I is shown in Fig. 2. The CR rate of acute emesis in the patients treated with 5HT3-receptor antagonist on day 1 was 35%. On the other hand, the CR rates for delayed emesis from days 2 through 6 were 75% or more. An especially notable finding was that the delayed vomiting was completely controlled from days 3 through 6. Fifteen (75%) patients achieved a CR for the entire duration from day 2 through day 6.

The mean CR rates and PR rates from days 2 through 6 according to the cancer treatment modalities are shown in Figure 3. The mean CR rates were 89% in the chemotherapy group and 80 % in the concurrent chemoradiotherapy group. There were no significant differences in the control rates

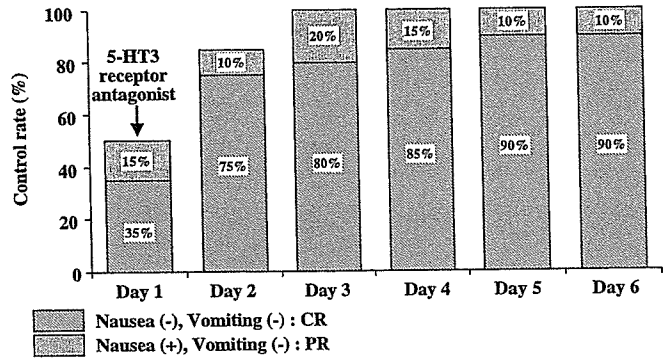

Fig. 2 The control rates of nausea and vomiting from days 1 to 6 in trial I. Twenty patients were entered into trial I.

between the two groups for nausea, and vomiting. The mean control rate for delayed emesis (CR+PR) was 97% for all patients. In addition, appetite loss, which is one of the most common side effects of anti-cancer drug therapy, was not observed in 90% of all the patients.

As shown in Fig. 4, the mean control rates of delayed emesis (CR+PR) according to the type of anti-emetic treatment in trial II was 96% for the treatment with betamethason plus lorazepam and 60% for the treatment with methylprednisolone plus metoclopramide ($P<0.001$). All patients reported the treatment with betamethason plus lorazepam in the second cycles of chemotherapy to be much better for the prevention of delayed nausea and vomiting than the treatment with methylprednisolone plus metoclopramide in the first cycle of chemotherapy.

Some mild toxicity was observed during the treatment. Hiccups occurred in 6 (30%), sleepiness in 2 (10%) and thirst in 1 (5%). However, all of these adverse events were manageable.

DISCUSSION

Cisplatin is one of the most effective anti-cancer drugs used in the treatment of various neoplasms[1]. Nausea and vomiting induced by cisplatin remains, however, a troublesome complication. The frequency of emesis in patients receiving cisplatin consisting of more than 50 mg/m^2 has been reported to be 90%, while in those receiving less than 50 mg/m^2 it has been reported to range from 60-90%[2,3].

The most common treatments for acute or delayed nausea and vomiting induced by cisplatin

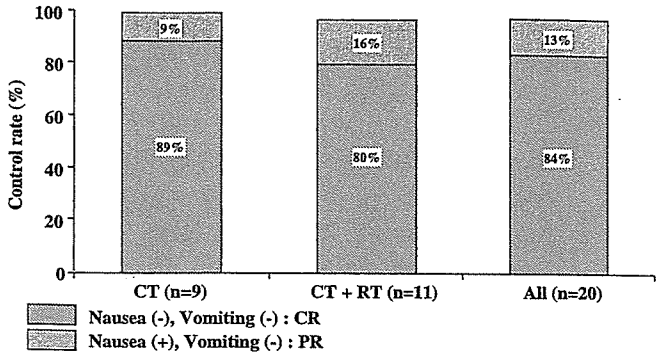

Fig. 3 The mean control rates of delayed nausea and vomiting from days 2 to 6 according to the treatment regimen used in trial I. CT: chemotherapy, RT: radiotherapy.

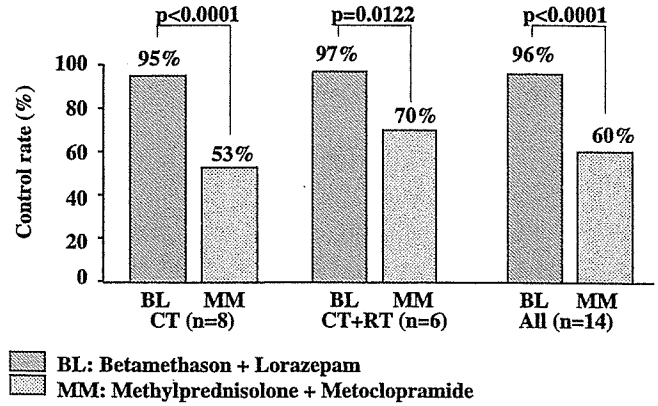

Fig. 4 The effects of betamethason and lorazepam (BL) vs. methylprednisolone and metoclopramide (MM) on cisplatin induced delayed nausea and vomiting in trial II. CT: chemotherapy, RT: radiotherapy.

are generally reported to be such drugs as adrenal cortical hormone, metoclopramide and serotonin antagonist[4-8,10-16]. Especially, the development of 5HT3-receptor antagonist has greatly helped to reduce the incidence of acute nausea and vomiting which occurs within 24 hours after the administration of anti-cancer drugs[4-7]. On the other hand, no effective treatment for delayed nausea and vomiting, occurring more than 24 hours after anti-cancer drug administration has yet been developed[9]. Either adrenal cortical hormone alone or a combination of adrenal cortical hormone and metoclopramide is generally used in order to control delayed nausea and vomiting, but the effectiveness of these agents is still not satisfactory. The control rate of delayed emesis has been reported to range from 40 to 70%[10-18]. In 1999, the American Society of Clinical Oncology (ASCO) proposed a clinical guideline for the management of delayed nausea and vomiting induced by cisplatin-based chemotherapy[19]. ASCO guidelines recommend corticosteroid plus metoclopramide (or plus a 5-HT3 antagonist) for the prevention of delayed emesis in all patients receiving cisplatin. However, the control rate of delayed emesis by using the above agents has been reported to range from 50 to 70%[15,17]. In fact, the mean control rate of delayed emesis by the combined usage of methylprednisolone and metoclopramide was also 60 % in the present study. On the other hand, in patients who received oral administration of betamethason plus lorazepam, the mean control rate of delayed emesis was 95% or more. In addition, 15 (75%) of all 20 patients in trial I experienced no delayed emesis at all from days 2 through 6.

Several trials have shown that benzodiazepins including an intravenous injection of lorazepam has an efficacy for acute emesis induced by cisplatin[20-22]. Therefore, these agents are listed as useful adjunctive agents in ASCO guidelines for the management of acute emesis[19]. In the present study, oral lorazepam with betamethason was used for the purpose of treatment for cisplatin-induced delayed emesis and an effect of these combination on the delayed emesis was observed. In addition, lorazepam may have a preventive effect on anticipatory emesis of patients who had poor control of emesis with prior chemotherapy[19], as shown in Trial II.

A result of recent randomized trials comparing neurokin-1 receptor antagonist plus standard antiemetics with standard antiemetics alone has been reported. The control rate of delayed emesis by the new combination ranged from 50% to 70% while the standard antiemetics had the control rate of approximately 50%[23-28]. These observations indicate that the combination of lorazepam plus betamethason in the present study may be worthy of further investigation.

The side effects of these oral drugs were mild and manageable. All patients (14 patients) in trial II who received the two different treatments (methylprednisolone plus metoclopramide vs oral betamethason plus lorazepam) reported the latter treatment would be better than the former, based on self evaluations. Regarding cost, the latter costs US$ 2.2 per day, while the former costs US$ 13.0.

Oral betamethason plus oral lorazepam demonstrated a good control of the delayed nausea and vomiting induced by cisplatin-based chemotherapy.

We are now planning a phase III trial study comparing this antiemetic regimen with a practice regimen in ASCO guidelines.

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REFERENCES

1) Loehrer P.J. and Einhorn L.H. Drugs five years later. Cisplatin. Ann Intern Med 100: 704-713, 1984.
2) Kris M.G., Gralla R.J., Clark R.A., Tyson L.B., O'Connell J.P., Wertheim M.S. and Kelsen D.P. Incidence, course, and severity of delayed nausea and vomiting following the administration of high-dose cisplatin. J Clin Oncol 3: 1379-1384, 1985.
3) Tavorath R. and Hesketh P.J. Drug treatment of chemotherapy-induced delayed emesis. Drugs 52: 639-648, 1996.
4) Heron J.F., Goedhals L., Jordaan J.P., Cunningham J. and Cedar E. Oral granisetron alone and in combination with dexamethasone: a double-blind randomized comparison against high-dose metoclopramide plus dexamethasone in prevention of cisplatin-induced emesis. The Granisetron Study Group. Ann Oncol 5: 579-574, 1994.
5) Chevallier B. Efficacy and safety of granisetron compared with high-dose metoclopramide plus dexamethasone in patients receiving high-dose cisplatin in a single-blind study. The Granisetron Study Group. Eur J Cancer 26 Suppl 1: S33-36, 1990.
6) Roila F., Tonato M., Cognetti F., Cortesi E., Favalli G., Marangolo M., Amadori D., Bella M.A., Gramazio V., Donati D. and et al. Prevention of cisplatin-induced emesis: a double-blind multicenter randomized crossover study comparing ondansetron and ondansetron plus dexamethasone. J Clin Oncol 9: 675-678, 1991.
7) Hesketh P.J., Harvey W.H., Harker W.G., Beck T.M., Ryan T., Bricker L.J., Kish J.A., Murphy W.K., Hainsworth J.D. and Haley B. A randomized, double-blind comparison of intravenous ondansetron alone and in combination with intravenous dexamethasone in the prevention of high-dose cisplatin-induced emesis. J Clin Oncol 12: 596-600, 1994.
8) Chevallier B., Marty M. and Paillarse J.M. Methylprednisolone enhances the efficacy of ondansetron in acute and delayed cisplatin-induced emesis over at least three cycles. Ondansetron Study Group. Br J Cancer 70: 1171-1175, 1994.
9) Prevention of cisplatin-induced delayed emesis: still unsatisfactory. Italian Group for Antiemetic Research. Support Care Cancer 8: 229-232, 2000.
10) Gebbia V., Testa A., Valenza R., Cannata G., Tirrito M.L. and Gebbia N. Oral granisetron with or without methylprednisolone versus metoclopramide plus methylprednisolone in the management of delayed nausea and vomiting induced by cisplatin-based chemotherapy. A prospective randomized trial. Cancer 76: 1821-1828, 1995.
11) Lebeau B., Depierre A., Giovannini M., Riviere A., Kaluzinski L., Votan B., Hedouin M. and d'Allens H. The efficacy of a combination of ondansetron, methylprednisolone and metopimazine in patients previously uncontrolled with a dual antiemetic treatment in cisplatin-based chemotherapy. The French Ondansetron Study Group. Ann Oncol 8: 887-892, 1997.
12) Handberg J., Wessel V., Larsen L., Herrstedt J. and Hansen H.H. Randomized, double-blind comparison of granisetron versus granisetron plus prednisolone as antiemetic prophylaxis during multiple-day cisplatin-based chemotherapy. Support Care Cancer 6: 63-67, 1998.
13) Moreno I., Rosell R., Abad A., Barnadas A., Carles J., Ribelles N., Solano V. and Font A. Comparison of three protracted antiemetic regimens for the control of delayed emesis in cisplatin-treated patients. Eur J Cancer 28A: 1344-1347, 1992.
14) Ondansetron+dexamethasone vs metoclopramide +dexamethasone+diphenhydramine in prevention of cisplatin-induced emesis. Italian Group For Antiemetic Research. Lancet 340: 96-99, 1992.
15) Roila F., Boschetti E., Tonato M., Basurto C., Bracarda S., Picciafuoco M., Patoia L., Santi E., Penza O., Ballatori E. and et al. Predictive factors of delayed emesis in cisplatin-treated patients and antiemetic activity and tolerability

of metoclopramide or dexamethasone. A randomized single-blind study. Am J Clin Oncol 14: 238-242, 1991.
16) Shinkai T., Saijo N., Eguchi K., Sasaki Y., Tamura T., Fujiwara Y., Mae M., Fukuda M., Ohe Y., Sasaki S. and *et al.* Control of cisplatin-induced delayed emesis with metoclopramide and dexamethasone: a randomized controlled trial. Jpn J Clin Oncol 19: 40-44, 1989.
17) Kris M.G., Gralla R.J., Tyson L.B., Clark R.A., Cirrincione C. and Groshen S. Controlling delayed vomiting: double-blind, randomized trial comparing placebo, dexamethasone alone, and metoclopramide plus dexamethasone in patients receiving cisplatin. J Clin Oncol 7: 108-114, 1989.
18) Sekine I., Nishiwaki Y., Kakinuma R., Kubota K., Hojo F., Matsumoto T., Ohmatsu H., Yokozaki M., Goto K., Miyamoto T., Takafuji J. and Kodama T. Phase II study of high-dose dexamethasone-based association in acute and delayed high-dose cisplatin-induced emesis -JCOG study 9413. Br J Cancer 76: 90-92, 1997.
19) Gralla R.J., Osoba D., Kris M.G., Kirkbride P., Hesketh P.J., Chinnery L.W., Clark-Snow R., Gill D.P., Groshen S., Grunberg S., Koeller J.M., Morrow G.R., Perez E.A., Silber J.H. and Pfister D.G. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. American Society of Clinical Oncology. J Clin Oncol 17: 2971-2994, 1999.
20) Maher J. Intravenous lorazepam to prevent nausea and vomiting associated with cancer chemotherapy. Lancet 1: 91-92, 1981.
21) Kris M.G., Gralla R.J., Clark R.A., Tyson L.B. and Groshen S. Antiemetic control and prevention of side effects of anti-cancer therapy with lorazepam or diphenhydramine when used in combination with metoclopramide plus dexamethasone. A double-blind, randomized trial. Cancer 60: 2816-2822, 1987.
22) Gonzalez Baron M., Chacon J.I., Garcia Giron C., Ordonez Gallego A., Garcia de Paredes M.L., Feliu J., Zamora P., Herranz C., Garrido P. and Artal A. Antiemetic regimens in outpatients receiving cisplatin and non-cisplatin chemotherapy. A randomized trial comparing high-dose metoclopramide plus methylprednisolone with and without lorazepam. Acta Oncol 30: 623-627, 1991.
23) de Wit R., Herrstedt J., Rapoport B., Carides A.D., Carides G., Elmer M., Schmidt C., Evans J.K. and Horgan K.J. Addition of the oral NK1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. J Clin Oncol 21: 4105-4111, 2003.
24) Hesketh P.J., Grunberg S.M., Gralla R.J., Warr D.G., Roila F., de Wit R., Chawla S.P., Carides A.D., Ianus J., Elmer M.E., Evans J.K., Beck K., Reines S. and Horgan K.J. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin--the Aprepitant Protocol 052 Study Group. J Clin Oncol 21: 4112-4119, 2003.
25) Navari R.M., Reinhardt R.R., Gralla R.J., Kris M.G., Hesketh P.J., Khojasteh A., Kindler H., Grote T.H., Pendergrass K., Grunberg S.M., Carides A.D. and Gertz B.J. Reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist. L-754, 030 Antiemetic Trials Group. N Engl J Med 340: 190-195, 1999.
26) Van Belle S., Lichinitser M.R., Navari R.M., Garin A.M., Decramer M.L., Riviere A., Thant M., Brestan E., Bui B., Eldridge K., De Smet M., Michiels N., Reinhardt R.R., Carides A.D., Evans J.K. and Gertz B.J. Prevention of cisplatin-induced acute and delayed emesis by the selective neurokinin-1 antagonists, L-758, 298 and MK-869. Cancer 94: 3032-3041, 2002.
27) Poli-Bigelli S., Rodrigues-Pereira J., Carides A.D., Julie Ma G., Eldridge K., Hipple A., Evans J.K., Horgan K.J. and Lawson F. Addition of the neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 97: 3090-3098, 2003.
28) de Wit R., Herrstedt J., Rapoport B., Carides A.D., Guoguang-Ma J., Elmer M., Schmidt C., Evans J.K. and Horgan K.J. The oral NK(1) antagonist, aprepitant, given with standard antiemetics provides protection against nausea and vomiting over multiple cycles of cisplatin-based chemotherapy: a combined analysis of two randomised, placebo-controlled phase III clinical trials. Eur J Cancer 40: 403-410, 2004.

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CASE REPORT

Multiple pulmonary metastases of lung adenocarcinoma to a different ipsilateral lobe after pulmonary lobectomy

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Summary Pulmonary metastases (PM) to different lobes are classified as M1 disease in non-small cell lung cancer. We report on three patients with lung adenocarcinoma who had undergone complete resection as the initial treatment and thereafter had recurrence of multiple PMs but only in a different ipsilateral lobe 19, 9, and 6 months after surgery. Two patients underwent completion pneumonectomy for the ipsilateral recurrent PM and are doing well without recurrence at 7 and 1 year after the second operations. The other patient received three regimens of chemotherapy over 2.5 years and is alive with PM but without any other metastases. Our findings suggest that some patients with recurrent multiple PM limited to a different ipsilateral lobe have a good prognosis with aggressive treatment, including surgery, and suggest that the PM in such patients occurs through a local route within the ipsilateral thorax.

1. Introduction

Pulmonary metastasis (PM) is generally considered to be a type of distant metastasis and is classified as stage IV disease in non-small cell lung cancer (NSCLC). However, PMs in the same lobe as the primary lesion, which are normally called satellite nodules, are reported to have a good prognosis and have been included in the T4 category of the TNM staging system since 1997 [1]. On the other hand, metastases to a different lobe, even if they are limited to the ipsilateral lung, are thought to have a more aggressive character and are thus classified as M1 disease. Several recent studies of surgical subjects have yielded data supporting this classification [2,3], whereas other papers have suggested opposite findings [4,5]; as a result, this classification remains controversial.

Recurrent disease with multiple PMs after complete resection of the primary tumor usually appears in both lungs and is usually accompanied by extrathoracic metastasis. We herein report on three patients with lung adenocarcinomas

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