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Risk factors of treatment-related death in chemotherapy and thoracic radiotherapy for lung cancer

Y. Ohe [a,*], S. Yamamoto [b], K. Suzuki [a], F. Hojo [a], R. Kakinuma [a], T. Matsumoto [a], H. Ohmatsu [a], Y. Nishiwaki [a]

[a] *Division of Thoracic Oncology, National Cancer Center Hospital East, Chiba, 6-5-1 Kashiwanoha, Kashiwa-City, Chiba 277-8577, Japan*
[b] *Cancer Information & Epidemiology Division, National Cancer Center Research Institute, Tokyo, Japan*

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Abstract

We retrospectively analysed the incidence and risk factors of treatment-related death in the treatment of chemotherapy- and thoracic radiotherapy-naïve patients with lung cancer. Between July 1992 and December 1997, 1799 patients were diagnosed as having lung cancer in our hospital and 926 patients received chemotherapy and/or thoracic radiotherapy. 25 patients (2.7%) died from toxicity of the treatment, 10 from pneumonia, 7 from radiation pneumonitis, 6 from sepsis, 1 from perforation of the small intestine and 1 for an unknown reason. 18 patients (2.3%) died from chemotherapy-related toxicity. The incidence of treatment-related death (TRD) from chemotherapy was highly correlated with the performance status (PS), PS 0: 0.7%, PS 1: 2.2%, PS 2: 4.0%, PS 3: 7.7% and PS 4: 25% ($P=0.004$). 7 patients (1.6%) died from pneumonitis after thoracic radiotherapy. Multivariate analyses demonstrated that poor PS (relative risk (RR): 1.95, 95% confidence interval (CI): 1.05–3.65, $P=0.034$) and chemotherapy using the cisplatin + vindesine + mitomycin C regimen (RR: 9.36, 95% CI: 1.29–68.0, $P=0.027$) are associated with treatment-related death from chemotherapy. Pulmonary fibrosis identified on a plain chest X-ray film (RR: 165.7, 95% CI: 8.79–3122, $P<0.001$), the combination of cisplatin + irinotecan (RR: 120.5, 95% CI: 2.90–4993, $P=0.012$), advanced age (RR: 1.17, 95% CI: 1.002–1.37, $P=0.047$), and elevated lactate dehydrogenase (LDH) (RR: 10.4, 95% CI: 1.20–90.2, $P=0.033$) were also associated with treatment-related death from thoracic radiotherapy. The administration of mitomycin C in addition to cisplatin-based regimens for patients with lung cancer should be carefully considered.

Keywords: Lung cancer; Treatment-related death; Risk factor; Chemotherapy; Thoracic radiotherapy; Mitomycin C; Irinotecan; Radiation pneumonitis; Performance status; Age

1. Introduction

Lung cancer is one of the most common carcinomas, not only in Japan, but also in the USA and Europe [1,2]. In 1990, the estimated number of patients with lung cancer worldwide was approximately 850 000 cases [1]. Approximately 45 000 patients die from lung cancer each year and the mortality is still increasing in Japan [3]. Surgery is the most curative treatment for early stage non-small cell lung cancer (NSCLC), however, only 30% of patients with NSCLC receive curative resection [4]. Cisplatin-based chemotherapy offers survival benefit and symptom relief for patients with inoperable NSCLC [5]. Combination chemotherapy is established as a standard therapy for extensive stage small cell lung cancer (SCLC) and the combination of chemotherapy with thoracic radiotherapy has also become a standard therapy for limited stage SCLC [6]. Thus, throughout the world a huge number of patients with lung cancer receive chemotherapy and/or thoracic radiotherapy.

Pneumonia and sepsis during neutropenia are common complications from chemotherapy and are sometimes lethal. Only a few reports have focused on the risk of treatment-related death in cases of inoperable lung cancer; those studies analysed patients with SCLC who were treated as a part of a clinical trial [7–9]. Radford and colleagues reported that 50 of 382 patients (13%) with SCLC developed severe or life-threatening sepsis and 20 patients (5%) died due to sepsis [8]. Stephens

* Corresponding author. Department of Medical Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel.: +81-3-3542-2511; fax: +81-3-3542-7006.
E-mail address: yohe@gan2.ncc.go.jp (Y. Ohe).

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and colleagues reported that 10% of patients with SCLC died within 3 weeks of the start of chemotherapy, and half of these may have been treatment related [9]. In these reports, poor performance status (PS), age >50 years, three-drug regimen, white blood cell count $\geqslant 10\times10^9$/l, hepatomegaly, higher alkaline phosphatase (Alp) and elevated blood urea (BUN) were listed as risk factors of treatment-related death in the treatment of SCLC [7–9]. Radiation pneumonitis is also a common toxicity after thoracic radiotherapy, and occasionally, it develops outside of the radiation field. Severe pneumonitis causes hypoxia and death. Several reports have proposed risk factors for radiation pneumonitis, but none have discussed the risk factors of treatment-related death from thoracic radiotherapy [10–13].

The incidence and risk factors of treatment-related death in the treatment of lung cancer using chemotherapy and/or thoracic radiotherapy are not well understood. Here, we analysed the incidence and risk factors of treatment-related death in the treatment of both SCLC and NSCLC including not only clinical trials, but also clinical practice-based treatments. In our hospital, approximately 50% of patients with lung cancer received chemotherapy and/or thoracic radiotherapy. It has been estimated that approximately 850 000 new cases are diagnosed each year worldwide [2]. If the same proportion of lung cancer patients worldwide, as in our hospital, receive chemotherapy and/or thoracic radiotherapy every year, it could be estimated that approximately 400 000 lung cancer patients receive chemotherapy and/or thoracic radiotherapy every year. Thus, if the incidence of treatment-related death could be reduced, even if it is only by 1% per year, 4000 patient deaths due to the toxicity of their treatment might be avoided. Thus, we believe that this study could provide useful information for lung cancer patients and for physicians who treat such patients.

2. Patients and methods

2.1. Patients

The National Cancer Center Hospital East (NCCHE) in Chiba, Japan was established in July 1992. Between July 1992 and December 1997, 1799 patients (adenocarcinoma: 1056, squamous cell carcinoma: 430, small cell carcinoma: 213, large cell carcinoma: 77, others: 23) were diagnosed as having lung cancer and 926 of the 1799 patients (51%) received chemotherapy and/or thoracic radiotherapy in the NCCHE. All patients who received treatment as their initial chemotherapy and/or initial thoracic radiotherapy were included in this analysis. All patients were followed for at least 4 weeks after the completion of treatment.

2.2. Treatments

Of the 926 patients receiving these treatments, 478 (52%), 142 (15%) and 306 (33%) patients received chemotherapy alone, thoracic radiotherapy alone and both chemotherapy and thoracic radiotherapy, respectively. In 372 of the 926 patients (40%), the treatments were given in the clinical trial setting. Most of the patients received cisplatin-based old generation chemotherapy such as cisplatin + vindesine + mitomycin C (cisplatin 80 mg/m^2 day 1, vindesine 3 mg/m^2 days 1 and 8, mitomycin C 8 mg/m^2 day 1), cisplatin + vindesine (cisplatin 80 mg/m^2 day 1, vindesine 3 mg/m^2 days 1 and 8), cisplatin + etoposide (cisplatin 80 mg/m^2 day 1, etoposide 100 mg/m^2 days 1–3) with or without minor modifications [14,15]. 85 patients received irinotecan; however, only 25, 16 and 9 patients received paclitaxel, vinorelbine and docetaxel, respectively.

Radiotherapy was given using megavoltage photons (6–10 MeV). Most of the patients received 2.0 Gy per fraction once a day or 1.5 Gy per fraction twice a day and the maximum total dose was 72.0 Gy. The primary tumour, ipsilateral hilar and mediastinal lymph nodes within at least a 2 cm margin were included in the radiation field in most of the patients. Supraclavicular nodes were included in the field when the primary tumour was located in an upper lobe and/or when supraclavicular node involvement was observed. No patients received radiotherapy with a field including contralateral hilum and more than half of the lung.

2.3. Selection of the treatment

Clinical trial enrolment was considered for all patients. However, if there was no appropriate ongoing clinical trials to enter, or if the patient refused to enter the clinical trial, the treatment was determined by each physician. In most cases, the combination of cisplatin + vindesine + mitomycin C was chosen for NSCLC and the combination of cisplatin + etoposide for SCLC.

2.4. Definition of treatment-related death

We defined treatment-related death as all deaths within 4 weeks after the completion of treatment without clear evidence of other causes, and all deaths due to obvious toxicity of the treatment. In cases where it was difficult to decide whether it was treatment-related or not related to the treatment, the patients were included in the treatment-related death group.

2.5. Statistical analysis

We investigated the associations between chemotherapy-related and thoracic radiotherapy-related treatment-related death, and the potential risk factors at the

time of diagnosis. Potential risk factors investigated were as follows; Eastern Cooperative Oncology Group PS (0, 1, 2, 3, 4), age (continuous variable), sex, stage (I–III versus IV or I–II versus III–IV), histology (small cell versus non-small cell), coincidental disease (with versus without pulmonary fibrosis: with versus without pulmonary emphysema), smoking history (with versus without smoking history), treatment according to clinical trial protocol (treatment given in clinical trial setting versus in practice), regimens of chemotherapy (with versus without cisplatin + vindesine + mitomycin C, cisplatin + vindesine, cisplatin + etoposide, irinotecan including chemotherapy or cisplatin + irinotecan, cisplatin + vincristine + doxorubicin + etoposide (CODE) regimen [16,17]), concurrent chemoradiotherapy (CT with concurrent TRT versus CT without concurrent TRT), HBV (hepatitis B surface antigen positive versus negative), HCV (hepatitis C antibody positive versus negative), pO_2 (partial pressure of oxygen <70 torr versus $\geqslant 70$ torr), WBC (white blood cell count $<8.5\times10^9$/l versus $\geqslant 8.5\times10^9$/l), haemoglobin (haemoglobin <120 g/l versus $\geqslant 120$ g/l), platelet (platelet count $>360\times10^9$/l versus $\leqslant 360\times10^9$/l), albumin (albumin <35 g/l versus $\geqslant 35$ g/l), GOT (glutamic-oxaloacetic transaminase >35 IU/l versus $\leqslant 35$ IU/l), Alp (alkaline phosphatase >249 IU/l versus $\leqslant 249$ IU/l), LDH (lactate dehydrogenase >474 IU/l versus $\leqslant 474$ IU/l), creatinine (creatinine >97 μmol/l versus $\leqslant 97$ μmol/l), Na (sodium <138 mmol/l versus $\geqslant 138$ mmol/l. In addition, total radiation dose (<50 Gy versus $\geqslant 50$ Gy), disease site (peripheral versus central, lower lobe versus other lobes) and combination with chemotherapy (with versus without chemotherapy) were evaluated as potential risk factors of treatment-related death from thoracic radiotherapy. The risk of having these potential risk factors were calculated and compared by Chi-squared test. To adjust for each factor, logistic regression analyses were also conducted. When analysing treatment-related death from chemotherapy, the factors of PS, age, clinical trial, small cell histology, the chemotherapy with cisplatin + vindesine + mitomycin C regimen, the chemotherapy with irinotecan and chemotherapy with CODE regimens were included in the model, and other factors such as sex, stage IV, pulmonary emphysema, pulmonary fibrosis, smoking history, HBsAg, HCV, pO_2, WBC, haemoglobin, platelet count, albumin, GOT, Alp, LDH, creatinine and Na levels were included in the model if P values were less than 0.15 in the preliminary analysis which included as many factors as possible. In the analysis of treatment-related death from thoracic radiotherapy, the factors of PS, age, clinical trial, small cell histology, chemotherapy with cisplatin + vindesine + mitomycin C regimen, chemotherapy with cisplatin + irinotecan, and cisplatin + etoposide regimen were included in the model and other factors such as sex, combination with chemotherapy, total radiation dose, stage I–II, pulmonary fibrosis, WBC, haemoglobin, albumin, GOT, LDH, creatinine were included in the model if the P values were less than 0.15 in the preliminary analysis, which included as many factors as possible. All the analyses were performed using the STATISTICA 4.1J™ program (StatSoftR, Inc., OK, USA).

Table 1
Patient characteristics

	CT *n* (%)	TRT *n* (%)	Total *n* (%)
Number of patients	784 (85)	448 (48)	926 (100)
Sex			
Male/female	588/196	366/82	707/219
Median age (range)	63 (22–83)	65 (36–85)	63 (22–85)
PS (ECOG)			
0	151 (19)	100 (22)	185 (20)
1	553 (71)	305 (68)	634 (68)
2	50 (6)	27 (6)	69 (7)
3	26 (3)	14 (3)	32 (3)
4	4 (1)	2 (0.4)	6 (1)
Histology			
Small cell lung cancer	202 (26)	101 (23)	205 (22)
Coincidental disease			
Pulmonary fibrosis	26 (3)	8 (2)	29 (3)
Pulmonary emphysema	27 (3)	23 (5)	36 (4)
Treatment modality			
CT alone	478 (61)	–	478 (52)
TRT alone	–	142 (32)	142 (15)
Both CT and TRT	306 (39)	306 (68)	306 (33)
Clinical trial			
Yes	372 (47)	152 (34)	372 (40)
CT regimen			
CDDP + VDS + MMC	301 (38)	77 (17)	301 (33)
CDDP + VDS	134 (17)	94 (21)	134 (14)
CDDP + ETOP	109 (14)	70 (16)	109 (12)
CODE	59 (8)	14 (3)	59 (6)
CDDP + CPT	35 (4)	11 (2)	35 (4)
PE/CPT	33 (4)	8 (2)	33 (4)
CBDCA + ETOP	17 (2)	7 (2)	17 (2)
CDDP + NVB + MMC	16 (2)	5 (1)	16 (2)
CPT + ETOP	16 (2)	3 (1)	16 (2)
PTX	15 (2)	3 (1)	15 (2)
CAV/PE	12 (2)	5 (1)	12 (1)
CDDP + PTX	10 (1)	3 (1)	10 (1)
DTX	4 (0.5)	1 (0.2)	4 (0.4)
CDDP + DTX	3 (0.4)	0	3 (0.3)
DTX + VDS	2 (0.3)	1 (0.2)	2 (0.2)
Others	18 (2)	4 (1)	18 (2)

CT, chemotherapy; TRT, thoracic radiotherapy; CDDP, cisplatin; VDS, vindesine; MMC, mitomycin C; ETOP, etoposide; CODE, cisplatin + vincristine + doxorubicin + etoposide (weekly); CPT, irinotecan; PE/CPT, cisplatin + etoposide + irinotecan (weekly); CBDCA, carboplatin; NVB, vinorelbine; PTX, paclitaxel; CAV/PE, cyclophosphamide + doxorubicin + vincristine/cisplatin + etoposide (alternating); DTX, docetaxel; ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Table 2
Causes and cumulative incidence of treatment-related death in chemotherapy and thoracic radiotherapy for lung cancer

	CT-related ($n=784$)	TRT-related ($n=448$)	Total ($n=926$)
Number of TRD	18	7	25
Cumulative incidence	2.3%	1.6%	2.7%
Sex			
Male/female	14/4	6/1	20/5
Median age (range)	63 (45–75)	68 (65–82)	66 (45–82)
Causes			
Pneumonia	10 (56%)	0	10 (40%)
Radiation pneumonitis	0	7 (100%)	7 (28%)
Sepsis	6 (33%)	0	6 (24%)
Perforation of the small intestine	1 (6%)	0	1 (4%)
Unknown	1 (6%)	0	1 (4%)

CT, chemotherapy; TRT, thoracic radiotherapy; TRD, treatment-related death.

3. Results

3.1. Patient characteristics

The patient characteristics before treatment are listed in Table 1. The median age of these patients (707 males and 219 females) was 63 years old and the range was 22–85 years old. Most of the patients had good PS, PS 2 or less, only 32 and 6 patients scored PS of 3 and 4, respectively. Of the 1799 patients, 213 had small cell histology and 205 patients with SCLC received chemotherapy and/or thoracic radiotherapy. Coincidental disease such as pulmonary fibrosis and pulmonary emphysema were diagnosed by plain chest X-ray films just before the treatment in all patients. Patients with fibrotic and emphysematous change detected only by computed tomography were not diagnosed as pulmonary fibrosis and pulmonary emphysema, respectively.

3.2. Cumulative incidence and causes of treatment-related death

The cumulative incidence and causes of treatment-related death are listed in Table 2. Of 926 patients, 25 (2.7%) died from toxicity of the initial chemotherapy and/or thoracic radiotherapy, 10 died from pneumonia, 7 from radiation pneumonitis, 6 from sepsis, 1 from perforation of the small intestine and 1 for an unknown reason. Another 16 patients died from disease progression within 4 weeks of the completion of treatment. Of the 16 patients 6 died from respiratory failure due to disease progression, 4 died from brain metastases, 2 died from heart failure due to pericarditis carcinomatous, 2 died from massive haemoptysis without thrombocytopenia, 1 died from hydronephrosis due to tumour invasion, 1 died from hypercalcaemia. The patients who died from massive haemoptysis had a moderately bloody sputum before the treatment. Thus, the cumulative incidence of treatment-related death and death within 4 weeks after the completion of the treatment was 4.4% (41/926). One patient who received combination chemotherapy consisting of cisplatin and irinotecan died from perforation of the small intestine. 18 of the 784 patients (2.3%) who received chemotherapy were considered to have died from a chemotherapy-related toxicity; 7 of 448 patients (1.6%) who received thoracic radiotherapy died from pneumonitis after thoracic radiotherapy, and 3 of 142 patients (2.1%) who received thoracic radiotherapy alone died from radiation pneumonitis.

3.3. Background differences in the patients receiving chemotherapy

The background of the patients varied in each chemotherapy regimen (Table 3). Most of the patients treated with cisplatin + vindesine regimen and chemotherapy with irinotecan had PS of 0 or 1. In contrast, 23 of 59 patients (38.9%) treated with the CODE regimen

Table 3
Background differences in patients receiving chemotherapy

	n	PS: 2-4	SCLC	Clinical trial	Stage IV
CDDP + VDS + MMC	301	9.9%	–	27.5%	51.1%
CDDP + VDS	134	1.4%	–	54.4%	13.4%
CT with CPT	85	1.1%	18.8%	87.0%	74.1%
CDDP + ETOP	109	11.9%	91.7%	41.2%	24.7%
CODE	59	38.9%	96.6%	27.1%	81.3%
Others	96	11.4%	30.2%	84.3%	66.6%
P value		$P<0.001$	$P<0.001$	$P<0.001$	$P<0.001$
Total	784	10.2%	25.8%	47.4%	47.7%

P values were calculated using Chi-squared test. SCLC, small cell lung cancer; CT, chemotherapy; CDDP, cisplatin; VDS, vindesine; MMC, mitomycin C; ETOP, etoposide; CODE, cisplatin + vincristine + doxorubicin + etoposide (weekly); CPT, irinotecan; PS, performance status.

Table 4
Risk factors for treatment-related death from chemotherapy ($n = 784$)

			Univariate analysis		Multivariate analysis	
	n (%)	Cumulative incidence (%)	RR (95% CI)	*P* values	RR (95% CI)	*P* values
PS (ECOG)						
0	151 (19)	0.7	Reference	0.004	1.95[a] (1.05–3.65)	0.034
1	553 (71)	2.2	3.27 (1.79–5.96)			
2	50 (6)	4.0	6.04 (2.43–14.9)			
3	26 (3)	7.7	11.6 (3.36–40.0)			
4	4 (1)	25	37.8 (6.03–236)			
Sex						
Male	588 (75)	2.3	1.16 (0.38–3.49)	0.783		
Female	196 (25)	2.0	Reference			
Age (years)						
⩾70	156 (20)	2.5	1.15 (0.38–3.44)	0.802	1.00[a] (0.95–1.05)	0.891
<70	628 (80)	2.2	Reference			
Stage						
I–III	410 (52)	1.2	Reference			
IV	374 (48)	3.4	2.85 (1.07–7.55)	0.035		
Histology						
NSCLC	582 (74)	1.8	Reference		Reference	
SCLC	202 (26)	3.4	1.83 (0.72–4.61)	0.197	3.25 (0.51–20.6)	0.210
Smoking history						
Yes	648 (83)	2.6	3.51 (0.54–22.7)	0.187		
No	134 (17)	0.7	Reference			
Unknown	2 (0.3)	–	–			
Fibrosis						
Yes	26 (3)	3.8	1.71 (0.23–12.2)	0.591		
No	758 (97)	2.2	Reference			
Emphysema						
Yes	27 (3)	7.4	3.50 (0.89–13.6)	0.071	3.44 (0.64–18.3)	0.147
No	757 (97)	2.1	Reference		Reference	
Clinical trial						
Yes	372 (47)	1.6	0.55 (0.21–1.43)	0.225	1.01 (0.30–3.41)	0.978
No	412 (53)	2.9	Reference		Reference	
CT Regimen						
CDDP + VDS + MMC	301 (38)	2.9	1.60 (0.64–3.96)	0.305	9.36 (1.29–68.0)	0.027
CDDP + VDS	134 (17)	–	0.0			
CDDP + ETOP	109 (14)	2.7	1.23 (0.36–4.20)	0.731		
CT with CPT	85 (11)	2.3	1.02 (0.24–4.39)	0.970	6.00 (0.76–47.2)	0.089
CODE	59 (8)	6.7	3.51 (1.25–9.82)	0.016	3.45 (0.64–18.6)	0.149
Concurrent chemoradiotherapy						
Yes	137 (17)	–	0.0	0.048		
No	647 (83)	2.7	Reference			
HBsAg						
Positive	10 (1)	10.0	4.52 (0.73–27.8)	0.103		
Negative	770 (98)	2.2	Reference			
Unknown	4 (1)	–	–			
HCV-Ab						
Positive	54 (7)	3.7	1.68 (0.39–7.06)	0.478		
Negative	726 (93)	2.2	Reference			
Unknown	4 (1)	–	–			
pO_2						
<70 torr	115 (15)	3.4	1.64 (0.55–4.86)	0.371		
⩾70 torr	661 (84)	2.1	Reference			
Unknown	8 (1)	–	–			

(continued)

Table 4 (*continued*)

			Univariate analysis		Multivariate analysis	
	n (%)	Cumulative incidence (%)	RR (95% CI)	*P* values	RR (95% CI)	*P* values
WBC						
$\geqslant 8.5\times10^9$/l	192 (24)	3.6	1.96 (0.78–4.91)	0.150		
$< 8.5\times10^9$/l	592 (76)	1.8	Reference			
Haemoglobin						
< 120 g/l	178 (23)	0	0.0	0.020		
⩾120 g/l	606 (77)	2.9	Reference			
Platelet count						
$> 360\times10^9$/l	138 (18)	3.6	1.80 (0.65–4.91)	0.251		
$\leqslant 360\times10^9$/l	646 (82)	2.0	Reference			
Albumin						
< 35 g/l	145 (18)	3.4	1.69 (0.61–4.64)	0.304		
⩾35 g/l	639 (82)	2.0	Reference			
GOT						
> 35 IU/l	91 (12)	5.4	2.92 (1.10–7.74)	0.030	2.65 (0.80–8.76)	0.109
⩽35 IU/l	693 (88)	1.8	Reference		Reference	
Alp						
> 249 IU/l	189 (24)	1.5	0.62 (0.18–2.12)	0.455	0.35 (0.09–1.37)	0.133
⩽249 IU/l	595 (76)	2.5	Reference		Reference	
LDH						
> 474 IU/l	208 (27)	3.3	1.76 (0.69–4.44)	0.229		
⩽474 IU/l	576 (73)	1.9	Reference			
Creatinine						
> 97 μmol/l	12 (2)	8.3	3.78 (0.59–24.1)	0.159		
⩽97 μmol/l	772 (98)	2.2	Reference			
Na						
< 138 mmol/l	249 (32)	2.0	0.82 (0.29–2.28)	0.713		
⩾138 mmol/l	535 (68)	2.4	Reference			

Relative risk (RR) in each chemotherapy regimen is obtained from the comparison between the incidence of treatment-related death in patients treated with and without the regimen. Variables for the multivariate analysis were selected as described in the statistical analysis section. CT, chemotherapy; CDDP, cisplatin; VDS, vindesine; MMC, mitomycin C; ETOP, etoposide; CODE, cisplatin + vincristine + doxorubicin + etoposide (weekly); CPT, irinotecan; CI, confidence interval; PS, performance status; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; HBsAg, hepatitis B surface antigen; HCV-Ab, hepatitis C antibody; PO_2, partial pressure of oxygen; WBC, white blood cell; GOT, glutamic oxaloacetic transaminase; Alp, alkaline phosphatase; LDH, lactate dehydrogenase.

[a] Continuous variable.

had a PS of 2 or worse. No patients with SCLC received cisplatin + vindesine + mitomycin C or the cisplatin + vindesine regimen whereas most of the patients treated with cisplatin + etoposide or the CODE regimen had small cell histology. The proportion of patients treated in clinical trials was significantly smaller in the groups treated with cisplatin + vindesine + mitomycin C (27.5%) or the CODE regimens (27.1%), however, 74 of 85 patients (87.0%) received chemotherapy with irinotecan in clinical trials. Only 13.4% and 24.7% of patients treated with the cisplatin + vindesine regimen and the cisplatin + etoposide regimen were stage IV patients, respectively. In contrast, 74.1% and 81.3% of patients treated with irinotecan including chemotherapy and the CODE regimen respectively were stage IV patients.

3.4. Univariate and multivariate analyses of risk factors for treatment-related death from chemotherapy

The results of univariate and multivariate analyses are listed in Table 4. The cumulative incidence of treatment-related death from chemotherapy in patients with PS 0, 1, 2, 3 and 4 was 0.7%, 2.2%, 4.0%, 7.7% and 25%, respectively. The cumulative incidence of treatment-related death from chemotherapy was closely associated with PS ($P = 0.004$). Stage IV (relative risk (RR): 2.85, 95% confidence interval (95% CI): 1.07–7.55, $P = 0.035$) and elevated GOT (RR: 2.92, 1.10–7.74, $P = 0.030$) were also significant risk factors of treatment-related death from chemotherapy in the univariate analyses. 9 of 301 patients (3.0%) died from toxicity of the cisplatin + vindesine + mitomycin C regimen [14]. In contrast,

Table 5
Risk factors for treatment-related death from thoracic radiotherapy ($n=448$)

			Univariate analysis		Multivariate analysis	
	n (%)	Cumulative incidence (%)	RR (95% CI)	*P* values	RR (95% CI)	*P* values
PS (ECOG)						
0	100 (22)	4.0	Reference	0.010	0.35[a] (0.09–1.36)	0.133
1	305 (68)	0.3	0.08 (0.02–0.31)			
2	27 (6)	7.4	1.85 (1.32–2.58)			
3	14 (3)	–	0.0			
4	2 (0.4)	–	0.0			
Sex						
Male	366 (82)	1.6	1.34 (0.16–10.8)	0.781		
Female	82 (18)	1.2	Reference			
Age (years)						
⩾65	243 (54)	2.8	–	0.014	1.17[a] (1.002–1.37)	0.047
<65	205 (46)	–	Reference			
Stage						
I–II	71 (16)	1.4	0.88 (0.10–7.21)	0.909		
III–IV	377 (84)	1.5	Reference			
Disease site[b]						
Peripheral	345 (77)	2.0	–	0.145		
Central	103 (23)	–	Reference			
Lower lobe	131 (29)	2.2	1.79 (0.41–7.77)	0.432		
Other lobe	314 (70)	1.2	Reference			
Histology						
NSCLC	347 (77)	1.7	Reference		Reference	
SCLC	101 (23)	0.9	0.57 (0.07–4.55)	0.598	0.06 (0.0002–13.2)	0.307
Smoking history						
Yes	405 (90)	1.7	–	0.396		
No	41 (9)	–	Reference			
Unknown	2 (0.4)					
Fibrosis						
Yes	8 (2)	25	22.0 (7.15–67.6)	<0.001	165.7 (8.79–3122)	<0.001
No	440 (98)	1.1	Reference		Reference	
Emphysema						
Yes	23 (5)	–	0.0	0.535		
No	425 (95)	1.6	Reference			
Clinical trial						
Yes	152 (34)	0.6	0.32 (0.04–2.38)	0.268	0.35 (0.02–4.87)	0.441
No	296 (66)	2.0	Reference		Reference	
Chemotherapy						
Yes	306 (68)	1.3	0.61 (0.14–2.69)	0.522		
No	142 (32)	2.1	Reference			
CT regimen						
CDDP + VDS + MMC	77 (17)	2.5	1.92 (0.38–9.52)	0.421	4.25 (0.31–58.2)	0.278
CDDP + VDS	94 (21)	–	0.0			
CDDP + ETOP	70 (16)	1.4	1.08 (0.23–5.00)	0.921	10.6 (0.03–2885)	0.407
CDDP + CPT	11 (2)	9.1	6.62 (1.07–40.7)	0.041	120.5 (2.90–4993)	0.012
CODE	14 (3)	–	0.0			
RT dose						
⩾50 Gy	342 (76)	1.1	0.41 (0.09–1.74)	0.228		
<50 Gy	106 (24)	2.8	Reference			
HBsAg						
Positive	6 (1)	–	0.0	0.755		
Negative	439 (98)	1.5	Reference			
Unknown	3 (1)	–	–			

(continued)

Table 5 (*continued*)

			Univariate analysis		Multivariate analysis	
	No. (%)	Cumulative incidence (%)	RR (95% CI)	*P* values	RR (95% CI)	*P* values
HCV-Ab						
Positive	31 (7)	–	0.0	0.465		
Negative	414 (92)	1.6	Reference			
Unknown	3 (1)	–	–			
pO_2						
< 70 torr	61 (14)	–	0.0	0.286		
⩾70 torr	382 (85)	1.8	Reference			
Unknown	5 (1)	–	–			
WBC						
$\geqslant 8.5\times10^9$/l	110 (25)	1.8	1.22 (0.24–6.23)	0.803		
$< 8.5\times10^9$/l	338 (75)	1.4	Reference			
Haemoglobin						
< 120 g/l	123 (27)	0.8	0.44 (0.05–3.39)	0.431		
⩾120 g/l	325 (73)	1.8	Reference			
Platelet count						
$> 360\times10^9$/l	66 (15)	–	0.0	0.267		
$\leqslant 360\times10^9$/l	382 (85)	1.8	Reference			
Albumin						
< 35 g/l	83 (19)	1.2	0.73 (0.09–5.93)	0.771		
⩾35 g/l	365 (81)	1.6	Reference			
GOT						
> 35 IU/l	48 (11)	2.0	1.38 (0.17–11.2)	0.758		
⩽35 IU/l	400 (89)	1.5	Reference			
Alp						
> 249 IU/l	95 (21)	–	0.0	0.166		
⩽249 IU/l	353 (79)	1.9	Reference			
LDH						
> 474 IU/l	73 (16)	2.7	2.05 (0.41–10.0)	0.375	10.4 (1.20–90.2)	0.033
⩾474 IU/l	375 (84)	1.3	Reference		Reference	
Creatinine						
> 97 μmol/l	15 (3)	6.6	4.81 (0.72–32.1)	0.105		
⩽97 μmol/l	433 (97)	1.3	Reference			
Na						
< 138 mmol/l	133 (30)	–	0.0	0.083		
⩾138 mmol/l	315 (70)	2.2	Reference			

Relative risk (RR) in each chemotherapy regimen is obtained from comparison between the incidence of treatment-related death in patients treated with and without the regimen. Variables for the multivariate analysis were selected as described in the statistical analysis section. CDDP, cisplatin; VDS, vindesine; MMC, mitomycin C; ETOP, etoposide; CODE, cisplatin + vincristine + doxorubicin + etoposide (weekly); CPT, irinotecan; RT, radiotherapy. For other abbreviations see Table 4.

[a] Continuous variable.

[b] There is more than one disease site in some patients.

none of the 134 patients treated with cisplatin + vindesine regimen died of toxicity [14]. 3 of 109 patients (3%) after receiving the cisplatin + etoposide regimen [15], 4 of 59 patients (7%) after receiving the CODE regimen [16–18], 1 of 35 patients (3%) after receiving the cisplatin + irinotecan regimen [19] and 1 of 16 patients (6%) after receiving irinotecan + etoposide regimen [20,21] died from toxicity following the chemotherapy. Chemotherapy with the CODE regimen was significantly associated with treatment-related death from chemotherapy in the univariate analysis (RR: 3.51, 95% CI: 1.25–9.82, $P = 0.016$). Poor PS (RR: 1.95, 95% CI: 1.05–3.65, $P = 0.034$) and the cisplatin + vindesine + mitomycin C regimen (RR: 9.36, 95%CI: 1.29–68.0, $P = 0.027$) were also significantly associated with treatment-related death from chemotherapy in the multivariate analysis.

3.5. Univariate and multivariate analyses of risk factors for treatment-related death from thoracic radiotherapy

The results of the univariate and multivariate analyses are listed in Table 5. None of 23 patients with pulmonary emphysema, but 2 of 8 patients with pulmonary

fibrosis identified on plain chest X-ray film died from pneumonitis after the thoracic radiotherapy. PS and the cumulative incidence of treatment-related death from thoracic radiotherapy had no consistent correlation. Pulmonary fibrosis (RR: 22.0, 95% CI: 7.15–67.6, $P < 0.001$) and chemotherapy with the cisplatin + irinotecan regimen (RR: 6.62, 95% CI: 1.07–40.7, $P = 0.041$) were significantly associated with treatment-related death from thoracic radiotherapy in the univariate analyses. Pulmonary fibrosis (RR: 165.7, 95% CI: 8.79–3122, $P < 0.001$), chemotherapy with the cisplatin + irinotecan regimen (RR: 120.5, 95% CI: 2.90–4993, $P = 0.012$), advanced age (RR:1.17, 95% CI: 1.002–1.37, $P = 0.047$), and elevated LDH (RR: 10.4, 95% CI: 1.20–90.2, $P = 0.033$) were significantly associated with treatment-related death from thoracic radiotherapy in the multivariate analysis.

4. Discussion

Numerous patients with SCLC and NSCLC are receiving chemotherapy and/or thoracic radiotherapy throughout the world. However, only a few reports have focused on treatment-related death from chemotherapy and/or thoracic radiotherapy in the treatment of SCLC in the clinical trial setting [7–9]. No studies have focused on treatment-related death in the treatment of NSCLC or in the treatment of SCLC in clinical practice. Here, we demonstrated that poor PS and cisplatin + vindesine + mitomycin C regimen are risk factors of treatment-related death from chemotherapy; and pulmonary fibrosis, chemotherapy with cisplatin + irinotecan, advanced age and elevated LDH are risk factors of treatment-related death from thoracic radiotherapy. We believe that this information is very useful to reduce the treatment-related death from chemotherapy and/or thoracic radiotherapy in the treatment of lung cancer.

The cumulative incidence of treatment-related death from chemotherapy in patients with PS 0, 1, 2, 3 and 4 was 0.7%, 2.2%, 4.0%, 7.7% and 25%, respectively. The cumulative incidence of treatment-related death from chemotherapy was closely correlated with PS in both the univariate and multivariate analyses. This result was very easy to understand and identical to our clinical experience, but it has never been shown from clinical data in the literature. Unexpectedly, age was not associated with treatment-related death from chemotherapy in our analysis. In Japan, the cisplatin + vindesine + mitomycin C regimen is frequently administered to patients with NSCLC due to the relatively higher response rate, and a survival rate comparable with the cisplatin + vindesine regimen [14,22]. Surprisingly, none of 134 patients died from toxicity due to the cisplatin + vindesine regimen, but 9 of 301 patients died from toxicity following treatment with the cisplatin + vindesine + mitomycin C regimen. This evidence was somewhat dependent upon differences in patient characteristics. Most of the patients treated with the cisplatin + vindesine regimen had a good PS, PS 0 or 1 and only 18 of 134 patients were stage IV. However, multivariate analysis demonstrated that the cisplatin + vindesine + mitomycin C regimen was a significant risk factor for treatment-related death from chemotherapy. We also performed multivariate analysis using data from patients with PS 0 or 1 only in order to reduce findings due to confounding. In this analysis, only the cisplatin + vindesine + mitomycin C regimen was significantly associated with treatment-related death from chemotherapy (data not shown). However, we could not completely disregard the possibility that the adverse risk of the cisplatin + vindesine + mitomycin C regimen was dependent upon the disproportionate representation of patients treated with the regimen in this study. After the analysis, we withdrew the cisplatin + vindesine + mitomycin C regimen from practical use as a palliative chemotherapy for patients with NSCLC. One limitation of this study was that most of the patients had received old generation cisplatin-based chemotherapy such as cisplatin + vindesine + mitomycin C, cisplatin + vindesine and cisplatin + etoposide regimens. Not many patients had received the so-called new agents such as irinotecan, paclitaxel, docetaxel and vinorelbine. No patients received gemcitabine. Thus, continuation of the monitoring and further study are essential to reduce the incidence of treatment-related death from chemotherapy and/or thoracic radiotherapy. Of the 784 patients who received chemotherapy, 137 patients received concurrent chemoradiotherapy. None of the patients died from toxicity of chemotherapy, such as pneumonia or sepsis; 1 patient died from radiation pneumonitis. These findings seemed to be highly dependent upon the differences in patient backgrounds, because most patients who received concurrent chemoradiotherapy had a good PS. In this analysis, we could not find evidence suggesting that concurrent chemoradiotherapy more frequently causes treatment-related death than chemotherapy alone.

Total radiation dose, dose per fraction, accelerated radiation schedule, radiation site and the concurrent use of irinotecan were reported as risk factors for radiation pneumonitis [10–13]. However, no reports have stated the risk factors of treatment-related death from thoracic radiotherapy. In our analysis, pulmonary fibrosis, chemotherapy with cisplatin + irinotecan, advanced age and elevated LDH were risk factors for treatment-related death from thoracic radiotherapy. Total dose and radiation site were not significantly associated with treatment-related death from thoracic radiotherapy. The radiation dose per fraction and accelerated radiation schedule were not available in our database. We considered that the number of patients who died from

radiation pneumonitis was not sufficient to draw any conclusions. Thus, this analysis was preliminary, but the results do not contradict our clinical experience or the reported evidence [13]. Irinotecan is used for patients with both SCLC and NSCLC in Japan; the pulmonary toxicity of irinotecan used as a single agent is reported to be in the range of 1.3–13% in clinical trials [13]. Moreover, the combination of irinotecan and thoracic radiotherapy is reported to be a risk factor for radiation pneumonitis [13]. These data could support the results of our analysis. None of 23 patients with pulmonary emphysema, but 2 of 8 patients with pulmonary fibrosis died from pneumonitis after the thoracic radiotherapy. In both the univariate and multivariate analyses, pulmonary fibrosis identified on plain chest X-ray film was a very strong risk factor for treatment-related death from thoracic radiotherapy.

In conclusion, thoracic radiotherapy for patients with pulmonary fibrosis has a risk of treatment-related death which is comparable with that of chemotherapy for patients with a PS of 4. We considered that both are contraindications [23]. Furthermore, the administration of mitomycin C, in addition to cisplatin-based regimens, for patients with lung cancer should be considered carefully.

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