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Persistent and Aggressive Treatment for Thymic Carcinoma

Results of a Single-Institute Experience with 25 Patients

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Key Words
Thymic carcinoma · Surgery · Radiotherapy · Chemotherapy, systemic

Abstract
Objectives: The aim of this study is to retrospectively evaluate the role of several therapies, mainly chemotherapy, for thymic carcinoma (TC). ***Methods:*** From July 1973 to July 2005, 25 patients (15 males and 10 females) with histologically proven TC were treated at our department. The median age of the patients was 59 years, with a range of from 30 to 78 years. According to Masaoka's staging system, there was 1 stage I patient, 3 stage II, 7 stage III, 6 stage IVa, and 8 stage IVb patients. The histological subtype was in all cases squamous cell carcinoma, nonkeratinizing type. ***Results:*** There were 6 complete surgical resections, 1 incomplete resection followed by chemoradiotherapy, 6 with radiotherapy alone, 3 with radiotherapy plus chemotherapy, and 9 with chemotherapy alone as the initial treatment. Eighteen patients were administered second-line therapy. The regimen obtaining the best response rate was doublet chemotherapy consisting of carboplatin (CBDCA) and paclitaxel. The median survival time and survival rate at 5 years for the patients excluding surgical cases with stage I/II disease were 32 months and 31%, respectively. ***Conclusion:*** The doublet of CBDCA and paclitaxel thus appears to be a promising regimen for TC and further investigation in a multi-institutional phase II trial is, therefore, strongly called for.

Introduction

Thymic carcinoma (TC) is a rare epithelial neoplasm of the thymus that differs from thymoma in its morphological and biological features. Kondo and Monden [1] reported 186 patients (14%) with TC among the compiled records of 1,320 patients with thymic epithelial tumors who were treated from 1990 to 1994 at 115 institutes certified as special institutes for general thoracic surgery by the Japanese Association for Chest Surgery. Most cases occur at middle age (mean age: 57.9 ± 13.2 years), and the male to female ratio was 1.52 (111 men and 73 women). In general, TC is characterized by extensive local invasion and distant metastasis, an aggressive course and a poor prognosis. According to the World Health Organization (WHO) classification of the tumors, TCs are classified as squamous cell carcinoma, basaloid carcinoma, mucoepidermoid carcinoma, lymphoepithelioma-like

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Table 1. Clinicopathological characteristics of the patients

Parameter	n	%
Median age, years	59 (30–78)	
Gender		
Male	15	60
Female	10	40
Histological type		
Squamous cell carcinoma	25	100
Stage		
I	1	4
II	3	12
III	7	28
IVa	6	24
IVb	8	32

Values in parentheses represent range.

Table 2. Initial treatment for TC

Therapy	n	%
Surgery only	4	16
Surgery + adjuvant therapy	3	12
Radiotherapy only	6	24
Radiotherapy + chemotherapy	3	12
Chemotherapy alone	9	36

carcinoma, sarcomatoid carcinoma (carcinosarcoma), clear cell carcinoma, adenocarcinoma, papillary adenocarcinoma, carcinoma with t(15;19) translocation, and undifferentiated carcinoma [2]. Whereas the clinicopathological features of TC have often been discussed, information about the optimal treatment modalities and long-term prognosis is limited due to the rarity of this disease. We retrospectively reviewed 25 cases of TC treated with various modalities and followed them long-term, while also discussing the overall management of this disease.

Material and Methods

Patients and Methods

From July 1973 to July 2005, 25 patients with histologically proven TC were treated at the Department of Thoracic Oncology, Kyushu Cancer Center. We excluded any thymic neuroendocrine tumors in this retrospective study, because their clinical behavior differs from that of the others. The clinical or pathological stage of the disease was based on the staging system described by Masaoka et al. [3]. The histological analysis of the tumor was based on the WHO classification of cell types [2]. Percutaneous biopsy was performed in the cases without a surgical resection to determine the pathological classification. The cases diagnosed before the establishment of the Masaoka criteria or WHO classification were reevaluated by two independent reviewers or pathologists. The clinicopathological characteristics of the patients are shown in table 1. All patients had a good performance status except for performance status 2 due to the superior vena cava syndrome in only 1 patient.

Treatment

The initial therapies are summarized in table 2. A complete resection as the initial therapy was performed in 6 patients, which included 1 patient who received postoperative radiotherapy and 1 postoperative chemotherapy. One patient had an incomplete resection followed by chemoradiotherapy, radiotherapy alone in 6, radiotherapy plus chemotherapy in 3, and chemotherapy alone in 9 as the initial treatment. Nine of the patients with unresectable tumors were treated with irradiation of from 40.0 to 61.2 Gy to the primary tumors. Eighteen patients were administered second-line therapy (chemotherapy in 10, radiotherapy in 4, chemoradiotherapy in 3 and surgical resection followed by radiotherapy in 1), while 12 received third-line (radiotherapy in 6, chemotherapy in 3, chemoradiotherapy, surgical resection and other treatment in 1 each), 10 had fourth-line (radiotherapy in 5, chemotherapy in 2, chemoradiotherapy in 2 and surgical resection followed by chemotherapy in 1), 4 had fifth-line (chemotherapy and radiotherapy in 2 each), 3 had sixth-line (surgical resection, radiotherapy and chemotherapy in 1 each) and 2 had seventh-line treatment (radiotherapy in 2) after the failure of the initial treatment. Several chemotherapy regimens were used, and the results of the first- or second-line chemotherapy for at least 4 patients are summarized in table 3.

Tumor Assessment during and after Treatment

The measurability of target lesions at baseline and the response criteria was based on the Response Evaluation Criteria in Solid Tumours (RECIST) [4]. In brief, lesions that can be accurately measured in at least one dimension as ≥20 mm with conventional techniques or as ≥10 mm with a spiral CT scan were defined as measurable lesions. The response criteria were categorized as follows: complete response: the disappearance of all target lesions; partial response: at least a 30% decrease in the sum of the pleural thickness at three separate levels; progressive disease: 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; stable disease: neither sufficient shrinkage to qualify for partial response nor a sufficient increase to qualify for progressive disease. The cases diagnosed before establishment of the RECIST criteria were reevaluated by two independent reviewers of our department.

Statistical Analysis

The duration of stable disease was measured from the start of the treatment until the criteria for disease progression was met. The survival was calculated from the date of the initial treatment until death due to any cause or the last follow-up (censored). The survival curve was made using the Kaplan-Meier method [5]. The

Table 3. Response to chemotherapy

Regimen	1st line				2nd line				Total			
	n	response		RR, %	n	response		RR, %	n	response		RR, %
CBDCA/paclitaxel	5	CR	0	100	1	CR	0	100	6	CR	0	100
		PR	5			PR	1			PR	6	
		SD	0			SD	0			SD	0	
		PD	0			PD	0			PD	0	
CDDP/GEM/VNR	2	CR	0	50	2	CR	0	50	4	CR	0	50
		PR	1			PR	1			PR	2	
		SD	0			SD	1			SD	1	
		PD	1			PD	0			PD	1	
P/E	2	CR	0	50	2	CR	0	50	4	CR	0	50
		PR	1			PR	1			PR	2	
		SD	1			SD	1			SD	2	
		PD	0			PD	0			PD	0	
CPA/ADR based	3	CR	0	0	1	CR	0	100	4	CR	0	25
		PR	0			PR	1			PR	1	
		SD	2			SD	0			SD	2	
		PD	1			PD	0			PD	1	

CBDCA = Carboplatin; CDDP = cisplatin; GEM = gemcitabine; VNR = vinorelbine; P = platinum; E = etoposide; CPA = cyclophosphamide; ADR = doxorubicin; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; RR = response rate.

results were considered to be significant if the calculated p value was <0.05. All data were analyzed using the Abacus Concepts, Survival Tools for StatView software package (Abacus Concepts, Berkeley, Calif., USA).

Results

Treatment Response

The responses to the first-line or second-line chemotherapy for at least 4 patients are summarized in table 3. The patients received the following dosage and schedule of major regimens: carboplatin (CBDCA) area under the treatment and response curve (AUC) = 6 and paclitaxel 200 mg/m^2 on day 1 every 3 weeks, or CBDCA (AUC = 2) and paclitaxel 80 mg/m^2 weekly, 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. Platinum plus etoposide (VP-16; 80–100 mg/m^2 for 3 days) regimens included CDDP (80–100 mg/m^2 on day 1) in 3 patients and CBDCA (AUC = 4 on day 1) in 1 patient every 4 weeks. The cyclophosphamide (CPA)- and doxorubicin (ADR)-based regimens included CPA, ADR, vincristine (VCR) and prednisone (CHOP) in 1 patient, CHOP plus CDDP in 2 and CPA, ADR and VP-16 in 1. The other regimens for 3 or fewer cases were ADR alone, cisplatin plus vindesine, or platinum plus CPT-11. However, there were no responders among patients on these regimens. The median cycle number (range) of CBDCA/paclitaxel-, CDDP/GEM/VNR-, platinum plus VP-16-, or CPA plus ADR-based chemotherapy shown in table 3 as major regimens was 6 (4–7), 4 (1–10), 2 (1–2) or 1 (1–2), respectively. Radiotherapy or chemoradiotherapy was used for the control of the primary site, distant metastases or local recurrence including the localized dissemination nodule. Regimens for concurrent chemoradiotherapy were ADR alone, CPA and ADR-based, or uracil-tegafur (UFT) plus CDDP. The response rate of radiotherapy alone or chemoradiotherapy as initial therapy for the primary site was 17 or 33%, respectively. The total number of treated and measurable lesions and the response rate of radiotherapy or chemoradiotherapy during this study were 22 and 23% or 9 and 33%, respectively.

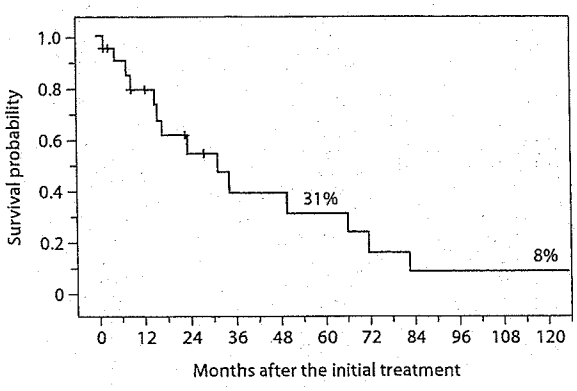

Fig. 1. Overall survival in the patients without a surgical resection for stage I/II disease (median survival time: 32 months).

Survival

Regarding the three main chemotherapy regimens, the median duration of stable disease on CBDCA/paclitaxel, CDDP/GEM/VNR, or platinum plus VP-16 was 11, 8 or 1 months, respectively. The median survival time and the overall survival rate at 5 years for the patients excluding surgical cases with stage I/II disease were 32 months and 31%, respectively (fig. 1).

Discussion

This is a sequel report about the multimodality treatment of TC over a 30-year period, and these findings represent a large single-institutional experience. We previously reported our initial experience of primary TC including two small cell carcinomas, treated with various modalities and followed long-term in our institute [6]. We excluded thymic neuroendocrine tumors in this study. They were classified as typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma, or small cell neuroendocrine carcinoma [2]. Gal et al. [7] showed that thymic neuroendocrine tumors were potentially aggressive tumors that could be morphologically grouped into distinct tumor categories by their analysis of current and previously published cases. The optimal treatment for TC remains to be defined, because the low incidence of this disease has precluded the development of well-designed prospective clinical trials. An initial complete resection is mandatory whenever possible. Radiotherapy plays an important role in treating TC in terms of reducing local recurrence and prolonging the survival time [8]. The role of chemotherapy in treating this malignancy remains controversial, whereas the majority of platinum-based chemotherapy regimens have now been accepted. Recent reports demonstrated a high response rate with combination chemotherapies involving CDDP, ADR, VCR and CPA (ADOC) [9], and CDDP, VCR, ADR and VP-16 (CODE) [10] in Japanese patients with advanced TC. However, these regimens including CPA, ADR and VCR were not effective in this study. A recent study demonstrated the efficacy of doublet chemotherapy consisting of CBDCA and paclitaxel on recurrent thymoma [11] and triplet chemotherapy consisting of CDDP, GEM and VNR on Japanese patients with other thoracic malignancies [12, 13]. Morio et al. [14] recently reported a case which demonstrated induction chemoradiotherapy with CDDP and paclitaxel followed by surgical resection to be useful for advanced TC because no evidence of viable cells was observed in a histopathological examination of the resected specimens and no sign of recurrence was found at 15 months after surgery. Hotta et al. [15] reported that combination chemotherapy consisting of CDDP plus a new agent yields a substantial survival advantage compared with CBDCA plus a new agent in patients with advanced non-small cell lung cancer using a meta-analysis of randomized clinical trials. However, there is no evidence of equivalency between CDDP and CBDCA for this rare malignancy.

Squamous cell carcinoma is the most frequent subtype in Japanese patients with TC (62%) [1]. The prognosis of moderate to poorly differentiated TC depends largely on the microscopic subtype, which is very poor for nonkeratinizing carcinoma (including lymphoproliferative-like tumor), sarcomatoid carcinoma, clear cell carcinoma, and undifferentiated (anaplastic) carcinoma and intermediate for the keratinizing squamous cell carcinoma [16]. Our cases were all nonkeratinizing squamous cell carcinomas. The multimodality approach should be considered to improve the survival of the patients with TC such as those described in this study (median survival time: 36 months, and survival rate at 5 years: 38%).

It is an undeniable fact that the long accrual period of this retrospective study may have resulted in some heterogeneity of the treatment and management of the patients. In the first stage of this study, a CPA/ADR-based chemotherapy regimen was selected, and a regimen including paclitaxel or GEM/VNR was selected in the second stage after the establishment of a new agent. Although the number of cases was too small to draw any

definitive conclusions, we especially feel that doublet chemotherapy consisting of CBDCA and paclitaxel appears to be a promising regimen for TC. The demonstrated antitumor activity is high, thus making this combined chemotherapy worthy of further investigation in a multi-institutional phase II trial.

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Establishment of a clinical pathway as an effective tool to reduce hospitalization and charges after video-assisted thoracoscopic pulmonary resection

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ORIGINAL ARTICLE

Establishment of a clinical pathway as an effective tool to reduce hospitalization and charges after video-assisted thoracoscopic pulmonary resection

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Abstract
Objective. The purpose of this study was to assess the effect of establishing a clinical pathway based on the length of hospitalization, hospital charges, and the outcome for video-assisted thoracoscopic pulmonary resection (VATPR).
Methods. We retrospectively analyzed consecutive patients who were diagnosed as having primary lung cancer, metastatic lung cancer, or a nodule that was suspected to be malignant and thus was operated on using VATPR during the 1-year period before ($n = 105$) and after ($n = 113$) pathway implementation.
Results. The mean economic cost and total hospital stay before and after pathway implementation were about $14439 and $13093 (US), and 29.4 and 18.6 days, respectively. These figures were significantly lower after pathway implementation than before establishment of the pathway.
Conclusion. A clinical pathway is thus considered useful for reducing the length of total hospital stay and the costs associated with VATPR while maintaining high-quality postoperative care.

Key words Clinical pathway · Video-assisted thoracoscopic surgery · Pumonary resection · Duration of hospitalization · Hospitalization cost

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Introduction

Clinical pathways have been developed for postoperative management in an attempt to contain costs in an era of rising health care costs and limited resources. Pathway implementation has been shown to reduce the hospital stay and costs for major thoracic surgery.[1–3]

Video-assisted thoracoscopic pulmonary resection (VATPR) is now routinely used as a minimally invasive approach for the treatment of early-stage lung cancer in our department. In addition, with public health spending under growing social and administrative pressure, we introduced a clinical pathway for VATPR in April 2003 to standardize patient care, shorten the total hospital stay, and reduce hospitalization costs. However, it remains unclear as to whether a clinical pathway reduces the hospital length of stay and costs to the same degree as was observed for major thoracic surgery.

Subjects and methods

From April 2003 to May 2004, a total of 113 consecutive patients were operated on by means of VATPR at the Department of Thoracic Oncology, Kyushu Cancer Center after we began this clinical pathway. The results were retrospectively compared to a series of 105 consecutive patients who underwent VATPR with the same surgical indications and techniques during the 1-year period from April 2000 to March 2001, prior to implementation of the clinical pathway. The characteristics of the patients are detailed in Table 1. The main steps of the postoperative care in the pathway are detailed in Table 2. A patient care pathway was developed that detailed the daily goals for the patient and for the care team. The

Table 1 Patient characteristics before and after clinical pathway implementation

Characteristic	Before (n = 105) April 2000 to March 2001	After (n = 113) April 2003 to May 2004	P
Sex			
Male	53	66	0.2988
Female	52	47	
Age (years), median and (range)	64 (15—83)	63 (17—84)	0.8685
Surgical procedure			
Lobectomy	58	64	0.6057
Segmentectomy or wedge resection	46	46	
Pneumonectomy or bilobectomy	1	3	
Pathology			
Primary lung cancer	67	79	0.3558
Metastatic lung cancer	19	22	
Benign tumor	6	6	
Inflammatory lesion	4	2	
Organized pneumonia	1	2	
Others	8	2	

Table 2 Programmed postoperative management regimen

Steps	Management regimen
Chest tube	Remove within four postoperative days if no air leakage is detected, regardless of pleural drainage
Oxygen support	Discontinue the morning after surgery; reintroduce support only if the patient complains of dyspnea and the saturation level is <95%
Antibiotic administration	Discontinue the evening of the day after surgery
Meal intake	Start the day after surgery
Ambulation	Start the day after surgery
Urinary catheterization and epidural analgesia	Discontinue when the patient is able to walk without assistance
Intravenous infusion	Discontinue when the patient is able to eat meals
Discharge	Patient feels prepared for discharge by 8–12 postoperative days under the conditions of adequate pain control, no evidence of infection, and self-support for life

items detailed on a daily basis included assessments (test ordering and guidelines), physical therapy, medications, diet, oxygen therapy, patient education, social services and case management, pain management, chest tube management, and wound care. Variance codes were developed for patients in whom the chest tube could not be removed or who could not be discharged by the target day to identify what factors led to the prolonged duration. Epidural catheters are usually left in until the chest tubes are removed.

Surgical techniques

The operation was performed with the patient under general anesthesia with or without epidural analgesia. Ventilation was commenced with a double-lumen endotracheal tube to allow one-lung ventilation and collapse of the ipsilateral lung. VATPR was performed as previously described.[4]

Statistical analysis

Statistical analyses were performed using either the chi-squared analysis or Fisher's exact test for the various clinicopathological factors. All values were expressed as the means. Differences in the operating time, blood loss, postoperative hospital stay, total hospital stay, and hospitalization costs were analyzed using the Mann-Whitney U-test.[5]

Results

There were no significant differences in the sex, age, or pathology between the patients treated before and after clinical pathway implementation. No patients required a transfusion, and there were no postoperative deaths in either group. No significant difference was observed in the operating time, wound scale, or presence of air

leakage immediately after operation for the two groups, as shown in Table 3. All patients treated after establishment of the pathway were managed postoperatively according to the program shown in Table 2. The patient was regarded as recovered from the operation when all steps had been completed. Chest tubes were removed by the target day (within 4 postoperative days) in 87 patients (77%). Common reasons for failure to remove the chest tubes were prolonged air leakage and chylothorax. Altogether, 73 patients (65%) were discharged by the target day (8–12 postoperative days). Common reasons for failure to be discharged on time were postoperative complications such as prolonged air leakage and chylothorax or a need to undergo adjuvant therapy. The postoperative course is detailed in Table 4. The cases with variances during the pathway were not excluded from this analysis. According to the analysis of differences of the postoperative hospital stay, total hospital stay, and hospitalization costs using the Mann-Whitney U-test, all parameters after the clinical pathway implementation were significantly less than those before the pathway was followed. After converting Japanese yen into US dollars, the mean economic cost after pathway implementation was about $13 093 (US), which was lower than that before the pathway (was introduced $14439 US). One US dollar was equivalent to 107 Japanese yen.

Table 3 Intraoperative course

Parameter	Before ($n = 105$)	After ($n = 113$)	P
Operating time (h)	4.0 ± 0.2	3.6 ± 0.1	0.07
Blood loss (g)	106 ± 11.1	96.3 ± 14.1	0.003
Wound scale (cm)	9.0 ± 0.4	8.4 ± 0.3	0.652
Presence of air leakage immediately after operation			
With	14	14	0.996
Without	91	99	

Results are means ± SE

Discussion

Now that medical expenses are being shifted to a prospective payment system, limiting the length of hospitalization after surgery benefits not only the patients but also the hospital management in terms of cost-effectiveness. VATPR represents the most suitable treatment of early lung cancer at present. It produces only minor surgical trauma, which is considered to be its main advantage over conventional surgery.

To shorten the total hospital stay and cut down on hospitalization costs, we began using this clinical pathway to manage postoperative care after VATPR in April 2003. The postoperative hospital stay and total hospital stay for VATPR after pathway implementation were found to be significantly shorter than before using the pathway. The mean economic cost of VATPR after pathway implementation was lower than that before the pathway, even when calculating the total cost including preoperative examinations. The examination and treatment of various complaints must be carried out during a long-term hospitalization for such patients. Under the rules of the Japanese medical insurance system, if the duration of hospital stays is 2–14 days, the base hospitalization cost is about $180 (US) per day for our hospital. If the duration of hospital stays extends beyond 14 days, the base hospitalization cost decreases to about $137 (US) per day. That is the reason the reduction in hospital cost was small in comparison to the shortened hospital stay after pathway implementation: it was due to the characteristics of the Japanese medical payment system. Regarding patient education, we have prepared another clinical pathway chart with illustrations that indicate the physical therapy, wound care, and social services after discharge so it is easy to understand the route from the administration and operation to discharge. As a result, the patients can thus be discharged without anxiety within the designated time limit.

Ueda et al. have reported six preoperative risk factors—age ≥65 years, breathlessness, performance status of 1, radiological emphysema, preoperative partial

Table 4 Postoperative course

Parameter	Before ($n = 105$)	After ($n = 113$)	P
Duration of chest tube	4.0 ± 0.2	3.6 ± 0.2	0.05
Postoperative hospital stay (days)	22.4 ± 2.0	13.3 ± 0.9	<0.0001
Total hospital stay (days)	29.4 ± 2.0	18.6 ± 1.0	<0.0001
Hospitalization cost in US dollars	14439 ± 430	13093 ± 280	0.0002

Results are means ± SE

pressure of arterial oxygen (Po_2) <80 mmHg, predictive postoperative forced expiratory volume at 1 s (FEV_1) <60%—to be statistically defined as prolonging the postoperative recovery after VATPR for lung cancer; and the overall number of these risk factors specifically predicted postoperative recovery rate.[6] Regarding the risk factors except for age, few patients had high risk in this study. No significant difference was observed regarding those five risks (except for the patient's age) between the two groups before and after pathway implementation (data not shown). Regarding patient age, the postoperative hospital stay and total hospital stay of the patients ≥65 years (elderly group) were similar to those <65 years of age (young group) before pathway implementation in this study. The mean economic cost for elderly patients was also similar to that for young patients. However, the postoperative hospital stay, total hospital stay, and mean economic cost of the elderly patients were significantly longer and higher than those of the young patients after pathway implementation (data not shown). Regarding the results stated above, elderly patients not only have various medical problems but also may feel anxiety when being discharged early after an operation. A patient demonstrating such risk factors may therefore not be suitable for the above clinical pathway because of the difficulty of standardizing the postoperative care.

Conclusion

Based on the above findings, we conclude that the establishment of a clinical pathway is a cost-effective modality for maintaining high-quality postoperative care after VATPR.

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ORIGINAL REPORT

Phase II Study of Etoposide and Cisplatin With Concurrent Twice-Daily Thoracic Radiotherapy Followed by Irinotecan and Cisplatin in Patients With Limited-Disease Small-Cell Lung Cancer: West Japan Thoracic Oncology Group 9902

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ABSTRACT

Purpose
We initially conducted a randomized phase II study to compare irinotecan and cisplatin (IP) versus irinotecan, cisplatin, and etoposide (IPE) after etoposide and cisplatin (EP) with concurrent twice-daily thoracic radiotherapy (TRT) in limited-disease small-cell lung cancer (LD-SCLC). We amended the protocol to evaluate IP after EP with concurrent twice-daily TRT in a single-arm phase II study because of an unacceptable toxicity in IPE.

Patients and Methods
Previously untreated patients with LD-SCLC were treated intravenously with etoposide 100 mg/m^2 on days 1 through 3 and cisplatin 80 mg/m^2 on day 1 with concurrent twice-daily TRT (1.5 Gy per fraction, a total dose of 45 Gy) beginning on day 2 followed by three cycles of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on day 1 of a 4-week cycle.

Results
Of the 51 patients enrolled, 49 patients were assessable for response and toxicity. The overall response rate and complete response rate were 88% and 41%, respectively. The median survival time for all patients was 23 months. The 2-year and 3-year survival rates were 49% and 29.7%, respectively. The median progression-free survival was 11.8 months. The major toxicities observed were neutropenia (grade 4, 84%), febrile neutropenia (grade 3, 31%), infection (grade 3 to 4, 33%), electrolytes imbalance (grade 3 to 4, 20%), and diarrhea (grade 3 to 4, 14%).

Conclusion
EP with concurrent twice-daily TRT followed by the consolidation of IP appears to be an active regimen which deserves further phase III testing in patients with LD-SCLC.

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INTRODUCTION

Small-cell lung cancer (SCLC), which accounts for approximately 15% of all lung cancer cases, is clinically categorized as the two stages, limited disease and extensive disease. Two meta-analyses have shown the combined modality of chemotherapy and thoracic radiotherapy (TRT) to improve the survival of patients with limited-disease (LD-) SCLC in comparison to chemotherapy alone.[1,2] The schedule, dose, and fractionation of TRT have previously been examined in patients with LD-SCLC in several randomized controlled studies.[3-7] On the basis of the results of these studies, etoposide and cisplatin (EP) with concurrent twice-daily TRT is currently a standard care for the treatment for LD-SCLC. However, the 5-year survival rate is less than 30%, and most patients experience a relapse of the primary tumor or distant metastasis.[3-6] To further improve the therapeutic efficacy, one approach is to develop a new chemoradiotherapy regimen incorporating with a novel active agent.

Irinotecan hydrochloride, a camptothecin derivative, is among the most active chemotherapeutic agents against SCLC with a response rate of 37% as a single agent.[8] A randomized phase III study revealed that irinotecan and cisplatin (IP) was superior to EP in patients with extensive-disease SCLC (ED-SCLC).[9] However, the role of IP in the treatment of LD-SCLC remains to be defined. To clarify the role of this combination regimen in LD-SCLC, we initially conducted a randomized phase II study to

compare two consolidation chemotherapy regimens, IP versus irinotecan, cisplatin and etoposide (IPE), after EP with concurrent twice-daily TRT in LD-SCLC.[10] However, EP with concurrent twice-daily TRT followed by IPE was not feasible because of unacceptable toxicity including grade 4 neutropenia (92%), grade 4 diarrhea (25%), grade 4 infection (25%) and one treatment-related death. We therefore amended the protocol to evaluate EP with concurrent twice-daily TRT followed by consolidation therapy with IP in a single-arm phase II study and herein report the results of this study.

PATIENTS AND METHODS

Eligibility Criteria

Patients with histologically or cytologically confirmed LD-SCLC (stage I disease was excluded) were eligible for this study. A limited stage was defined as disease confined to one hemithorax, the mediastinum, and the bilateral supraclavicular area. Cases with a small amount of pleural effusion and a negative cytology were included in the limited-stage group. Other eligibility criteria included the following: no prior chemotherapy or radiotherapy; measurable disease; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; age between 20 and 70 years; life expectancy of at least 3 months; adequate baseline organ function defined as leukocyte count ranging from 4,000 to 12,000/mm^3, hemoglobin concentration of at least 9.5 g/dL, platelet count at least 100,000/mm^3, AST and ALT 2.0× the upper limit of the normal range (ULN) or less, serum total bilirubin 1.5 mg/dL or less, serum creatinine ULN or less, 24-hour creatinine clearance of at least 60 mL/min, and Pao_2 at rest of at least 70 mmHg. The radiation portal should be equal or less than half of one lung.

The patients were ineligible if they had the following criteria: interstitial pneumonitis or pulmonary fibrosis; other respiratory diseases that precluded TRT; malignant pleural effusion or malignant pericardial effusion; active concomitant or a recent (< 3 years) history of any malignancy; uncontrolled angina pectoris, myocardial infarction less than 3 months before the enrollment or congestive heart failure; uncontrolled diabetes mellitus or hypertension; severe infection; intestinal paralysis or obstruction; pregnancy or lactation; or other serious concomitant medical conditions. The study protocol was approved by each institutional review board for clinical use. All patients gave their written informed consent before enrollment.

Study Evaluation

The pretreatment baseline evaluation included a complete medical history and physical examination, a CBC, blood chemistry studies, flexible bronchoscopy, electrocardiography, chest radiography, computed tomography of the chest, computed tomography or ultrasound study of the abdomen, computed tomography or magnetic resonance imaging of the brain, bone scintigraphy and bone marrow aspiration with or without biopsy. A CBC and blood chemistry studies were repeated every week. At the end of the study, all of these studies except for flexible bronchoscopy and bone marrow aspiration were repeated unless the patient had stable or progressive disease.

Treatment Schedule

The patients initially received induction chemoradiotherapy consisting of etoposide 100 mg/m^2 on day 1 through 3 and cisplatin 80 mg/m^2 on day 1 with concurrent twice-daily TRT. After the induction chemoradiotherapy, the patients received three cycles of consolidation chemotherapy consisting of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on days 1. Consolidation chemotherapy was repeated every 4 weeks for three cycles.

The first cycle of consolidation chemotherapy was begun 4 week after the initiation of induction chemoradiotherapy if the leukocyte count was at least 4,000/mm^3; the platelet count was at least 100,000/mm^3; AST and ALT 2.0× ULN or less; serum bilirubin 1.5 mg/dL or less; serum creatinine of ULN or less; the patient did not have fever (≥ 38°C), diarrhea within the past 24 hours, or intestinal paralysis or obstruction; and Pao_2 of at least 70 mmHg. The subsequent cycle of consolidation chemotherapy was repeated if the leukocyte count was at least 3,500/mm^3; the platelet count was at least 100,000/mm^3; AST and ALT 2.0× ULN or less; serum bilirubin 1.5 mg/dL or less; serum creatinine ULN or less; the patient did not have fever (≥ 38°C), diarrhea within the past 24 hours, or intestinal paralysis or obstruction. The use of granulocyte colony-stimulating factor (GCSF) was recommended after day 4. However, its administration was withheld on the day of administration of irinotecan.

TRT was performed with 6 MV or higher photons from a linear accelerator and began on day 2 of the induction chemoradiotherapy. Patients received 1.5 Gy per fraction twice daily with at least a 4-hour interval (preferably a 6-hour interval or more) between each fraction over a 3-week period (a total dose of 45 Gy). A radiation field included the primary tumor, the bilateral mediastinal and ipsilateral hilar lymph nodes with a margin of 1.5 to 2.0 cm. Radiation to the supraclavicular lymph nodes was administered only if they were involved. The inferior border extended 5 cm below the carina or to a level including ipsilateral hilar structures, whichever was lower. After initial irradiation with a dose of 30 Gy, off-cord (ie, the spinal cord was outside the field) oblique boost fields were used. The radiation field in the afternoon was not different from that in the morning. Computed tomography planning was not required and lung density corrections were not performed. Prophylactic cranial irradiation (PCI) was administered to the patients achieving complete response or good partial response with a total dose of 25 Gy in 10 fractions.

Dose Modification

Dose modification based on the toxicity of the induction chemoradiotherapy was not allowed at the time of the first administration of IP. In each cycle of IP, irinotecan on day 8 or 15 was withheld if a leukocyte count of less than 2,000/mm^3 or a platelet count of less than 50,000/mm^3 was determined, or if a patient had fever (≥ 38°C) or grade 2 or higher hepatotoxicity or any diarrhea within the last 24 hours or intestinal paralysis or obstruction. In the second and the third cycle of consolidation chemotherapy, the dose modification was made as follows. If a leukocyte nadir count of less than 1,000/mm^3 or a neutrophil nadir count of less than 500/mm^3 for 3 or more days or if febrile neutropenia developed or if a platelet nadir count of less than 25,000/mm^3 was observed or if grade 2 hepatotoxicity or diarrhea was observed, irinotecan was decreased by 10 mg/m^2 in the subsequent cycle, if grade 2 or lower renal toxicity was observed during the previous course of treatment, only cisplatin decreased by 25%, if grade 3 or higher nonhematologic toxicity (excluding nausea, vomiting, and hair loss) developed, then cisplatin decreased by 25% and irinotecan decreased by 10 mg/m^2 in the following cycle. The patients were removed from the study if the following toxicities were observed: grade 4 diarrhea; grade 3 or higher renal toxicity or creatinine of at least 2.0 mg/dL; grade 3 or higher hepatotoxicity; grade 2 or higher pulmonary toxicity or Pao_2 at rest less than 60 mmHg.

Evaluation

The Response Evaluation Criteria in Solid Tumors (RECIST) were used for the response assessment.[11] Toxicity was evaluated according to the National Cancer Institute–Common Toxicity Criteria (version 2.0). An extramural review was conducted to validate the eligibility of the patients, staging, and response.

Statistical Analysis

The primary end point of this study was the 2-year survival rate. We calculated the sample size based on Fleming's single-stage design of the phase II study.[12] We set a 2-year survival rate of 35% as a baseline survival rate and 20% as the high level of interest with a power of 0.9 at a one-sided significance level of .05, requiring an accrual of 53 eligible patients. The study was initially begun as a randomized phase II study to compare two consolidation arms, namely IP versus IPE after concurrent chemoradiotherapy. Because of the unacceptable toxicity in the triplet regimen, the study was modified to a single-arm phase II study to evaluate IP after EP with concurrent TRT and 11 patients in the IP arm were included in the analysis of this study.

The duration of survival was measured from the day of entry onto the study, and the overall survival curve and progression-free survival curve were calculated according to the method of Kaplan and Meier.[13]

RESULTS

Patients Characteristics

Between February 2000 and November 2002, 51 patients were enrolled onto this study. Table 1 lists the baseline characteristics of the patients. Two patients were considered to be ineligible because a secondary primary tumor was found after the administration of EP with concurrent TRT. Therefore, 49 patients were assessable for response and toxicity.

Treatment Administration

Seven patients were removed from the study after the administration of EP with concurrent TRT because of treatment delay due to toxicity (six patients) and patient rejection (one patient). Eight patients each discontinued the treatment after each cycle of IP. The major reasons for the discontinuation of IP included treatment delay due to toxicity (three patients), diarrhea (three patients), and ileus (three patients), patient rejection (two patients), and the doctor's judgment (two patients). Overall, 34 patients (69%) received at least two cycles of IP and 26 patients (53%) completed the entire treatment. Irinotecan was omitted in 35 (11%) of 306 cycles. The dose-intensity of irinotecan was 30.5 mg/m^2/wk (68% of the planned dose) and cisplatin 11.6 mg/m^2/wk (77% of the planned dose) in the consolidation chemotherapy.

Response and Survival

On an intention-to-treat basis, the overall response rates and the complete response rates were 88% (95% CI, 78.6% to 96.9%) and 41%, respectively. After a median follow-up of 29.9 months, the median survival time for all patients was 23 months (Fig 1). The 2-year and 3-year survival rates were 49% and 29.7%, respectively. The median progression-free survival was 11.8 months (Fig 2).

Toxicity

Tables 2 and 3 show the major toxicities. Grade 4 neutropenia was observed in 80% of the patients and 10 (20%) patients had febrile neutropenia in concurrent chemoradiotherapy, whereas grade 4 neutropenia was observed in 40% of the patients and seven patients (17%) had febrile neutropenia in consolidation chemotherapy. In contrast, anemia and thrombocytopenia were relatively mild. One patient had grade 4 esophagitis in concurrent chemoradiotherapy. In the consolidation chemotherapy, grade 3 or 4 diarrhea was observed in six patients (14%) and grade 3 or 4 infection was observed in seven patients (17%). Two patients had grade 3 or 4 radiation pneumonitis. Grade 4 adhesive ileus developed in a patient who had a history of abdominal surgery and ileus. The major toxicities observed through the entire course of the treatment were neutropenia (grade 4, 84%), febrile neutropenia (grade 3, 31%), infection (grade 3 to 4, 33%), electrolytes imbalance (grade 3 to 4, 20%) and diarrhea (grade 3 to 4, 14%). There was one treatment-related death caused by radiation pneumonitis.

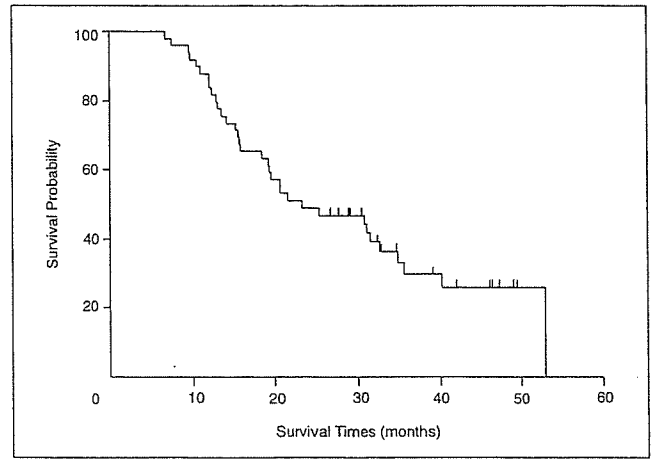

Fig 1. Kaplan-Meier survival curve of 49 eligible patients with limited-disease small-cell lung cancer. The median survival time was 23 months, and the 2-year and 3-year survival rates were 49% and 29.7%, respectively.

Patterns of Relapse

Table 4 lists first sites of relapse. Of 12 patients (24%) with local relapse (defined as relapse within the radiation portal), only one had a relapse solely at locoregional sites and 11 at both local and distant site including three with brain metastasis. Of 27 patients (55%) with distant relapse only, 13 had brain metastasis. Overall, 16 patients (33%) showed brain metastasis as the initial site of relapse, and eight of them had received PCI.

Table 1. Patient Characteristics (N = 51)

Characteristic	No.	%
Age, years		
Median	62	
Range	45-70	
Sex		
Male	42	82
Female	9	18
ECOG performance status		
0	22	43
1	28	55
2	1	2
Stage		
II	2	4
IIIA	35	69
IIIB	14	27

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

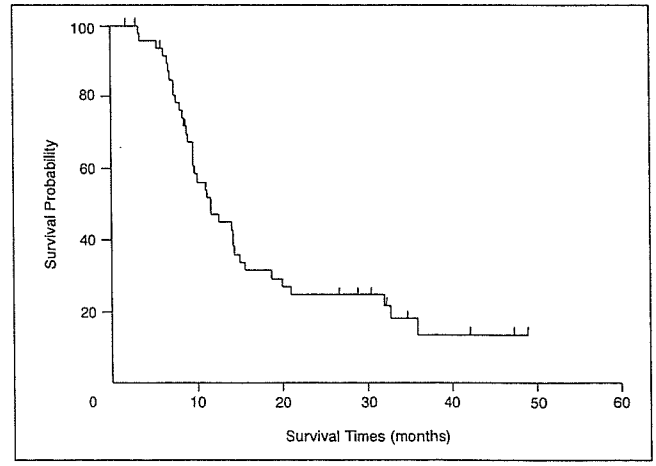

Fig 2. Kaplan-Meier progression-free survival curve of 49 eligible patients with limited-disease small-cell lung cancer. The median progression-free survival time was 11.8 months.

Table 2. Major Toxicities During Concurrent Chemoradiotherapy (n = 49)

Toxicity	Grade 3		Grade 4	
	No.	%	No.	%
Hematologic				
Leukopenia	27	55	19	39
Neutropenia	8	16	39	80
Anemia	2	4	1	2
Thrombocytopenia	10	20	0	0
Febrile neutropenia	10	20	0	0
Nonhematologic				
Nausea/vomiting	7	14	0	0
Diarrhea	0	0	0	0
Constipation	0	0	0	0
Infection	9	18	0	0
Mucositis	0	0	0	0
Esophagitis	0	0	1	2
Dyspnea	1	2	0	0
Pneumonitis	0	0	0	0
Hepatic	0	0	0	0
Electrolytes	2	4	2	4

DISCUSSION

In this phase II study, we evaluated the consolidation of IP after EP with concurrent twice-daily TRT and thus achieved an overall response rate of 88%, a 2-year-survival rate of 49% and a 3-year-survival rate of 29.7%. Although the number of assessable patients was slightly smaller than the planned sample size, this study confirmed 24 2-year survivors, and the power calculation showed a 97% probability to correctly reject inactive treatment, thus yielding only a 35% or less 2-year-survival rate. These results are comparable to those in phase III studies evaluating EP with concurrent twice-daily TRT.[3-6] Jeremic et al[7] reported a better survival outcome by using daily carboplatin and etoposide with concurrent twice-daily TRT followed by EP. However, this result has rarely been confirmed by other groups. The Japanese Clinical Oncology Group (JCOG) conducted a pilot study to evaluate the feasibility of IP after EP with concurrent TRT (JCOG9903).[14] The doses and schedule of cisplatin, etoposide, and irinotecan and dose, fractionation and schedule of TRT were similar to ours. They reported that this regimen was feasible with a response rate of 97%, a 2-year survival rate of 41% and a 3-year survival rate of 38%, which are similar to those in our study. Although a phase III study conducted in Japan showed the superiority of IP over EP in ED-SCLC,[9] another phase III study conducted in North America failed to confirm the superiority of IP over EP.[15] A randomized phase III study to compare IP versus EP after EP with concurrent TRT is currently ongoing in patients with LD-SCLC in Japan.

Table 3. Major Toxicities During Consolidation Chemotherapy (n = 42)

Toxicity	Grade 3		Grade 4	
	No.	%	No.	%
Hematologic				
Leukopenia	27	64	8	19
Neutropenia	18	43	17	40
Anemia	17	40	5	12
Thrombocytopenia	8	19	0	0
Febrile neutropenia	7	17	0	0
Nonhematologic				
Nausea/vomiting	9	21	0	0
Diarrhea	5	12	1	2
Constipation	3	7	2	5
Ileus	2	5	1	2
Infection	9	21	1	2
Mucositis	0	0	0	0
Esophagitis	0	0	0	0
Dyspnea	2	5	0	0
Pneumonitis	1	2	1	2
Hepatic	1	2	0	0
Electrolytes	4	10	1	2

Table 4. Site of First Failure (n = 49)

Site	No. of Patients	%
Progression free	10	20
Locoregional	1	2
Locoregional and distant	11	22
Distant	27	55
Brain only	8	16
Brain and others	5	10
Others	14	29

Although a potential approach is to substitute irinotecan for etoposide in the combination of EP with concurrent TRT, we did not combine IP concurrently with TRT because two phase I studies demonstrated that combining IP with concurrent TRT was not feasible when the full dose of irinotecan was administered on days 1, 8, and 15.[16,17] On the basis of these results, we administered IP as consolidation therapy after EP with concurrent twice-daily TRT. After this article was initially submitted, Langer et al[18] reported phase I study of once every 3 weeks scheduling of IP with concurrent twice-daily TRT (45 Gy) or once-daily TRT (70 Gy) in patients with LD-SCLC, thus concluding that IP with concurrent twice-daily TRT was safe and feasible. A further evaluation of this regimen is thus warranted.

One group evaluated IP administered as an induction followed by EP with concurrent twice-daily TRT.[19] Their results are comparable to those of our study and EP with concurrent twice-daily TRT.[3-6] However, this regimen was highly myelotoxic (grade 4 neutropenia, 91%) with febrile neutropenia in 60% of the patients. Furthermore, early TRT is an important issue to obtain the improved outcome in LD-SCLC. Recent meta-analyses revealed that when platinum-based chemotherapy was concurrent with TRT in LD-SCLC, an improved survival was associated with early TRT.[20-22] Another group evaluated the addition of paclitaxel to EP with concurrent TRT.[23] Although their results are comparable to those of our study and EP with concurrent twice-daily TRT,[3-6] they concluded that the triplet regimen would not further improve the survival outcome in patients with LD-SCLC.

Esophagitis is a toxicity of a particular concern in concurrent chemoradiotherapy. We observed grade 3 or 4 esophagitis in one patient (2%), whereas the JCOG9903 trial reported it in 7% of the patients. These figures contrast with those in the studies evaluating etoposide and a platinum with concurrent twice-daily TRT (9% to 32%).[3-7] The substitution of irinotecan for etoposide may reduce the incidence of grade 3 or 4 esophagitis. Furthermore, a lower incidence of esophagitis has been noted in a Japanese trial.[4] A possible explanation for this includes differences in the

chemotherapy interval (once every 4 weeks *v* once every 3 weeks) and in ethnic background. Neutropenia was the most prominent toxicity in this study and its incidence is higher than that in the Turrisi et al study.[3] However, no toxic death resulting from neutropenia was observed. Diarrhea was the most troublesome nonhematologic toxicity of irinotecan and one of the major causes for treatment discontinuation in this study.

Brain metastasis as an initial site of relapse was observed in 33% of our patients. The JCOG9903 trial reported brain metastasis in 37% of their patients. These rates were higher than those in the studies evaluating etoposide and a platinum with concurrent twice-daily TRT.[4,7] The rate of local recurrence solely was observed in only one patient and none in the JCOG9903 trial. This contrasts with the higher rate of distant failure either with or without local failure in these two studies (77% and 67%, respectively). These increased rates of distant failure including brain metastasis may be partly explained by insufficient administration of IP as consolidation.

A limitation of this study is the treatment feasibility. In this study, 53% of the patients completed the entire treatment and 69% received two or more cycles of IP. The respective values were 58% and 73% in the JCOG9903 trial.[14] In contrast, Takada et al reported that 86% of the patients completed the treatment in EP with concurrent twice-daily TRT.[4] Although the optimal duration of consolidation chemotherapy remains unclear, we consider that at least two cycles of IP is clinically meaningful in view of encouraging survival outcomes in these phase II studies. Whether the relatively low completion rate of IP causes increased distant metastasis and detrimentally affects the outcome will be addressed by the ongoing phase III study. To improve the feasibility, certain supportive measures including the prophylactic GCSF and/or antidiarrheal measures[24] and different dose scheduling (eg, 3-weekly scheduling of IP) should be considered in future studies.

In conclusion, EP with concurrent twice-daily TRT followed by the consolidation of IP appears to be active in patients with LD-SCLC, thus supporting the conduct of the currently ongoing phase III study to compare EP with concurrent twice-daily TRT followed by the consolidation of either EP or IP.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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Original Article

The Use of a Water Seal to Manage Air Leaks after a Pulmonary Lobectomy: A Retrospective Study

Junichi Okamoto, MD, Tatsuro Okamoto, MD, Yasuro Fukuyama, MD, Chie Ushijima, MD, Masafumi Yamaguchi, MD, and Yukito Ichinose, MD

Background: The methods for managing chest drainage tubes during the postoperative period differ among thoracic surgeons and, as a result, the optimal method remains controversial.
Patients and Methods: We reviewed 170 consecutive patients undergoing a pulmonary lobectomy for either primary lung cancer or metastatic lung cancer from January 1998 to December 2002. After the operation, the chest drainage tube was placed on a suction pump with a negative pressure of −10 cmH_2O in 120 patients before 2001, while such drainage tubes were kept on water seal in 47 cases mainly since 2001.
Results: Regarding the preoperative and postoperative variables, postoperative air leak as well as the video-assisted thoracic surgery (VATS) procedure were more frequently observed in the water seal group than in the suction group ($p=0.01580$, $p<0.001$, respectively). In comparing these different populations, each Kaplan-Meier curve, which presented the duration of the postoperative air leak seemed to be similar between the two methods.
Conclusion: These observations suggest that applying chest tubes on water seal seems to be an effective method for preventing postoperative air leak in clinical practice. However, a prospective randomized trial using a larger series of patients is warranted for this subject. (Ann Thorac Cardiovasc Surg 2006; 12: 242–4)

Key words: chest tube, drainage, air leak, lobectomy

Introduction

Prolonged air leakage after a lung resection is still one of the most frequent complications in chest surgery. Such air leaks may increase the duration of the chest drainage, thus resulting in a longer hospitalization. Recently, some prospective trials have shown that applying water seal to chest tubes after a lung resection reduced the duration of air leakage in comparison to suction.[1,2] As a result, we have used the water seal as an alternative procedure to the use of suction −10 cmH_2O. However, a more recent study has also described a negative finding.[3] Therefore, the optimal method for managing postoperative chest tubes remains controversial. We retrospectively investigated whether or not the water seal resulted in a better outcome than suction in clinical practice at our institution.

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Patients and Methods

We reviewed 170 consecutive patients who underwent pulmonary lobectomy for either primary lung cancer or metastatic lung cancer at National Kyushu Cancer Center, from January 1998 to December 2002.

All pulmonary lobectomies were performed through either a standard posterolateral incision or video-assisted thoracic surgery (VATS) procedures. The VATS procedure performed in our institution has been described previously.[4] The operative techniques were standardized for all surgeons. A mediastinal lymphadenectomy (ND2a) was performed after completion of a lobectomy. Before

Table 1. Comparison between the two groups regarding the preoperative and operative variables

Group		Suction (n=120)	Water seal (n=47)	p value
Gender	Male	70 (58.3%)	27 (57.4%)	>0.999
	Female	50 (41.7%)	20 (42.6%)	
Age		64.6±10.3	63.8±10.8	0.7244
Smoking history	Presence	61 (50.8%)	27 (57.4%)	0.4928
	Absence	59 (49.2%)	20 (42.6%)	
Thoracotomy procedure	Antero-lateral	68 (56.7%)	2 (4.3%)	<0.001
	VATS	52 (43.3%)	45 (95.7%)	
Pulmonary adhesion		38 (31.7%)	14 (29.8%)	0.7152
Incomplete fissures		64 (53.3%)	24 (51.1%)	0.8637
Pathological stage	I	94 (78.3%)	40 (85.1%)	0.6240
	II	9 (7.5%)	4 (8.5%)	
	III	15 (12.5%)	3 (6.4%)	
	IV	1 (0.8%)	0 (0.0%)	
Postoperative air leak		30 (25.0%)	20 (42.6%)	0.0158

VATS, video-assisted thoracic surgery.

closing the thoracic cavity, an air leak test was performed using warmed normal saline. If an air leak was detected, it was repaired by either a suture, a synthetic sealant, or both. One 28F chest double-lumen tube was positioned posteriorly into the thorax, and the tubes were placed on suction (−10 cmH_2O) after the closure. After returning to the ward, on the same day of the operation, the tube was placed either on −10 cmH_2O suction again or on water seal. The chest tubes in all patients undergoing an operation before 2001 were used for suction. After 2001, either suction or water seal was used at the discretion of a surgeon. In fact, 120 and 47 patients underwent suction or water seal placement, respectively. Chest radiographs were routinely performed almost everyday until the chest tube was removed. When the pleural effusion was less than 200 ml in a 24-hour period and no air leak was evident, then the chest tubes were removed. Before removing the chest tube, the absence of any air leak in the water seal group was checked by −10 cmH_2O suction.

The following preoperative and operative variables were considered and compared between the suction group and the water seal group: the patient's age, gender, smoking history, type of thoracotomy procedure, degree of pleural adhesion, the status of pulmonary fissures, pathological stage, and postoperative air leak. The two-sample χ^2-test and Fisher's exact test, when appropriate, were used to compare categorical variables. The Kaplan-Meier method was used to estimate the duration of air leakage and the duration that a drainage tube remained in place. Comparisons were made using the log-rank test; a value of $p<0.05$ was considered significant.

Results

The details of the preoperative and operative variables of the patients are shown in Table 1. The VATS procedure and postoperative air leak were more frequently observed in the water seal group than in the suction group ($p<0.001$, $p=0.01580$). Thirty (25.0%) of 120 patients in the suction group and 20 (42.6%) of 47 patients in the water seal group demonstrated air leaks immediately after the operation. There was no difference in gender, age, smoking history, pulmonary adhesion, the presence of incomplete fissures, pathological stage and histological type between the two groups. Using the Kaplan-Meier method, the curves of air leak duration in both the suction group and the water seal group are shown in Fig. 1. The two curves diverged just after the operation, which represented a difference in the postoperative air leakage at the starting point between the two groups. However, the two curves had become closely similar by the next day. The mean ± standard error (SEM) of air leakage duration was 39.2±5.5 hours in the patients with postoperative air leak of the suction group and 31.6±7.3 hours in those in the water seal group (log-rank test, $p=0.29$). The mean±SEM of duration of chest drainage was 4.6±0.33 days for the suction group and 3.6±0.19 days for the water seal group (log-rank test, $p=0.01$).

Discussion

Recently, two prospective studies have shown that placing a chest tube on water seal after a lung resection can

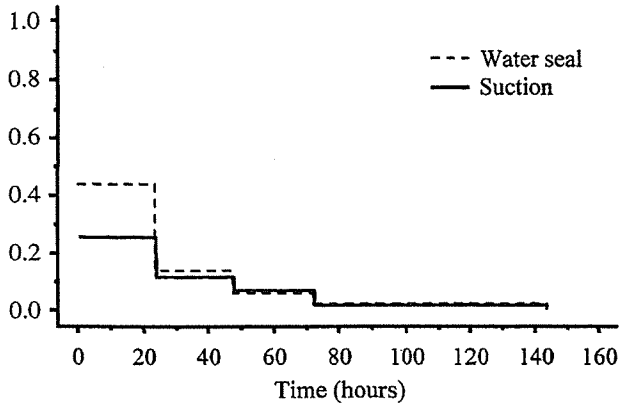

Fig. 1. Duration of postoperative air leakage in the suction group and the water seal group.

reduce the duration of air leakage in comparison to the use of suction. Cerfolio and his colleagues cited that 66% of all air leaks resolved on the 3rd postoperative day (POD3) when the water seal tubes were placed on POD2, whereas only 7% of the patients whose tubes were continuously placed on –20 cm suction showed a resolution of the air leak by POD3.[1] Another group also demonstrated the duration of air leakage to be shorter in the water seal group than in the suction group (mean±SEM, 1.50±0.32 days vs 3.27±0.80 days, respectively; p=0.05).[2] However, in both studies, the number of patients with a postoperative air leak was so small (33 and 30 patients, respectively) that they did not seem to have enough statistical power to show any true differences. Moreover, there were some variations in the types of operations performed in these trials. Brunelli and colleagues showed in their randomized clinical trial that chest tubes placed on water seal after a pulmonary lobectomy did not show a reduced duration of air leakage in comparison with suction (–20 cmH_2O).[3] As a result, the optimal way to use chest tubes remains controversial among surgeons.

Before 2001, the use of –10 cmH_2O suction had been adopted as the standard method for chest drainage after a pulmonary lobectomy at our institution. After 2001, based on the findings of Cerfolio and his colleagues, either suction or water seal was selected at the discretion of the surgeon in charge.[1] In addition, we also began using the VATS procedure as a surgical approach since 1999 in place of the standard posterolateral thoracotomy. This is the reason why a significantly large number of patients (95.7%) in the water seal group underwent a VATS lobectomy in comparison to only 43.3% in the suction group. Table 1 also shows the water seal group to demonstrate more patients with air leak than the suction group patients in the immediate postoperative period (p=0.0158). The main reason for this is due to the fact that the water seal method tended to be selected by surgeons for patients with postoperative air leaks. In the present study, the duration of air leakage was similar in both groups. Our observations indicated that the water seal method therefore appears to be a safe and effective method for treating postoperative air leaks.

Regarding the duration of chest drainage, the mean duration of chest drainage in the water seal group tended to be shorter than in the suction group in the present study. The reason of this difference is not clear because of difference in the two groups. At our institution, the decision to remove the chest tube is based on the 24-hour amount of drained fluid with no air leak. In the present study, the amount of pleural effusion in the water seal group was significantly smaller than in the suction group (average, 800 ml vs 1,132 ml; p<0.001), and this difference might influence the duration of the chest drainage.

In conclusion, our data suggests that applying chest drainage tubes on water seal seems to be an effective method for treating postoperative air leakage. Whether or not this modality provides any advantages regarding reduction in the duration of such air leakage could be evaluated by a prospective randomized trial with a large series of patients.

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