Clarification of clinical features of interstitial lung disease induced by irinotecan based on postmarketing surveillance data and spontaneous reports

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Irinotecan-induced interstitial lung disease (ILD) requires accurate diagnosis, followed by prompt and appropriate treatment. This study was conducted to compile information and imaging data to define the characteristics of irinotecan-induced ILD. Searches were performed on information collected for a drug reexamination application and on data from spontaneous safety reports submitted to Daiichi Sankyo Company, Limited. These database searches revealed 153 cases of serious ILD that occurred in association with irinotecan therapy, and which were reported as adverse drug reactions. Computed tomographic findings obtained after the onset of ILD were categorized based on four typical patterns. A total of 66 patients (including 15 for whom a relationship between death and serious ILD could not be excluded; incidence of serious ILD: 0.74%; death rate of ILD: 0.17%) were detected during the postmarketing surveillance along with 87 patients (22 deaths) that were identified from spontaneous reports. Within 16 weeks of starting treatment, 80.7% of the patients developed ILD. A total of 61.3% of the cases treated using steroids responded to the steroid therapy. These results indicate that there is no specific clinical or imaging feature associated with ILD related to irinotecan and that the prognosis of ILD related to irinotecan was poor in patients with preexisting ILD. The relative risk calculated for the association between preexisting ILD and death was 2.25 ($P=0.29$). During irinotecan treatments, patients need to be carefully observed for symptoms, especially at 16 weeks after starting treatment. In addition, when patients are receiving this type of therapy, they also need to undergo chest imaging studies. *Anti-Cancer Drugs* 22:563–568 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Interstitial lung disease (ILD) is one of the typical adverse drug reactions (ADRs) seen with the use of anticancer agents and is a serious event that must be taken into consideration by physicians at all times. In recent years, problems associated with pulmonary disorders induced by anticancer agents, especially ILD, have led to the publication of many studies that have examined the mechanisms involved, ethnic differences associated with the incidence, and the risk/prognostic factors. This information has helped to improve our understanding of ILD caused by anticancer therapy.

During treatment with Topotecin (irinotecan), ILD has been shown to have a lower incidence (approximately 1%, regardless of the seriousness according to postmarketing surveillance) than either diarrhea or myelosuppression, although it can progress to respiratory failure and have a fatal outcome in some cases. Thus, ILD is considered to be a severe irinotecan-caused ADR [1–3]. Irinotecan-induced ILD, similar to that induced by other anticancer agents such as gefitinib and gemcitabine, requires accurate diagnosis, followed by prompt and appropriate treatment.

Anticancer drugs can cause pulmonary damage that manifests as a diffuse change of the lung fields. This can be detected by imaging studies, provided the patient is suspected of having ILD. Accordingly, a high index of suspicion, based on the risk factors for each drug or patient, is important for early detection and treatment of this ADR.

Marketing of irinotecan in Japan was approved in 1994 and this drug has been used to treat an estimated 200 000 patients as of May 2008. With the help of attending physicians, this study was designed to collect and compile clinical information and imaging data for use in helping to define the characteristics of irinotecan-induced ILD.

This study was conducted under the Pharmaceutical Affairs Act, Good Post-Marketing Surveillance Practice, and Good Vigilance Practice in Japan.

Authors' contributions: Akihiko Gemma and Noritoshi Yoshii adjudicated imaging findings. Noritoshi Yoshii, Koji Kakihata, and Tadamichi Suzuki conceived the analysis. Masaki Nagashima performed the analysis. All authors discussed the results and commented on the manuscript.

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Methods

Data collection

The participants of this study were patients who had serious ILD that occurred during or after treatment with irinotecan and were reported to Daiichi Sankyo Company, Limited, during the survey period (from the release of irinotecan up to May 2008).

The data used in this study were originally collected for the drug reexamination application and from spontaneous adverse reaction reports that specifically focused on cases with ILD during the postmarketing surveillance.

The original postmarketing surveillance was only conducted in Japan and covered the period from April 1994 (after approval of this product in Japan) until January 2000. All 8864 patients administered Topotecin (irinotecan) were enrolled in this postmarketing surveillance study.

ILD patient data and information were also collected from spontaneous reports submitted to Daiichi Sankyo Company, Limited, between January 2000 (after completion of the postmarketing surveillance) and May 2008. Specific case data were retrieved from these reports by using 'ILD' and 'pneumonitis' as the search terms (preferred terms).

Out of the initially identified cases, those patients having ILD for which the reporting physician could not exclude a causal relationship to irinotecan were regarded as having ILD induced by irinotecan. A total of 153 cases of serious ILD were associated with irinotecan therapy and reported as ADRs.

For each of the patients, sex, age, and type of cancer were collected. In addition, the interval (number of days) from the initiation of treatment with irinotecan to the onset of ILD was also determined, as well as the response to steroid therapy.

Evaluation of clinical information and imaging findings

Between September 2006 and 2008, respiratory physicians (A.G., N.Y.) reviewed chest imaging data collected from 31 of 153 patients at the onset of ILD. The information and images were evaluated to adjudicate whether features of ILD were associated with irinotecan. If pretreatment images were available, these were used to assess the presence or absence of preexisting ILD.

Clinical information and images were then assessed to confirm the validity of the ILD diagnosis, with patients classified into three categories: (i) patients in whom the diagnosis was judged to be valid; (ii) patients in whom the diagnosis could not be confirmed or excluded on the basis of the available images; and (iii) patients in whom the available images suggested a high likelihood of some other disease. In addition, we also evaluated patients who received steroid therapy for their ILD to assess the response to such therapy on the basis of posttreatment imaging findings.

Classification of the imaging patterns

Computed tomographic (CT) findings obtained after the onset of ILD can be categorized into the following four patterns [4,5]:

(1) Hypersensitivity pneumonia (HP) pattern: mild ground-glass changes in the bilateral lung fields, without shrinkage of the lung parenchyma or traction bronchiectasis.
(2) Organizing pneumonia (OP) pattern: infiltrative changes that are more prominent in the peripheral lung fields.
(3) Diffuse alveolar damage (DAD) pattern: bilateral patchy or diffuse infiltrative ground-glass changes, which are accompanied by structural abnormalities such as traction bronchiectasis.
(4) Nonspecific interstitial pneumonia (NSIP) pattern: patterns that do not correspond to categories 1 through 3.

Statistical analysis

The relative risk was examined by analyzing the correlation between the presence of preexisting ILD and a fatal outcome. Data were analyzed using the two-sided Fisher's exact test.

Irinotecan dosage and number of patients treated

The average dose of irinotecan administered during the postmarketing surveillance was 0.9357 g per patient. The average dose of irinotecan and the shipping volume were used to calculate the number of patients treated after the postmarketing surveillance.

Results

Clinical features of interstitial lung disease

Table 1 presents the clinical profiles of 153 patients included in this analysis. A relationship between the patient's death and ILD could not be excluded in a total of 37 cases.

With regard to the source of ADR information, to date, 66 patients [including 15 for whom a relationship between death and serious ILD could not be excluded; incidence of serious ILD: 0.74% (66 of 8864); death rate: 0.17% (15 of 8864)] have been detected as serious ILD during the postmarketing surveillance (from 1994 to 2000) and 87 patients (22 deaths) have been identified as serious ILD from spontaneous reports received after completion of the postmarketing surveillance. ILD was predominantly found in male patients (80.3%) and in patients aged 65 years or older (64.1%), with similar tendencies seen among the fatal cases.

The most common types of cancer observed were non-small cell lung cancer (26.8%), colorectal cancer (24.8%), and small cell lung cancer (24.8%). There was no association between the type of cancer and the death rate from ILD.

Table 1 Summary of patients with interstitial lung disease induced by irinotecan

	Number of patients (deaths)	Percentage (death)[a]
Sex		
Male	122 (31)	80.3 (86.1)
Female	30 (5)	19.7 (13.9)
Unknown	1 (1)	–
Age (years)	Number of patients	Percentage
<65	55 (15)	35.9 (40.5)
≥ 65	98 (22)	64.1 (59.5)
Type of cancer	Number of patients	Percentage
Non-small cell lung cancer	41 (10)	26.8 (27.0)
Colorectal cancer	38 (10)	24.8 (27.0)
Small cell lung cancer	38 (6)	24.8 (16.2)
Gastric cancer	13 (6)	8.5 (16.2)
Ovarian cancer	8 (3)	5.2 (8.1)
Lung cancer (unspecified)	7 (0)	4.6 (0)
Malignant pleural mesothelioma	2 (1)	1.3 (2.7)
Other	6 (1)	3.9 (2.7)
Time until onset (weeks)	Number of patients	Percentage[b]
≤ 2	9 (4)	10.8 (20.0)
2–4	14 (3)	16.9 (15.0)
4–8	25 (7)	30.1 (35.0)
8–16	19 (1)	22.9 (5.0)
≥16	16 (5)	19.3 (25.0)
Unknown	70 (17)	–
Anterior chemotherapy drugs	Number of patients[c]	Percentage
Platinum-containing	29	40.8
Fluoropyrimidines	23	32.4
Taxanes	6	8.5
Others or none	24	33.8
Concomitant drugs	Number of patients[d]	Percentage
Platinum-containing	40	46.5
Fluoropyrimidines	20	23.3
Taxanes	5	5.8
Others or none	13	15.1
Response to steroid therapy	Number of patients[e]	Percentage
Recovered/improved	46	61.3
Not recovered	5	6.7
Fatal	22	29.3
Unknown	2	2.7

[a]Percentage of the total number of patients analyzed ($N=153$) [percentage of the total number of deaths ($n=37$)].
[b]Percentage of the total number of patients with available data ($N=83$) [percentage of the total number of deaths with data ($n=20$)].
[c]Patients confirmed to be on anterior chemotherapy drugs ($n=71$).
[d]Patients confirmed to be on concomitant drugs ($n=86$).
[e]Patients receiving steroid therapy ($n=75$).

When the intervals between the treatment initiation and the onset of ILD were examined in the 83 patients identified from the spontaneous reports and whose clinical courses could be followed, there were 57.8% of patients who developed ILD within 8 weeks and 80.7% patients who developed ILD within 16 weeks (median: 54 days; range: 2–673 days) of starting treatments.

In 71 patients in whom the anterior chemotherapy drugs could be identified and confirmed from the spontaneous reports, 40.8, 32.4, and 8.5% were administered platinum-containing drugs, fluoropyrimidines, and taxanes, respectively. In 86 patients identified from spontaneous reports for concomitant drugs, 46.5, 23.3, and 5.8% were administered platinum-containing drugs, fluoropyrimidines, and taxanes, respectively. With regard to steroid therapy, 61.3% of 75 patients in whom the outcome of the therapy could be assessed showed a response to the steroids.

Imaging findings

Imaging information was examined in 31 patients for whom chest X-ray films or chest CT scans were available. Among these patients, 27 cases (including nine who died) had imaging evidence of ILD or pulmonary changes for which an association with irinotecan could not be excluded.

The diagnosis of ILD was judged to be unlikely in four of these 31 patients. Other possible diagnoses included infection (pneumonia), cardiogenic pulmonary edema, and lymphangitis carcinomatosis. In six other patients, ILD diagnosis was difficult to confirm based on the images provided. Of the 27 patients reported to have ADRs, five (including three deaths) had preexisting ILD at the initiation of the irinotecan treatment.

Table 2 shows the details of 18 patients in whom the images were of sufficient quality to assess the pattern of their lung disease. An HP pattern was found in seven patients, a DAD pattern in six patients, an OP pattern in three patients, an NSIP pattern in one patient, and a combination of the HP and OP patterns in one patient.

Among the 15 patients that received steroid therapy, all of the four nonresponders showed a DAD pattern of pulmonary involvement. Spontaneous improvement of the ILD without steroid therapy was noted in one patient who had an HP pattern. Serum KL-6 levels were measured at the onset of ILD in five patients, including in three patients with HP pattern (418, 449, and 597 IU/l), and in one patient with DAD pattern (3272 IU/l) and one patient with NSIP (3250 IU/l). The median interval from the initiation of irinotecan treatment to the onset of ILD was 47 days in the patients with the HP pattern and 25 days in those with the DAD pattern. Chest CT scans obtained in patient no. 5 (DAD pattern) and patient no. 6 (HP pattern) are shown in Figs 1 and 2, respectively.

In 20 of the 31 patients, it was possible to investigate each of the cases for the presence of a preexisting ILD. When the relative risk of a fatal outcome was compared between five patients with and 15 patients without preexisting ILD, the relative risk ratio was 2.25 ($P=0.29$).

Discussion

When using any anticancer drug, it is essential that we know the clinical features and incidence of relevant lung disorders [6]. As the first reports that gefitinib induced acute ILD, our understanding of how ILD is induced by molecular-targeting anticancer agents has continued to grow [7–11]. However, there have been few reports that focused on the occurrence of ILD due to cytotoxic agents such as irinotecan, and thus, the mechanism of this disease remains relatively unclear [5,6,12].

When compared with previous reports regarding other anticancer drugs, the incidence of ILD noted during this postmarketing surveillance was not particularly high

Table 2 Summary of 18 patients in whom the pattern of interstitial lung disease could be determined

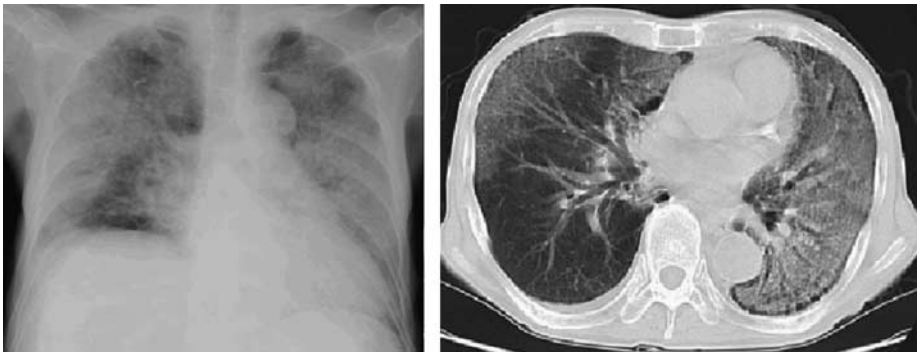
Number	Age (years)	Preexisting lung disease	Clinical type	Imaging findings	Response to steroid therapy[a]	Death[b]	Serum KL-6 (IU/L)	Onset (days)	Anterior chemotherapy	Concomitant chemotherapy
1	74	Unknown	HP	Bilateral, nonsegmental ground-glass changes	○	×	NA	37	PL, FP	FP
2	73	No	HP + OP	Infiltrative changes were seen at sites of severe involvement. Shadows were darker in the right lung and nonsegmental and ground-glass changes were noted throughout almost the entire lung	○	×	NA	63	Unknown	FP
3	62	Yes	DAD	Bilateral traction bronchiectasis was prominent	×	Death	NA	24	Others	None
4	73	Unknown	DAD	Mild traction bronchiectasis	Not given	Death	NA	286	None	PL, GM
5	73	Unknown	DAD	Traction bronchiectasis was prominent. Severe bronchiectasis was noted in the peripheral areas as well	×	×	NA	22	PL, Others	FP
6	61	Yes	HP	Mainly ground-glass changes were seen	Not given	×	NA	34	PL, FP	FP
7	76	No	DAD	Ground-glass changes were mainly seen at the onset, but traction bronchiectasis subsequently occurred	○	×	NA	25	FP	FP
8	71	No	OP	Consolidation was prominent and widespread ground-glass changes were also seen. Consolidation was seen near the mantle area	○	×	NA	189	Unknown	FP
9	73	No	HP	Bilateral, nonsegmental, mild ground-glass changes	○	×	449	45	PL	PL
10	82	No	DAD	Ground-glass changes occurred throughout both lung fields. Traction bronchiectasis was seen in some areas. Interlobular septal hypertrophy was not marked	×	Death	3272	24	FP	Others
11	82	No	OP	Bilateral, nonsegmental ground-glass changes were seen with some dark infiltrative shadows. A banded lesion was also noted	○	×	NA	26	PL, TX	None
12	65	No	OP	Bilateral, nonsegmental ground-glass changes mainly in the lower lung fields. An infiltrative lesion was also noted	○	×	NA	43	None	FP
13	59	No	HP	Mild ground-glass changes	○	×	418	55	PL, FP	FP
14	65	No	DAD	Structural changes and traction bronchiectasis were found bilaterally	×	Death	NA	34	PL, FP	FP
15	73	Unknown	HP	Ground-glass changes	○	×	NA	239	PL	PL
16	68	Unknown	HP	Nonsegmental ground-glass changes. Part of the interlobular septum showed hypertrophy	Unknown	Death	597	47	None	TX
17	70	Yes	HP	Bilateral, nonsegmental ground-glass changes. In the later stage, a dark funicular infiltrative shadow was observed	○	×	NA	300	None	FP
18	71	Unknown	NSIP	Bilateral, nonsegmental ground-glass changes	○	×	3250	85	PL, FP	FP

DAD, diffuse alveolar damage pattern; FP, fluoropyrimidines; GM, gemcitabine; HP, hypersensitivity pneumonia pattern; NSIP, nonspecific interstitial pneumonia pattern; OP, organizing pneumonia pattern; PL, platinum-containing drugs; TX, taxanes.

[a]○: response to steroid therapy, ×: no response to steroid therapy.

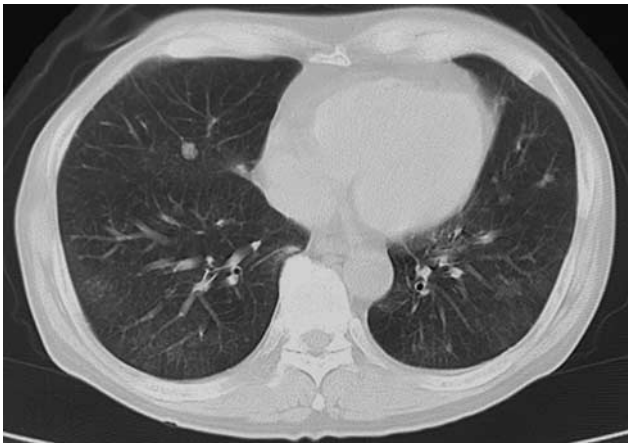
[b]Death: a causal relationship between interstitial pneumonia and death could not be excluded.

Fig. 1



Diffuse alveolar damage pattern of interstitial lung disease associated with irinotecan.

Fig. 2



Hypersensitivity pneumonia pattern of interstitial lung disease associated with irinotecan.

[6,7,13–17]. There were 103 total ILD cases (66 serious cases and 37 nonserious cases) reported during this postmarketing surveillance period. This means the percentage of ILD-related deaths in patients with ILD during the postmarketing surveillance was 14.6% (15/103). In a case–control study of gefitinib performed in Japan, the prognosis of ILD cases (ILD-related deaths in patients with ILD: 31.6%) was shown to be similar to the results found for the control (other chemotherapy) group (27.9%) [8].

Previous studies have also reported that DAD is a type of ILD characteristically caused by busulfan, carmustine, or bleomycin, whereas NSIP is associated with methotrexate [13–15]. Although a few individual cases of ILD induced by irinotecan have been reported in conjunction with imaging findings [16–17], comprehensive classifications of the patterns of the lung involvement have not been previously examined. This study was unable to determine any specific clinical or imaging features among the patients in which occurrence of ILD could potentially be related to irinotecan administration.

Outcomes and responses to steroid therapy were unfavorable when patients had diffuse alveolopathy (a DAD pattern), accompanied by traction bronchiectasis. This is in agreement with other reports that have examined the relationship between the clinical features of ILD and the response to steroid therapy [18,19].

Our steroid therapy findings raise the possibility that ILD induced by irinotecan may be either cytotoxic or noncytotoxic [20]. A previous report has suggested the possibility that mast cells could play an important role in irinotecan-induced ILD [21]. Unfortunately, owing to the small number of participants with adequate histopathological data and the scarcity of previous literature on the histopathological features of drug-induced ILD, this study was not able to further investigate the mechanism of occurrence [2,17,21–22].

However, even though this study was only able to assess 18 patients, our results do suggest that there was no specific imaging pattern related to the interval between the irinotecan treatment initiation and the onset of ILD. None of the patients in this study exhibited any progression of ILD from HP to DAD during the follow-up period.

Serum KL-6 levels were measured at the onset of ILD in five of the 18 patients. Previous studies that examined the relationship between the clinical features of drug-related ILD and KL-6 found that the serum KL-6 level was significantly elevated in patients who had DAD, whereas those with HP exhibited no increase [23–25]. KL-6 has also been reported to be one of the prognostic factors for ILD [26]. The profile of KL-6 in this study corresponded to that previously reported in the literature.

In patients being treated with irinotecan who are suspected of having ILD, the possibility exists that the condition could potentially be aggravated by continuing treatment, and thus, results in a fatal outcome. As a result of this, irinotecan has been contraindicated in patients with ILD since its original approval [27]. There have also been reports that irinotecan and other drugs are associated with an increased risk of ILD in patients who have pulmonary complications at the initiation of treatment [8,12,16,28–29].

This study showed that the prognosis of ILD related to irinotecan was poor in patients with preexisting ILD, with a relative risk for the association between preexisting ILD and death calculated to be 2.25 ($P = 0.29$). However, due to the small sample size, a statistically significant difference was not seen. When the prognostic factors for ILD associated with gefitinib were investigated, men who had a performance status of more than or equal to 2 along with an early onset of the disease were all found to be significantly associated with a poor outcome. When a multivariate analysis of risk factors for ILD associated with gefitinib was performed, it was found that being male, smoking, and having idiopathic ILD were all significant risk factors [7,8].

For ILD related to bleomycin, it has been reported that the total dose, age, and concomitant radiotherapy enhanced the risk [13–15]. As no data were available for patients without ILD in this study, attempts to assess the risk factors for ILD were considerably limited.

Due to international differences in the handling of drug-associated ILD, the degree of attention currently paid to ILD and the terminology used in case reports tend to vary from country to country [30]. In the USA, the section on adverse reactions in the irinotecan package insert states that preexisting lung disease, use of pneumotoxic drugs, radiation therapy, and treatment with colony-stimulating

factors are known risk factors for the occurrence of ILD. In addition, the insert also emphasizes that relevant patients must be closely monitored [31].

This study found a significant frequency of administration of platinum-containing drugs, fluoropyrimidines, and taxanes as both concomitant and anterior chemotherapy drugs in Japanese patients. Although it is well known that each of these drugs can cause ILD [6,9,12], this study could not assess how much irinotecan impacted the onset of ILD. Due to the limited amount of data that have been collected, clarification of the interaction of these drugs is not possible at this time. In addition, there are no apparent trends between the usage of these drugs and the imaging categorizations that can be defined based on this study data.

Conclusion

Irinotecan is contraindicated in patients with preexisting ILD, as their symptoms may be aggravated, possibly leading to death. Therefore, physicians need to confirm patients' eligibility before dosing and if treatment is possible, patients' conditions must be carefully followed after initial administration of the drug.

When patients are given irinotecan, especially within 16 weeks after treatment initiation, they need to be carefully observed for ILD-specific symptoms such as wheeze, rales, cough, and pyrexia. In addition, chest imaging studies should be conducted periodically, and if required, arterial blood gases or SpO_2 should also be measured.

In the event of any of the above abnormalities, physicians need to discontinue treatment and transfer such patients to other appropriate therapies.

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References

1 Yamada M, Kudoh S, Hirata K, Nakajima T, Yoshikawa J. Risk factors of pneumonitis following chemoradiotherapy for lung cancer. *Eur J Cancer* 1998; **34**:71–75.
2 Masuda N, Fukuoka M, Kusunoki Y, Matsui K, Takifuji N, Kudoh S, *et al.* CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol* 1992; **10**:1225–1229.
3 Oshita F, Noda K, Nishiwaki Y, Fujita A, Kurita Y, Nakabayashi Y, *et al.* Phase 2 study of irinotecan and etoposide in patients with metastatic non-small-cell lung cancer. *J Clin Oncol* 1997; **15**:304–309.
4 Sakai F, Noma S, Kurihara Y, Yamada H, Azuma A, Kudoh S, *et al.* Leflunomide-related lung injury in patients with rheumatoid arthritis: imaging features. *Mod Rheumatol* 2005; **15**:173–179.
5 Muller NL, White DA, Jiang H, Gemma A. Diagnosis and management of drug-associated interstitial lung disease. *Br J Cancer* 2004; **91** (**Suppl 2**): S24–S30.
6 Vahid B, Marik PE. Pulmonary complications of novel antineoplastic agents for solid tumors. *Chest* 2008; **133**:528–538.
7 AstraZeneca and Iressa Expert Committee. *Final report on interstitial lung disease (ILD) related to gefetinib (Iressa Tablet 250)*. Tokyo, Japan: AstraZeneca Japan; 2003.
8 Kudoh S, Kato H, Nishiwaki Y, Fukuoka M, Nakata K, Ichinose Y, *et al.* Interstitial lung disease in Japanese patients with lung cancer, a cohort and nested case-control study. *Am J Respir Crit Care Med* 2008; **177**:1348–1357.
9 Gemma A. Drug-induced interstitial lung disease associated with molecular-targeted anticancer agents. *J Nippon Med Sch* 2009; **76**:4–8.
10 Makris D, Scherppereel A, Copin MC, Colin G, Brun L, Laffite JJ, *et al.* Fatal interstitial lung disease associated with oral erlotinib therapy for lung cancer. *BMC Cancer* 2007; **7**:150.
11 Liu V, White DA, Zakowski MF, Travis W, Kris MG, Grinsberg MS, *et al.* Pulmonary toxicity associated with erlotinib. *Chest* 2007; **132**:1042–1044.
12 Camas P, Kudoh S, Ebina M. Interstitial lung disease associated with drug therapy. *Br J Cancer* 2004; **91** (**Suppl 2**):S18–S23.
13 Cooper JA Jr, White DA, Matthay RA. Drug-induced pulmonary disease. Part 1: cytotoxic drugs. *Am Rev Respir Dis* 1986; **133**:321–340.
14 Cooper JA Jr, White DA, Matthay RA. Drug-induced pulmonary disease. Part 2: cytotoxic drugs. *Am Rev Respir Dis* 1986; **133**:488–505.
15 Erasmus JJ, McAdams HP, Rossi SE. High-resolution CT of drug-induced lung disease. *Radiol Clin North Am* 2002; **40**:61–72.
16 Madarnas Y, Webster P, Shorter AM, Bjarnason GA. Irinotecan-associated pulmonary toxicity. *Anticancer Drugs* 2000; **11**:709–713.
17 Michielin O, Udry E, Périard D, Matzinger O, Lobrinus JA, Stupp R. Irinotecan-induced interstitial pneumonia. *Lancet Oncol* 2004; **5**:322–324.
18 Takatani K, Miyazaki E, Nureki S, Ando M, Ueno T, Okubo T, *et al.* High-resolution computed tomography patterns and immunopathogenetic findings in drug-induced pneumonitis. *Respir Med* 2008; **102**:892–898.
19 Cleverley JR, Screaton NJ, Hiorns MP, Flint JD, Muller NL. Drug-induced lung disease: high-resolution CT and histological findings. *Clin Radiol* 2002; **57**:292–299.
20 Fraser RS, Müller NL, Colman N, Pare PD. Pulmonary disease caused by toxins, drugs, and irradiation. In: Fraser RS, Müller NL, Colman N, Pare PD, editor. *Fraser and Pare's diagnosis of diseases of the chest*. Philaderphia: WB Saunders; 1999. pp. 2517–2592.
21 Inoue K, Hiraoka N, Kasamatsu Y, Kawahito Y, Yoshioka K, Yokoo A. A case of irinotecan-induced pneumonitis. *Jpn J Lung Cancer* 2000; **40**:219–221.
22 Maitland ML, Wilcox R, Hogarth DK, Desai AA, Caligiuri P, Abrahams C, *et al.* Diffuse alveolar damage after a single dose of topotecan in a patient with pulmonary fibrosis and small cell lung cancer. *Lung Cancer* 2006; **54**:243–245.
23 Ohnishi H, Yokoyama A, Yasuhara Y, Watanabe A, Naka T, Hamada H, *et al.* Circulating KL-6 levels in patients with drug-induced pneumonitis. *Thorax* 2003; **58**:872–875.
24 Rossi SE, Erasmus JJ, MacAdams HP, Sporn TA, Goodman PC. Pulmonary drug toxicity: radiologic and pathologic manifestations. *Radiographics* 2000; **20**:1245–1259.
25 Muller NL, Naidich DP. Disease characterized primarily by linear and reticular opacities. In: Webb WR, Muller NL, Nadich DP, editors. *High-resolution CT of the lung*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2001. pp. 193–257.
26 Nakajima M, Kawahara Y, Yoshida K, Miyashita N, Niki Y, Matsushima T, *et al.* Serum KL-6 as a possible marker for amiodarone-induced pulmonary toxicity. *Internal Med* 2000; **39**:1097–1100.
27 Daiichi Sankyo Company Limited. *Topotecin package insert*. Tokyo: Daiichi Sankyo Company Limited; 2009.
28 Naito Y, Tsuchiya S, Ishihara S, Minato K, Shitara Y, Takise A, *et al.* Impact of preexisting pulmonary fibrosis detected on chest radiograph and CT on the development of gefitinib-related interstitial lung disease. *Am J Clin Oncol* 2008; **31**:340–344.
29 Niho S, Goto K, Yoh K, Kim YH, Ohmatsu H, Kubota K, *et al.* Interstitial shadow on chest CT is associated with the onset of interstitial lung disease caused by chemotherapeutic drugs. *Jpn J Clin Oncol* 2006; **36**:269–273.
30 Koo LC, Clark JA, Quesenberry CP, Higenbottam T, Nyberg F, Wilf MK, *et al.* National differences in reporting 'pneumonia' and 'pneumonia interstitial': an analysis of the WHO international drug monitoring database on 15 drugs in nine countries for seven pulmonary conditions. *Pharmacoepidemiol Drug Saf* 2005; **14**:775–787.
31 Pfizer. *CAMPTOSAR prescribing information*. New York: Pfizer; 2009.