Pergamon

European Journal of Cancer, Vol. 34, No. 1, pp. 71–75, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)00377-8

Original Paper

Risk Factors of Pneumonitis Following Chemoradiotherapy for Lung Cancer

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The purpose of this retrospective study was to identify risk factors associated with development of pneumonitis following chemoradiotherapy (CRT). We examined 60 patients (pts) who received CRT from May 1993 to August 1995. Factors evaluated included total radiation dose, field-size, irradiated site, type of chemotherapy, pulmonary fibrosis and treatment schedule (concurrent versus sequential). There were 17 pts (28.3%) who had $\geq$ Grade 2 pulmonary toxicity. There was no significant relationship between total radiation dose, field-size $\geq 200\,cm^2$, pulmonary fibrosis or treatment schedule and risk of pneumonitis. In the sequential treatment group (22 pts), no relationship was noted between any factor and the risk of pneumonitis, while in the concurrent treatment group (38 pts), the incidence of pneumonitis was more frequent (53.8%) in patients with field-size $\geq 200\,cm^2$ than in patients with field-size $< 200\,cm^2$ ($P < 0.05$). In those who received concurrent treatment, including weekly CPT-11, pneumonitis was more frequent (56.3%) than in those without CPT-11 (13.6%, $P < 0.01$). When the lower lung field was included in the radiation site, the incidence of pneumonitis was 70% compared with 20% for other sites ($P < 0.01$). Multivariate analysis revealed a significant relationship between radiation site and the risk of pneumonitis ($P = 0.0096$). CPT-11 was significant ($P = 0.038$) only in the concurrent group. Pneumonitis was reversible in all but one pt by steroid therapy. Thus, irradiated site (included lower lung field) and concurrent CRT used with weekly CPT-11 were treatment factors significantly associated with a higher risk of pneumonitis following CRT. © **1998 Elsevier Science Ltd.**

Key words: lung cancer, chemotherapy, radiation therapy, pneumonitis, risk factor, irinotecan, multivariate analysis
Eur J Cancer, Vol. 34, No. 1, pp. 71–75, 1998

INTRODUCTION

RECENT STUDIES have demonstrated that combined multimodality therapy is associated with a survival advantage for patients with both locally advanced non-small-cell lung cancer (NSCLC) and limited-stage small-cell lung cancer (SCLC). Although the contribution of surgery to chemoradiotherapy in stage IIIa NSCLC must be evaluated in randomised trials, it is known that combined treatment with thoracic radiation therapy and cisplatin alone or cisplatin-based combination improves the survival of patients who have unresectable stage IIIa or IIIb NSCLC [1–3]. On average, median survival is increased by approximately 3 months, and 2- and 3-year survival rates are nearly doubled by these treatments. For limited-stage SCLC, meta-analyses have disclosed survival advantages when radiation therapy is added [4, 5]. Since some chemotherapeutic agents enhance the effects of radiation and also have intrinsic pulmonary toxicity, it is not surprising that a higher incidence of pulmonary toxicity has been observed among patients treated with chemoradiotherapy (CRT) rather than with radiation alone [6]. Prediction of the incidence and severity of potential complications such as radiation pneumonitis and drug-induced pneumonitis is important if patients are to be safely treated with CRT. In the present study, we retrospectively evaluated the various risk factors that could contribute to the occurrence of pneumonitis.

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Received 1 Apr. 1997; revised/accepted 25 Jul. 1997.

Table 1. *Patients' characteristics*

Characteristics	No. ($n = 60$)
Sex	
Male	50
Female	10
Age (year)	
Mean (range)	66.6 (43–86)
Histology	
Squamous cell carcinoma	22
Adenocarcinoma	27
Large-cell carcinoma	1
Small-cell carcinoma	10
Stage of disease	
I/II/IIIa/IIIb/IV	1/2/18/37/2
Treatment schedule	
Concurrent chemoradiation	38
Sequential chemoradiation	22
Chemotherapy regimen	
CPT-11	18
CVM	14
CBDCA	11
CBDCA + EP	4
CV	4
CIV	3
CPT-11 + CDDP	3
CPT-11 + EP	1
CDDP + EP	1
CAE	1

CPT-11, irinotecan; CVM, cisplatin, vindesine, mitomycin; C, CBDCA, carboplatin; EP, etoposide; CV, cisplatin, vindesine; CIV, cisplatin, ifosphamide, vindesine; CDDP, cisplatin; CAE, cyclophosphamide, doxorubicin, etoposide.

PATIENTS AND METHODS

Patients who had histologically or cytologically documented primary lung cancer and received CRT from May 1993 to August 1995 were retrospectively and consecutively evaluated. Patients who could not be followed for at least 6 months were excluded. However, those who had pneumonitis within 6 months of CRT were included. Patient characteristics are shown in Table 1. We evaluated 60 patients, whose ages ranged from 43 to 86 years (mean, 66.6 years), including 50 men and 10 women.

The risk factors of pneumonitis analysed in this study were chemoradiation schedule (concurrent versus sequential), radiation field-size, mean total radiation dose (given over 40 Gy), type of chemotherapy used and irradiated site. To evaluate the irradiated site, we divided the whole lung into 3×3 areas. In this manner, the right lung was divided into three equal areas from upper to lower lung field, as were the left lung and mediastinum.

Radiation therapy had been administered with 6- or 10 MV X-rays generated with a 20 MTX linear accelerator (Mitsubishi, Japan). The treatment fields included the primary tumour and regional lymph nodes with a 1.5 cm margin. Patients were treated using customised shaped blocks with parallel-opposed anterior and posterior fields. The incidence and severity of pneumonitis were noted using the modified pulmonary toxicity grading scale of the Radiation Therapy Oncology Group (RTOG) and European Organization for the Research and Treatment of Cancer (EORTC): grade 0 is no pneumonitis; grade 1 (mild) is assigned when radiographic appearance is present in the area of irradiation and the patient is asymptomatic or has only mild symptoms (dry cough); grade 2 (moderate) is assigned when the patient is moderately symptomatic (severe cough), has fever, the radiographic appearance is patchy and steroids are often required; grade 3 (severe) is assigned when the patient is severely symptomatic and dense radiographic changes are present; grade 4 (life-threatening) is assigned when assisted ventilation is required; and grade 5 is assigned when death directly related to radiation effects occurs. Patients with grades above 2 were considered to have clinically significant pneumonitis; therefore, in this study incidence of pneumonitis refers to that of patients with $\geq$ grade 2 pulmonary toxicity.

Variables were tested for any possible relationship with the probability of pneumonitis due to CRT, first by univariate analysis and subsequently by application of a multiple regression model. The univariate analysis was based on 2×2 tables, and differences were tested by χ^2 test. P values less than 0.05 were considered significant.

RESULTS

Table 2 lists pulmonary toxicity grades according to radiation treatment schedule, field-size, mean total radiation dose, and mean time to development of pneumonitis. There were 17 patients (28.3%) who had $\geq$ grade 2 pneumonitis. There

Table 2. *Distribution of pneumonitis by selected characteristics*

Variable	Pulmonary toxicity grade (No. of patients)						No. of patients with grade ≥ 2 (%)
	0	1	2	3	4	5	
Treatment schedule							
concurrent ($n = 38$)	7	19	6	4	1	1	12 (31.6)
sequential ($n = 22$)	2	15	2	3	0	0	5 (22.7)
Radiation field-size (cm^2)							
50–100 ($n = 6$)	0	4	1	1	0	0	2 (33.3)
100–150 ($n = 17$)	3	10	2	2	0	0	4 (23.5)
150–200 ($n = 19$)	4	12	1	2	0	0	3 (15.8)
200–300 ($n = 15$)	2	6	4	1	1	1	7 (46.7)
300–400 ($n = 1$)	0	1	0	0	0	0	0 (0)
400 $\leq$ ($n = 2$)	0	1	0	1	0	0	1 (50.0)
Mean total radiation dose (Gy)	50.8	55.1	52.5	54.9	60.0	58.0	
Mean time to pneumonitis (days) (range)		88.8 (12–342)	12.5 (0–36)	15.6 (0–47)	0	0	

was no significant relationship between mean total radiation dose and toxicity. The mean time to development of pneumonitis was 88.8 days for grade 1, 0–15.6 days for ≥ Grade 2. 2 patients had grade 4 or 5 pneumonitis which occurred during concurrent CRT. The rates of pneumonitis were 31.6% and 22.7%, respectively, in concurrent and sequential groups; this difference was not significant. Chest X-ray films revealed patchy shadows in all lung fields in three patients who had grade 3, 4 and 5 pneumonitis. The other patients who had ≥ grade 1 pneumonitis had fibrosis within the field of irradiation. The mean arterial oxygen tension (PaO_2) in patients with ≥ grade 2 pneumonitis decreased from 83.0 ± 10.1 mm Hg to 66.8 ± 9.3 mm Hg. There was no deterioration of PaO_2 in patients with grade 0 or 1 pneumonitis. After the occurrence of pneumonitis, pulmonary function tests were not done.

On univariate analysis, there was no relationship between histology, $\%DL_{CO}$, number of lymphocytes, sex or age and the incidence of pneumonitis (data not shown). Patients who had pulmonary fibrosis on plain chest X-ray films did not receive radiation therapy. One of 4 patients with fibrotic change, which was detected only by computed tomography, had pneumonitis and the risk of pneumonitis was no different whether patients had fibrotic change or not. Table 3 shows the incidence of pneumonitis for each of the nine irradiated sites. In the lower lung fields, the incidence of pneumonitis varied from 50.0% to 83.3%. Table 4 shows the results of the univariate analysis of risk factors. First we divided the field-size into < or ≥ 50, 100, 150, 200, 300 and 400 cm^2, respectively, and subsequently by univariate analysis for each cut-off point, we found that the field-size ≥ 200 cm^2 was associated with pneumonitis. Thus, we decided on this cut-off point. There was no significant association between a field size ≥ 200 cm^2 and pneumonitis for all patients ($P = 0.07$). When the lower lung field was included in the radiation site, the incidence of pneumonitis was 70% compared with 20% for other sites ($P < 0.01$). The mean field-size was larger when the lower lung field was included than when it was not included ($P = 0.05$). In the sequential group ($n = 22$), no relationship was found between any factor and the risk of pneumonitis, while in the concurrent group ($n = 38$), the incidence of pneumonitis was more frequent (53.8%) in patients with field-size ≥ 200 cm^2 than in patients with field-size < 200 cm^2 ($P < 0.05$). Patients in the concurrent group treated with weekly irinotecan (CPT-11) more frequently had pneumonitis (56.3%) than those without this treatment (13.6%, $P < 0.01$). Multivariate analysis revealed a significant relationship between irradiated site and weekly CPT-11 and the risk of pneumonitis ($P = 0.0096$ and $P = 0.038$) (Table 5). Pneumonitis was reversible in all patients but one by steroid therapy.

DISCUSSION

The combination of chemotherapy and radiotherapy is now the most promising strategy for locally advanced lung cancer. In this study, the risk of pneumonitis was higher in patients treated concurrently with radiation with field-size ≥ 200 cm^2 and in those treated concurrently with weekly CPT-11. Multivariate analysis revealed a significant relationship between the radiation site and risk of pneumonitis for all patients. It also revealed a significant relationship between weekly CPT-11 and risk of pneumonitis only for the concurrent group.

The diagnosis of radiation pneumonitis can be made clinically based on symptoms and typical chest radiographic appearance [7, 8]. Usually, there are infiltrates corresponding to the margins of the irradiated portal. In some cases, radiation pneumonitis develops outside the field of irradiation. In this study, 3 patients had patchy opacities throughout both lungs on chest films and severe hypoxemia. Radiotherapy sometimes causes a generalised lymphocyte-mediated hypersensitivity reaction [9, 10]. Also, it was difficult to distinguish radiation pneumonitis from drug-induced pneumonitis due to the combination therapy. Therefore, we have regarded both as types of pneumonitis. Generally, the incidence and degree of lung damage are related to radiation dose, the volume of lung irradiated and the rate of delivery of radiation [11–13]. The likelihood of significant clinical and roentgenographic disturbances is proportional to the volume of lung tissue irrradiated. For example, 3000 rad delivered in fractions to 25% of the lung volume rarely produces symptoms, whereas the same dose delivered in the same manner to the entire volume of both lungs very likely will produce a fatal reaction [14]. Roach and associates [15] reported that, in a multivariate analysis of 1911 assessable patients, the number of daily fractions and total dose were associated with risk of radiation pneumonitis. The use of fractions greater than 2.67 Gy was the most significant factor associated with an increased risk of pneumonitis. They evaluated neither field-size nor irradiated site. In our series, the 7/13 (54%) patients with a field-size ≥ 200 cm^2 developed ≥ grade 2 pneumonitis compared with 5/25 (20%) with a field-size < 200 cm^2 ($P > 0.05$). Hayakawa and associates [16] reported that patients

Table 3. Incidence of pneumonitis by irradiated site

	Irradiated site		
	Right (%)	Mediastinum (%)	Left (%)
Upper	7/32 (21.9)	16/57 (28.1)	1/11 (9.1)
Middle	12/44 (27.3)	17/58 (29.3)	4/18 (22.2)
Lower	5/6 (83.3)	6/12 (50.0)	2/4 (50.0)

Table 4. Univariate analysis of risk factor

	Pneumonitis (Grade ≧ 2)		
Risk factor	–	+	*P* value
Radiation field-size (cm^2) (in all patients)			NS
< 200	33	9	
≥ 200	10	8	
(in concurrent group)			< 0.05
< 200	20	5	
≥200	6	7	
Chemotherapy (in all patients)			NS
CTP-11 included	13	9	
CPT-11 not included	30	8	
(in concurrent group)			< 0.01
CPT-11 included	7	9	
CPT-11 not included	19	3	
Radiation site			< 0.01
Lower	3	7	
Middle, upper	40	10	
Pulmonary fibrosis			NS
None	40	16	
Mild	3	1	

Table 5. Multivariate analysis of risk factors (logistic regression method)

Factor	Poor risk	Good risk	Odds ratio	*P* value	95% confidence interval
All patients					
Field-size	$\geq 200\,cm^2$	$< 200\,cm^2$	1.39	0.3471	0.70–2.77
Radiation site	Lower	Middle, Upper	2.85	0.0096	1.29–6.30
Treatment schedule	Concurrent	Sequential	1.11	0.7564	0.56–2.20
Chemotherapy	CPT-11 included	CPT-11 not included	1.42	0.2999	0.73–2.74
Pulmonary fibrosis	None	Mild	0.95	0.9381	0.25–3.59
Concurrent treatment					
Field-size	$\geq 200\,cm^2$	$< 200\,cm^2$	1.51	0.3779	0.60–3.79
Radiation site	Lower	Middle, Upper	2.85	0.0640	0.94–8.64
Chemotherapy	CPT-11 included	CPT-11 not included	2.67	0.0380	1.06–6.73
Pulmonary fibrosis	None	Mild	1.34	0.7165	0.28–6.39

with epidermoid carcinoma of the lung with a radiation field-size of 100 cm^2 or less had a good prognosis. However, he did not report any association between field-size and pneumonitis, and did not give any justification for their cut-off point.

If the irradiated site included the lower field, the irradiated volume of lung tends to be larger. Microcapillary vascular damage occurs as a result of radiation exposure, producing ischaemic tissue injury that eventually results in fibrotic healing. In addition, damage to type I and II pneumocytes in the presence of increased vascular permeability results in altered surfactant production, atelectasis, reduced ventilation and secondary vascular atrophy [11, 17, 18]. Pulmonary fibrosis is due to radiation-induced local cytokine production, and radiation pneumonitis developing outside the field of irradiation is an immunologically mediated process resulting in a bilateral lymphocytic alveolitis [19]. It is apparent that the extent of radiation-induced pulmonary injury depends on the total dose, fractionation, treatment volume and chemotherapy administered. Martel and associates [20] found that analysis of three-dimensional dose distributions and dose–volume histograms yielding data were useful for characterisation of the dose–volume relationship and determination of the risk of development of pneumonitis. It is necessary to evaluate the relationship between irradiated lung volume and pneumonitis. One possible solution for reducing the risk of pneumonitis would be to use multiple, small, daily fractions of radiation which can facilitate the administration of higher doses [15]. In addition, three-dimensional treatment plans can be used to decrease the volume of normal lung irradiated.

CPT-11 is an active antitumour agent, results of which are very promising [21]. Dose-limiting factors including leucopenia, neutropenia and diarrhoea are prominent. Rarely, cases of interstitial pneumonitis have occurred with the use of CPT-11. Pulmonary toxicity in clinical trials of single-agent CPT-11 was observed in the range of 1.3% (data on file; Yakult, Tokyo, Japan) to 13% [22–25]. Studies of the combination of CPT-11 and chemotherapeutic agents or radiation are underway to determine which regimen possesses superior antineoplastic effects. Pulmonary toxicity has not been observed when CPT-11 is combined with radiation. We have already reported that of 26 patients treated with the combination of concurrent weekly CPT-11 and thoracic radiotherapy for unresectable locally advanced NSCLC, 3 (11.5%) had grade 3 pneumonitis [26]. *In vitro* and *in vivo* studies revealed synergistic effects of CPT-11 and radiation [27–30], suggesting that injury to normal pulmonary tissue was enhanced. In our study, of 22 patients treated with the combination of radiation and weekly CPT-11 (once weekly for 6 weeks), pneumonitis frequently occurred, especially when CPT-11 was given concurrently, although pneumonitis might be manageable using steroids. Further clinical trials are warranted to determine which scheduling effects and toxicities are observed when CPT-11 is combined with radiation.

Although our results suggest that radiation site and CPT-11 are variables strongly associated with pneumonitis, there were some problems associated with our retrospective analysis. First, various antitumour drugs were included, although cisplatin and CPT-11 were the main drugs used. Second, pulmonary toxicity is thought to occur as a result of both direct damage and an immunologically mediated pathway. The development of pneumonitis may depend on many individual factors such as genetic susceptibility and underlying degree of pulmonary dysfunction. The heterogeneity of the patient population make this retrospective analysis difficult to interpret. Further prospective studies with more patients may clarify these results. However, it is possible that the use of three-dimensional treatment planning technology and appropriate combination with CRT will permit reduction of the volume of lung irradiated, resulting in reduction of the risk of pneumonitis.

We conclude that the irradiated site (including lower lung field) and concurrent CRT used with weekly CPT-11 are treatment factors significantly associated with a higher risk of pneumonitis.

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