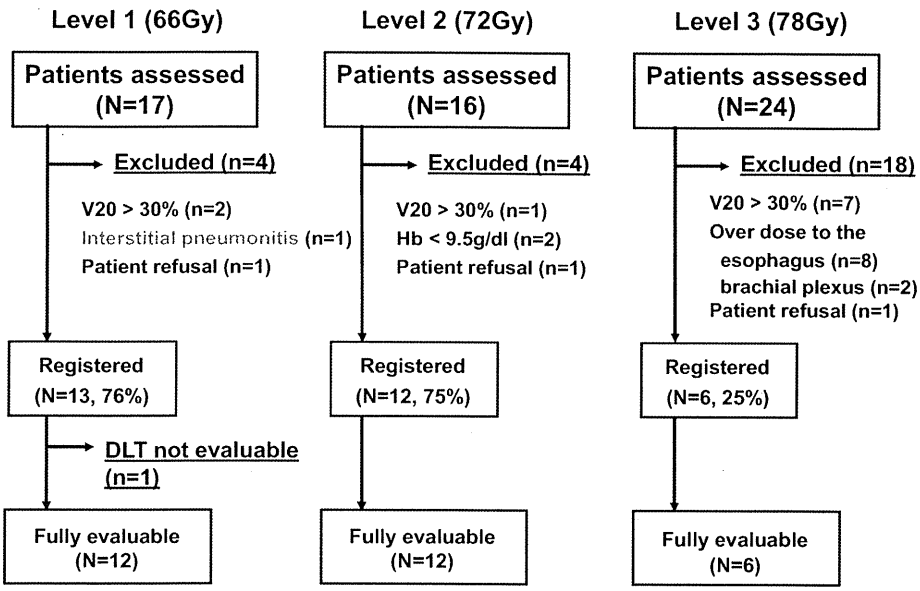

Fig. 1. Algorithm illustrating the flow of the patients. Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were actually enrolled at dose levels 1, 2, and 3, respectively.

The pretreatment characteristics of the patients enrolled in this trial are shown in Table 1. The majority of the patients were in good general condition, with a PS of 0 in 25 (81%) and no weight loss in 26 (84%) patients. Adenocarcinoma was the predominantly encountered histological characteristic, seen in 23 (74%) patients.

Treatment delivery

The treatment delivery to the patients was fairly good (Table 2). The planned dose of radiotherapy was administered to all patients of all the three dose levels. More than 80% of the patients received three to four cycles of chemotherapy without or with only one omission of vinorelbine on Day 8, regardless of the dose levels.

Toxicity and DLTs

The hematologic toxicity was comparable to that of other concurrent chemoradiotherapy (Table 3). Grade 4 septic shock was encountered during the fourth cycle of chemotherapy in 1 patient enrolled at dose level 1, but it was manageable by standard care with antibiotics. Other nonhematologic toxicities were mild and acceptable.

Table 1. Patient characteristics

Characteristic	*n*	(%)
Sex		
M	26	(84)
F	5	(16)
Age (y)		
Median (range)	60	(41–75)
Performance status		
0	25	(81)
1	6	(19)
Body weight loss (%)		
0	26	(84)
0.1–5.0	2	(6)
≤5.0	3	(10)
Histology		
Adenocarcinoma	23	(74)
Squamous cell carcinoma	4	(13)
NSCLC, not otherwise specified	4	(13)
Stage		
IIIA	20	(65)
IIIB	11	(35)

Abbreviation: NSCLC = non–small-cell lung cancer.

Table 2. Treatment delivery

	Level 1 (*n* = 13)	Level 2 (*n* = 12)	Level 3 (*n* = 6)
Radiotherapy			
Total dose (Gy)			
66	13 (100)	–	–
72	–	12 (100)	–
78	–	–	6 (100)
Delay (days)			
≤5	11 (85)	5 (42)	5 (83)
6–10	2 (15)	6 (50)	0
11–15	0	1 (8)	1 (17)
Chemotherapy			
No. of cycles			
4	6 (46)	6 (50)	4 (67)
3	6 (46)	4 (33)	2 (33)
2	0	1 (8)	0
1	1 (8)	1 (8)	0
No. of VNR omissions			
0	10 (77)	7 (58)	2 (33)
1	2 (15)	4 (33)	3 (50)
2	0	0	1 (17)
3	1 (8)	1 (8)	0

Abbreviation: VNR = vinorelbine administered on Day 8.

Table 3. Toxicity

	Grade										
	Level 1			(*n* = 13)	Level 2			(*n* = 12)	Level 3			(*n* = 6)
Toxicity	2	3	4	(3+4 %)	2	3	4	(3+4 %)	2	3	4	(3+4 %)
Leukopenia	4	6	2	(62)	1	3	8	(92)	1	3	2	(83)
Neutropenia	4	4	4	(62)	0	1	10	(92)	1	3	2	(83)
Anemia	8	2	2	(31)	7	3	1	(33)	2	2	0	(50)
Thrombocytopenia	0	0	0	(0)	1	1	0	(8)	0	0	0	(0)
Febrile neutropenia	–	1	0	(8)	–	3	0	(25)	–	1	0	(17)
Infection	0	0	1	(8)	0	1	0	(8)	2	0	0	(0)
Esophagitis	1	1	0	(8)	2	1	0	(8)	0	0	0	(0)
Lung toxicity	2	0	0	(0)	0	0	0	(0)	0	1	0	(17)
Anorexia	3	0	0	(0)	2	2	0	(17)	0	0	0	(0)
Nausea	3	0	0	(0)	3	0	0	(0)	0	0	0	(0)
ALT elevation	1	1	0	(8)	0	0	0	(0)	1	0	0	(0)
CRN elevation	7	0	0	(0)	4	0	0	(0)	0	0	0	(0)

Abbreviations: ALT = alanine aminotransferase; CRN = creatinine.

Of the 13 patients at dose level 1, one was excluded from the analysis of the DLT because he received only one cycle of chemotherapy as a result of the development of cisplatin-induced renal toxicity. Two (17%) of the remaining 12 patients at this dose level developed DLT: Grade 3 esophagitis in 1 patient and Grade 4 septic shock in the other. At dose level 2, two (17%) DLTs were noted: Grade 3 esophagitis in 1 patient and treatment delay by more than 15 days in the other. One (17%) of the 6 patients at dose level 3 developed Grade 3 bronchial stenosis without local recurrence of the disease. This was considered to be a Grade 3 lung toxicity and was counted as DLT. No other DLTs were noted. Thus, inasmuch as the incidence of DLT was below 33% at all dose levels, MTD was not reached.

Preliminary efficacy results

Objective responses and survival were evaluated in the 31 patients. Two patients showed complete responses and 27 showed partial responses, which represented a response rate (95% CI) of 94% (79–99). Disease progression was noted in 23 patients, and the median PFS was 11.6 months with a median duration of follow-up of 30.5 (range, 9.0–49.5) (Fig. 2). The first relapse sites aresummarized in Table 4. Brain metastasis alone as the first relapse site was noted in 7 (23%) patients. The median OS was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively (Fig. 3).

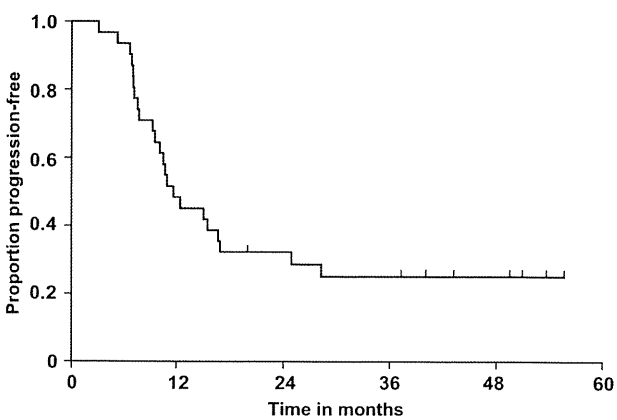

Fig. 2. Progression-free survival (*n* = 31). The median progression-free survival was 11.6 months, with a median duration of follow-up of 30.5 months (range, 9.0–49.5 months).

DISCUSSION

This study showed that concurrent 3D-CRT to the thorax with cisplatin plus vinorelbine chemotherapy was safe even up to 78 Gy in patients with unresectable Stage III NSCLC. This does not mean, however, that doses as high as 78 Gy can be given to all patients with this disease, because the safety in this study was shown only in highly selected patients by a PET/CT and DVH evaluation and by the standard staging procedure. Twenty-five of the 33 patients met the eligibility criteria for enrollment at dose levels 1 and 2, whereas only 6 of the 24 patients could be enrolled at dose level 3 in this study—that is, only one fourth of the patients could be treated with 78 Gy. Thus, this study showed that 72 Gy was the maximum dose that could be achieved in most patients given the predetermined normal tissue constraints, which forced three quarters of the enrolled patients at the 78-Gy level to not

Table 4. First relapse sites (*n* = 31)

Sites	*n*	(%)
Local recurrence alone	6	(19)
Local and distant metastasis	6	(19)
Distant metastasis alone	11	(35)
Brain alone	7	(23)
No relapse	8	(26)

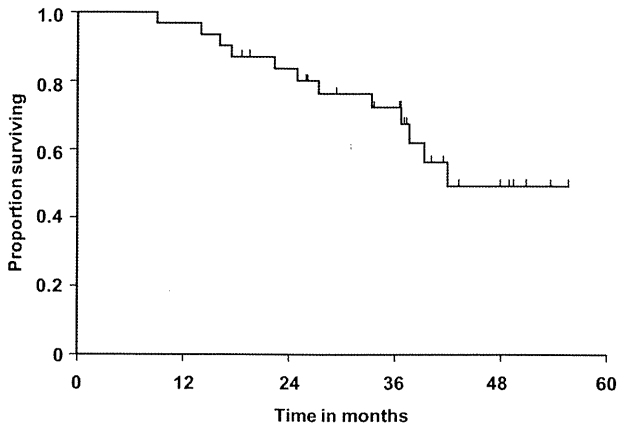

Fig. 3. The median overall survival was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively.

be eligible on the basis of those normal tissue constraints, and that the maximum tolerated dose was not determined because of this issue.

One obstacle to enrolling patients at dose level 3 was that the lung V_{20} often exceeded 30% when the total dose was increased to 78 Gy. This lung V_{20} dose constraint might have been too strict. According to a recent review, it is prudent to limit V_{20} to ≤30–35% with conventional fractionation, but there is no sharp dose threshold below which there is no risk for severe radiation pneumonitis (17). This is partly because DVH-based parameters will change at specific phases of the respiratory cycle when CT images for DVH evaluation have been obtained, there is uncertainty regarding how much of the bronchus should be defined as lung, and the lung edges may vary with the CT window level setting. In addition, patient-associated factors such as age, smoking status, lung function, and preexisting lung damage may influence the incidence and severity of radiation pneumonitis (18). If the threshold of V_{20} were set at higher than 30% (*e.g.*, 35%), then more patients would meet the eligibility criteria, but safety might not be guaranteed. Given that the definite threshold cannot be determined, a strict constraint should be introduced. This study showed that the lung toxicity was acceptable when the V_{20} was kept within 30%; therefore, we decided to use this eligibility criterion for concurrent chemotherapy and high-dose radiotherapy for a subsequent Phase II study.

Another obstacle was overdose to the esophagus and brachial plexus, which were close to the subcarinal (No. 7) and supraclavicular lymph nodes, respectively, that were frequently involved in patients with advanced NSCLC; therefore, the volume of these serial organs were included, in part, in the PTV in many patients with Stage III disease. The radiation tolerance doses of these organs have been defined as no higher than 72 Gy when one third of the organs are included in the irradiation volume (19). However, few data are available on the radiation tolerance doses of normal organs in humans; therefore, whether or not radiation doses above 72 Gy may be tolerated is unknown, especially when only small percentages of the organs are actually included in the irradiation volume. Notwithstanding, we do not agree that the radiation dose can be increased close to the intolerable level, because serious radiation toxicity to these serial organs could be irreversible, frequently leaves severe sequelae, and is fatal in some cases.

The toxicity observed in this trial was comparable to that in our previous study of concurrent chemoradiotherapy with vinorelbine and cisplatin chemotherapy plus thoracic radiation at a total dose of 60 Gy administered in 30 fractions: Grade 3–4 neutropenia in 77% and 67% of patients, Grade 3–4 esophagitis in 6% and 12% of patients, and Grade 3–5 lung toxicity in 3% and 7% in the current and previous studies, respectively (5). This suggests that patient selection using PET/CT and DVH evaluation may be useful to keep the toxicity associated with high-dose thoracic radiation within the range of toxicity induced by conventional-dose thoracic radiation.

In this study, a remarkably high proportion (74%) of subjects had adenocarcinoma, which may provide an explanation for the high rate of subsequent brain metastases. Patient selection also affects the treatment efficacy considerably; therefore, it is difficult to compare it between the current and previous studies. However, the median PFS of 11.6 months and median OS of 41.9 months sound promising. We are conducting a Phase II study of concurrent 3D-CRT at a total dose of 72 Gy and chemotherapy with cisplatin and vinorelbine.

In conclusion, concurrent 3D-CRT with cisplatin and vinorelbine chemotherapy was feasible up to 72 Gy, in patients with unresectable Stage III NSCLC. At the level of 78 Gy, however, only 25% of the patients assessed for eligibility were found to be actually eligible. Thus, 72 Gy in 36 fractions was the maximum dose that could be achieved in most patients given the predetermined normal tissue constraints when administered concurrently with cisplatin and vinorelbine.

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Risk Factors for Treatment-Related Death Associated with Chemotherapy and Thoracic Radiotherapy for Lung Cancer

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Introduction: The aim of the study is to evaluate the current status of treatment-related death (TRD) in lung cancer patients.

Methods: We retrospectively analyzed the incidence and risk factors of TRD in lung cancer patients who received chemotherapy and/or thoracic radiotherapy using logistic regression analyses.

Results: Between January 2001 and December 2005, 1225 (222 small cell and 1003 non-small cell lung cancers) patients received chemotherapy and/or thoracic radiotherapy as the initial treatment. Of these, 43 patients receiving chemotherapy followed by thoracic radiotherapy were included into both the chemotherapy-alone and radiotherapy-alone groups. There were a total of 23 (1.9%) TRDs. Chemotherapy-related deaths occurred in 7 of 927 (0.8%) patients, including 4 from drug-induced lung injury, 2 from pneumonia, and 1 from unknown cause. Concurrent chemoradiotherapy-related deaths occurred in 12 of 245 (4.9%) patients, including 11 from radiation pneumonitis and 1 from pneumonia. Thoracic radiotherapy-related deaths occurred in 4 of 96 (4.2%) patients. The incidence of chemotherapy-related death was correlated with poor performance status (odds ratio [OR]: 11.4, 95% confidence interval [CI]: 3.53–37.1), the presence of hypoxia (OR: 19.3, CI: 6.06–61.7), hyponatremia (OR: 45.5, CI: 13.4–154), and treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (OR: 8.56, CI: 2.48–29.5), whereas the incidence of concurrent chemoradiotherapy-related death was correlated with pulmonary fibrosis (OR: 22.2, CI: 5.61–87.8). Radiotherapy results were not analyzed because there were too few patients.

Conclusions: TRD occurred in 1.9% of the patients as a result of treatment-related lung injury in the majority of the cases.

Key Words: Lung cancer, Treatment-related death, Risk factor, Chemotherapy, Thoracic radiotherapy.

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Before any medical interventions are undertaken in patients with lung cancer, they must be clearly informed about the risks and benefits of the intervention(s) and about alternative treatment options. Careful delivery of this is particularly important if the planned treatment may not only result in cure but may also be harmful. Provision of accurate information to help patients make the most appropriate decision is therefore crucial. However, the risks of death from drug toxicity and the incidences of such events tend to be uncertain[1–4] and also constantly change with the wide use of newer agents, such as third-generation chemotherapy agents, and molecular-targeted agents. In addition, the incidence of treatment-related deaths (TRDs) has not been thoroughly examined in clinical settings outside of clinical trials. Prospective clinical trials for poor-risk patients are often difficult to perform because of poor accrual, reflecting the reluctance of physicians to subject patients with underlying comorbid illness to the toxic effects of chemotherapy and radiation.

Our ultimate goal is to prospectively identify individuals who are at a high risk of TRD so as to provide the most precise estimation of the possible risks to each patient. In this study, we retrospectively examined the data of patients with locally advanced or metastatic lung cancer who were treated at the National Cancer Center Hospital, Tokyo, Japan, focusing on the risks and incidences of TRD associated with chemotherapy and radiotherapy.

PATIENTS AND METHODS

Patients

Between January 2001 and December 2005, a total of 1623 lung cancer patients were admitted to the thoracic oncology ward at the National Cancer Center Hospital. All patients were admitted in this period to be treated as part of standard practice in Japan. Patients who received chemotherapy alone usually stayed in the hospital for 7 to 10 days for one cycle of chemotherapy, and those who received concurrent chemoradiotherapy stayed for 6 weeks. Among these, a total of 1225 patients who had received first-line chemotherapy and/or radiotherapy on an inpatient basis were extracted from the institutional database. Additional details about the patients, including the diagnostic imaging findings, were then reviewed from the patients' medical records. The data of patients receiving chemotherapy and/or thoracic radiotherapy

as the initial treatment were evaluated. They included patients with stage III to IV disease and postoperative recurrent disease who received chemotherapy; those with stage III disease who received chemoradiotherapy or radiotherapy alone; and those with stage III disease who received preoperative induction therapy or postoperative adjuvant therapy. All the patients had been followed for at least 4 weeks after the completion of treatment.

Treatment Selection

After a thorough evaluation of the operability and/or curability, the eligibility of each patient for enrollment in an open clinical trial was determined. Although patient recruitment for protocol treatments is a priority of ours, patients were free to refuse treatment. If no appropriate clinical trials were scheduled or under way, the known best standard treatments were administered.

Best Standard Treatments

For first-line treatment, patients with non-small cell lung cancer (NSCLC) who were deemed inoperable but curable with good local control with chemoradiotherapy received three to four cycles of cisplatin (CDDP) 80 mg/m^2 on day 1 + vinorelbine (VNR) 20 mg/m^2 on days 1 and 8, every 4 weeks, along with early concurrent thoracic radiotherapy, usually at a total dose of 60 Gy/30 fractions.[5] Sequential chemoradiotherapy, rather than concurrent chemoradiotherapy, was offered if the calculated percentage of the total lung volume receiving radiation in excess of 20 Gy (V_{20}) was more than 40%.[6] Thoracic radiotherapy alone was selected if chemotherapy could not be given due to comorbidity. If the radiation field involved the contralateral hilum or if the patients had malignant effusion and/or distant metastasis, platinum doublet therapy was administered; the most common combination was four cycles of carboplatin (CBDCA) area under the curve = 6 on day 1 + paclitaxel (PTX) 200 mg/m^2 on day 1, every 3 weeks.[7] For limited-disease SCLC, four cycles of a combination of CDDP 80 mg/m^2 on day 1 + etoposide 100 mg/m^2 on days 1 to 3, every 4 weeks, were administered concurrently with hyperfractionated thoracic radiotherapy at a total radiation dose of 45 Gy in fractional doses of 1.5 Gy, administered twice a day.[8] In patients with extensive-disease SCLC, four cycles of a combination of CDDP 60 mg/m^2 on day 1 and irinotecan (CPT) 60 mg/m^2 on days 1, 8, and 15, every 4 weeks, were usually administered.[9] Radiotherapy was given using megavoltage photons (6–15 MV). The routine radiation schedule without chemotherapy for locally advanced NSCLC was a total radiation dose of 60 to 66 Gy, or as high as 70 Gy, administered in fractional doses of 2.0 Gy once a day.

Definition of TRD

Chemotherapy-related death was defined as death occurring within 4 weeks of the completion of treatment, without clear evidence of any other cause of death, or death obviously caused by treatment toxicity. Radiotherapy-related death was defined as death secondary to hypoxia or to complications of corticosteroid administration after the diagnosis of radiation pneumonitis. Steroid therapy was administered based on the attending physician's discretion, without a standardized treatment dose or duration, for the management of radiation-induced lung injury.[10]

Definition of Treatment-Induced Lung Injury

The criteria of drug-induced lung injury in this study were as follows: (1) appearance of new symptoms and radiological abnormalities in the course of chemotherapy with the onset within a few months of the start of the therapy; (2) diffuse or multifocal ground-glass opacities and intralobular interstitial thickening without segmental distribution in computed tomography (CT) scans of the chest; and (3) no evidence of underlying heart disease, infection, or lymphangitic carcinomatosis. Lung biopsy was not routinely performed in our hospital because patients were frequently too frail to undergo biopsy. The criteria of radiation-induced lung injury were (1) appearance of new symptoms and radiological abnormalities with the onset within 6 months of the end of thoracic radiotherapy; (2) opacification, diffuse haziness, infiltrates, or consolidation conforming to the outline of the sharply demarcated irradiated area in CT scans; and (3) a reduction in lung volume within the irradiated area and linear, ground-glass opacities or reticular shadows beyond the irradiated area developing during clinical course. In contrast, the criteria of bacterial pneumonia were (1) clinical suspicion of pneumonia including rapidly developing fever and/or productive cough; and (2) consolidation spreading through anatomical structure of the lung in CT scans.

Statistical Analysis

We investigated the associations between chemotherapy-related or concurrent chemoradiotherapy-related death and the potential risk factors at the time of diagnosis. The following potential risk factors were investigated: sex, age (≥70 years versus <70 years), performance status (Eastern Cooperative Oncology Group criteria; 2–4 versus 0–1), smoking history (presence versus absence), partial pressure of oxygen (70 mmHg ≤ PO_2 versus >70 mmHg), hemoglobin (Hgb < 13.7 g/dl versus ≥ 13.7 g/dl), platelet (Plt > 367 × 10^9/L versus ≤367 × 10^9/L), albumin (Alb < 3.7 g/dl versus ≥3.7 g/dl), sodium (Na < 138 mEq/L versus ≥138 mEq/L), clinical trial (in versus out), and chemotherapy regimen (The cutoff values of hemoglobin, platelet, albumin, and sodium are the institutional normal limits [above or below]). For concurrent chemoradiotherapy-related factors, the presence of coincidental diseases such as emphysema (with versus without) or pulmonary fibrosis (with versus without) and the location of the primary tumor (lower lobe versus other lobes) were also included in the analyses. The diagnostic criteria of pulmonary fibrosis were a linear, ground-glass attenuation or reticular shadows on chest radiographs and CT scans before treatment that were predominant in the lower zone of the lung. Also, the influence of the chemotherapy regimens was evaluated.

In the univariate preliminary analysis, the relation between previously defined variables at the time of presentation and the occurrence of the outcome variable (toxic death) was assessed using the χ^2 test. To adjust for each factor, multivariate logistic regression analyses were planned. When the number of observed events was less than 10, multivariate

analysis was not performed. When the number of patients for each factor was small, the factor was excluded from the model, even when it appeared to be statistically significant. All the analyses were performed using the STATISTICA 4.1J program (StatSoft, Inc., Tulsa, OK).

RESULTS

Patient Characteristics

The patient characteristics before treatment are listed in Table 1. Of the 1225 patients (SCLC: 222; adenocarcinoma: 652; squamous cell carcinoma: 194; NSCLC not otherwise specified: 111; large cell carcinoma: 7; others: 39), chemotherapy alone was administered in 884 patients, concurrent chemoradiotherapy in 245, sequential chemoradiotherapy in 43, and thoracic radiotherapy alone in 53 patients. To evaluate the incidence of TRD among the patients who received chemotherapy, radiotherapy, or a combination of these modalities, we included the 43 patients who received sequential chemoradiotherapy into both the chemotherapy-alone group and the thoracic radiotherapy-alone group. Therefore, the patients who received sequential chemoradiotherapy were regarded as having been exposed to the risks of treatment twice. The groups were therefore analyzed as chemotherapy alone in 927 patients, concurrent chemotherapy in 245 patients, and thoracic radiotherapy alone in 96 patients. In these groupings, the percentages of patients enrolled in clinical trials were 62, 53, and 23%, respectively.

Cumulative Incidence and Causes of TRD

The cumulative incidence and causes of TRD are listed in Table 2. Of the 1225 patients, a total of 23 (1.9%) TRDs occurred. Chemotherapy-related deaths occurred in 7 of 927 (0.8%) patients, including 4 (0.4%) from drug-induced lung injury (gefitinib, $n = 3$ and CBDCA + gemcitabine, $n = 1$), 2 (0.2%) from pneumonia (CBDCA + PTX, $n = 2$), and 1 (0.1%) from unknown cause. The patient who died of unknown cause experienced hemodynamic instability (shock) of unknown etiology within 24 hours of ingestion of the first dose of gefitinib (250 mg). No TRDs from sepsis occurred in this series.

Concurrent chemoradiotherapy-related deaths occurred in 12 of 245 (4.9%) patients, including 11 (4.5%) from radiation pneumonitis and 1 (0.4%) from pneumonia during the last planned cycle of CDDP + VNR. Radiotherapy-

TABLE 1. Patient Characteristics

Characteristics	Chemotherapy Alone[a] ($n = 927$)	Concurrent Chemoradiotherapy ($n = 245$)	Radiotherapy Alone[a] ($n = 96$)
Sex			
Male	639	201	43
Female	288	44	53
Age			
Median (range)	64 (27–86)	59 (18–77)	67 (35–81)
Performance status			
0–1	871	245	88
2	140	0	8
3–4	16	0	0
Stage			
III	297	235	71
IV	454	2	17
Postoperative recurrence	176	8	8
Histology			
Non-small cell carcinoma	760	191	88
Small cell carcinoma	167	54	8
Coincidental lung disease			
Pulmonary fibrosis	34	1	4
Pulmonary emphysema	69	30	1
Chemotherapy regimen			
Platinum + taxane	368	21	—
Platinum + irinotecan	133	1	—
EGFR-TKI	125	0	—
Platinum + etoposide	95	54	—
Platinum + antimetabolite	85	0	—
Platinum + vinca alkaloid	37	168	—
Others	84	1	—

[a] Forty-three patients who received sequential chemotherapy followed by radiotherapy are included in the analysis of both the chemotherapy-alone group and radiotherapy-alone group, as described in the text.

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

TABLE 2. Treatment-Related Death and Its Cumulative Incidence

Characteristics	Chemotherapy Alone[a] (n = 927)	Concurrent Chemoradiotherapy (n = 245)	Radiotherapy Alone[a] (n = 96)
No. of treatment-related deaths	7	12	4
Cumulative incidence (%)	0.8	4.9	4.2
Sex			
Male	5	11	4
Female	2	1	0
Age of patients who died of treatment (yr)			
Median (range)	69 (46–77)	68 (50–77)	75 (65–77)
Causes			
Treatment-induced lung injury	4	11	4
Infectious pneumonia	2	1	0
Unknown	1	0	0
Chemotherapy regimen			
Platinum + taxane	2	2	—
EGFR-TKI	4	—	—
Platinum + antimetabolite	1	—	—
Platinum + etoposide	0	1	—
Platinum + vinca alkaloid	0	8	—
Others	0	1	—

[a] Forty-three patients who received sequential chemotherapy followed by radiotherapy are included in the analysis of both the chemotherapy-alone group and radiotherapy-alone group, as described in the text.

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

related deaths occurred in 4 of 96 (4.2%) patients: all 4 (4.2%) patients died of radiation pneumonitis.

Risk Factors for TRD from Chemotherapy

Statistically significant factors identified by the univariate analysis were a performance status of 2 to 4, hypoxia, hypoalbuminemia, hyponatremia, out of clinical trials, and treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) (Table 3). Although statistically significant, the degrees of hyponatremia in the events were neither clinically significant nor symptomatic for the range of 133 to 137 mEq/L. Pulmonary fibrosis and emphysema were noted in 34 and 69 patients, respectively, among the 927 patients. None of these patients with lung disease died of treatment in this study. Multivariate analysis was not performed because the number of observed events was too small (n = 7).

Risk Factors for TRD from Concurrent Chemoradiotherapy

None of the factors, except for pulmonary fibrosis, were found to be statistically significant in the univariate analysis, although a trend toward increase in the risk of TRD was observed in patients of advanced age (>70 years) and with lower lobe as the primary tumor site (Table 4). Pulmonary fibrosis appeared to be a statistically significant risk factor for TRD; however, it was excluded from the multivariate analysis because of its limited incidence. Thus, we did not perform multivariate analysis for chemoradiotherapy group, and an analysis of the risk of TRD associated with thoracic radiotherapy alone was not conducted because of the limited number of cases.

DISCUSSION

We identified a total of 23 TRDs out of the 1225 patients (1.9%) enrolled in this study, which is lower than the rate (2.7%) indicated in a previous report, particularly in relation to the number of TRDs from infections, including pneumonia and sepsis.[1] The reason for the decrease in the incidence of infection-related deaths is likely explained by the infrequent use of triplet regimens when compared with previous studies. Especially, mitomycin-C-containing regimens are regarded as effective regimens in the treatment of lung cancer; however, prolonged neutropenia has been observed with these regimens. Ohe et al.[1] reported that combined mitomycin-C + vindesine + CDDP (MVP regimen) therapy is a risk factor for chemotherapy-related TRD (toxic deaths occurred in 9 of 301 patients; odds ratio [OR] = 9.36, 95% confidence interval [CI] = 1.29–68.0, p = 0.027). In this study, only 35 patients, the majority (89%) of whom were enrolled in a clinical trial, received the MVP regimen. In the past, however, the MVP regimen was widely used as part of practice-based regimens (only 28% recorded under clinical trials). In most cases, patients who were not eligible for clinical trials ended up receiving the MVP regimen. Another reason is the relatively frequent use of EGFR-TKI (in 13.5% of the patients in this study) at present, which does not induce myelosuppression. The reduction in the frequency of TRD might also be explained by a progress in supportive care in the treatments given for cancer treatment toxicities.

This study revealed that drug-induced lung injury was the most frequent cause of TRD in the era of molecular-targeted therapy. Three (75%) of four TRDs from drug-induced lung injury were associated with gefitinib. The re-

TABLE 3. Risk Factors for Treatment-Related Death from Chemotherapy

Factors	No. of Patients	Cumulative Incidence (%)	Univariate Analysis OR (95% CI)	*p*
Sex				
Female	288	0.8	1	
Male	639	0.7	1.13 (0.22–5.76)	0.89
Age				
<70	689	0.6	1	
≥70	238	1.3	2.17 (0.51–9.30)	0.30
PS				
0–1	870	0.5	1	
2–4	57	5.2	11.4 (3.53–37.1)	<0.001
Smoking history				
No	271	0.4	1	
Yes	656	0.9	2.49 (0.30–20.8)	0.40
PaO_2 (Torr)				
≥70	812	0.2	1	
<70	105	4.8	19.3 (6.06–61.7)	<0.001
Hemoglobin (g/dl)				
≥13.7	371	0.5	1	
<13.7	556	0.9	1.67 (0.33–8.39)	0.54
Albumin (g/dl)				
≥3.7	663	0.3	1	
<3.7	264	1.9	6.28 (1.51–26.1)	0.012
AST (IU/L)				
≤33	831	0.6	1	
>33	96	2.1	3.46 (0.75–16.0)	0.11
Na (mEq/L)				
≥138	819	0.1	1	
<138	108	5.6	45.5 (13.4–154)	<0.001
Clinical trial				
No	355	1.7	1	
Yes	572	0.2	0.10 (0.58–0.019)	0.001
Platinum + taxane				
No	559	0.9	1	
Yes	368	0.5	0.61 (0.12–3.14)	0.55
EGFR-TKIs				
No	802	0.4	1	
Yes	125	3.2	8.56 (2.48–29.5)	0.001
Platinum + antimetabolite				
No	842	0.7	1	
Yes	85	1.1	1.66 (0.20–13.9)	0.64

Multivariate analysis was not performed because the number of observed events was too small ($n = 7$).

OR, odds ratio; CI, confidence interval; PS, performance status; AST, aspartate transaminase; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors.

TABLE 4. Risk Factors for Treatment-Related Death from Concurrent Chemoradiotherapy

Factors	No. of Patients	Cumulative Incidence (%)	Univariate Analysis OR (95% CI)	*p*
Sex				
Female	44	2.3	1	
Male	201	5.2	2.41 (0.35–16.6)	0.37
Age (yr)				
<70	221	4.1	1	
≥70	24	12.5	3.07 (0.92–10.3)	0.069
PS				
0	114	5.3	1	
1	131	4.6	0.87 (0.29–2.62)	0.81
Smoking history				
No	32	3.2	1	
Yes	213	5.2	1.65 (0.23–11.9)	0.24
Fibrosis				
No	244	4.5	1	
Yes	1	100	22.2 (5.61–87.8)	<0.001
Emphysema				
No	215	4.7	1	
Yes	30	6.7	1.43 (0.33–6.25)	0.63
Location of the tumor				
Other lobes	189	3.7	1	
Lower lobe	56	8.9	2.41 (0.82–7.13)	0.11
Histology				
SCLC	54	1.9	1	
NSCLC	191	5.8	3.11 (0.47–20.6)	0.24
Hemoglobin (g/dl)				
≥13.7	146	4.1	1	
<13.7	99	6.1	1.48 (0.49–4.42)	0.48
Albumin (g/dl)				
≥3.7	198	4.5	1	
<3.7	47	6.4	1.40 (0.40–4.99)	0.6
Na (mEq/L)				
≥138	219	5.0	1	
<138	26	3.8	0.77 (0.11–5.60)	0.79
Clinical trial				
No	114	5.3	1	
Yes	131	4.6	0.87 (0.29–2.62)	0.81
Platinum + taxane				
No	224	4.5	1	
Yes	21	9.5	2.25 (0.46–11.0)	0.32
Platinum + vinca alkaloid				
No	77	5.2	1	
Yes	168	4.8	0.91 (0.27–3.13)	0.88

Multivariate analysis was not performed because only fibrosis was significant in univariate analysis.

OR, odds ratio; CI, confidence interval; PS, performance status; NSCLC, non-small cell lung cancer.

ported risk factors for interstitial lung disease in NSCLC patients treated with gefitinib are male sex, history of smoking, and underlying interstitial pneumonitis.[11] In this study, however, none of these factors were associated with TRD from chemotherapy. Another TRD from drug-induced lung injury occurred in a patient who received gemcitabine, but this patient was also free from underlying pulmonary disease or concomitant use of taxanes, which are reported to be risk factors for gemcitabine-associated interstitial lung disease.[12]

For patients who receive concurrent chemoradiotherapy, we would like to emphasize the previous finding that the

presence of evidence of pulmonary fibrosis on a plain chest x-ray is an extremely strong risk factor for TRD (OR = 166, 95% CI = 8.79–3122, $p < 0.001$).[1] In this study, only one patient with pulmonary fibrosis was identified, and pulmonary fibrosis was not included in the multivariate analysis because of the small number of patients with this factor, because we generally exclude patients with evidence of pulmonary fibrosis on the chest x-ray from consideration of concurrent chemoradiotherapy. This study also suggested that advanced age may be a risk factor for TRD. This is consistent with the results of previous studies.[1,13–15] The association between advanced age and fatal radiation-induced lung injury may be explained by the increased likelihood of these patients developing comorbid lung disease, particularly among patients with a history of heavy tobacco exposure. A meta-analysis of chemoradiotherapy using individual data from 1764 patients with locally advanced NSCLC showed that the benefit of chemoradiotherapy was obtained in elderly patients (≥71 years) as well as in younger patients. However, it might be assumed that patients who are included in such trials are fit patients with minimal comorbidities. In addition, despite the increase in toxicity that accompanied chemoradiotherapy in elderly patients, it seemed that they had disease control and survival rates similar to those of younger patients.[16]

In conclusion, TRD occurred in a total of 1.9% of patients and was caused in the majority of the cases by treatment-related lung injury. This finding is in clear contrast with previous reports which suggested that the principal cause of TRD in lung cancer patients was septic shock.

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PHASE III STUDIES

The notorious "drug lag" for oncology drugs in Japan

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Summary This study aimed to analyze the oncology "drug lag" (i.e., the delay in time required for the approval of oncology drugs) in Japan compared with that in the United States of America (US) or the European Union (EU) and to identify the factors associated with this lag. Using publicly available information, we collected data on 42 approvals of 30 oncology drugs in Japan, the US, and the EU that included dates of drug development initiation, submission, review, and approval. Lags in each step of the process were then examined and compared among the three regions. We found that median submission and approval lag times between Japan and the US were 20.0 and 29.9 months, respectively, while those between Japan and the EU were 14.9 and 21.3 months, respectively. The median review periods for Japan, the US, and the EU were 14.3, 6.0, and 13.2 months, respectively, and the median lag in initiation of oncology drug development between Japan and the US/EU was 38.9 months. The proportion of approvals for which Japanese Phase I registration trials started after corresponding approvals in the US were 39% compared with 47% for the EU. Multivariate analysis suggests that delays in the initiation of drug development and the extended length of the regulatory review period in Japan may contribute to the longer oncology drug lag observed in Japan compared with that of the US or EU.

Keywords Oncology · Drug lag · Delay · Registration trial · Approval · Drug development

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Introduction

New drug development is a gradual process involving several stages of scientific and objective evaluation. After preclinical trials using cultured cells or animal models are conducted to evaluate a drug's potential efficacy, toxicology, or mechanism of action, Phase I clinical trials involving humans are undertaken to determine the recommended administration dose and schedule depending upon the safety profile derived from dose-limiting toxicity studies. Then, the Phase II and Phase III (or "pivotal") clinical trials are carried out to develop preliminary and confirmatory evidence, respectively, for efficacy and safety of the new agent as compared with conventional treatment.

After these registration trials, a pharmaceutical company submits a new drug application (NDA) or supplemental NDA (sNDA) that includes all trial data to the regulatory agency of the country, and the regulatory agency reviews the risk/benefit balance of the NDA or sNDA. When such an application is positively reviewed and approved, thus, patients allows to benefit from the approved drug treatment.

Each country has specific laws and regulatory controls that govern pharmaceutical affairs for NDAs or sNDAs; however, these controls often differ from country to country. Therefore, the time required for approval of an NDA or sNDA may vary depending on each country's regulatory process. In Japan, the notorious "drug lag" (i.e., the delay in time required for the approval of drugs) for

NDA and sNDA approvals has recently become a major social issue [1, 2]. One study showed that the delay between the approval of a new drug in the United States (US) versus approval of the same drug in Japan was approximately 2.5 years [3]. Another study reported that the mean time required for approval of new biologics was 3.7 months in the US, 7.5 months in the European Union (EU), and 52.6 months in Japan [4].

Oncology drugs are prescribed for the treatment of cancer, which is a major cause of mortality in developed countries; therefore, a lag in the availability of oncology drugs is a direct threat to life and is naturally of particularly high interest to the public. To the best of our knowledge, no report regarding the drug lag for oncology drugs in Japan has yet been published, and the factors associated with this problem remain unknown. Therefore, identifying the actual status of the oncology drug lag in Japan and the factors that influence the drug approval process not only in Japan but also in other countries would provide important information that could be used in efforts to resolve this issue.

In the present study, we discuss the oncology drug lag in Japan through an examination of the delays inherent in processes related to drug development, submission, and approval in Japan compared with the US/EU; we also examine in detail the timing of the regulatory review process for the three regions.

Materials and methods

Data sources and analyses

The Pharmaceuticals and Medical Devices Agency (PMDA) is a Japanese regulatory agency working in conjunction with the Ministry of Health, Labour and Welfare (MHLW) [5]. The major functions of the PMDA include conducting drug and medical device reviews, evaluating post-marketing safety, and providing relief services related to adverse drug effects. The PMDA conducts scientific reviews of marketing authorization applications for pharmaceuticals and medical devices as well as clinical trial consultations. On the basis of these reviews, the MHLW evaluates NDAs and sNDAs for Japan for approval or disapproval.

We examined 88 approvals for 53 drugs that were approved in Japan between 2000 and 2009. Multiple approvals for the same drug involved its use in the treatment of multiple malignant diseases. For these 88 approvals, the dates of drug development initiation, review submission, review duration, and approval in Japan, the US, and the EU were collected. The date of drug development initiation was defined as the date of first patient enrollment in the earliest phase registration trial for an NDA or sNDA. These data were extracted from the PMDA's review reports and from documents submitted by the application sponsors, as publicly released on the PMDA website [6]. Additionally, for each drug, the following information was collected: target cancer type (solid malignancy/hematologic malignancy), drug type (molecular-targeted drugs/small-molecular-targeted agents or antibody agents/other non-molecular-targeted drugs), application type (NDA/sNDA), review type (regular/priority), orphan drug status (yes/no), and whether approval was being sought for a public domain application (yes/no). The same data for the US and EU were also gathered from review reports of each region's regulatory agency [7–9]. Not all of these data could be collected for each approval; therefore, the analyzed number of approvals from Japan and the US/EU are not identical.

Among the 88 approvals, 16 applications were approved without registration trial data because the applications were eligible for being in the public domain (Fig. 1). Further, 30 approvals had not yet been approved in the US or EU at the time of approval in Japan. These approvals were excluded from the evaluation; therefore, 42 approvals for 30 drugs were examined in this study. The lags in the dates of development, submission, and approval between Japan and the US and/or EU and the periods required for review among three regions were calculated. The factors associated with the lag in approval between Japan and the other two regions were explored by multivariate analysis.

Results

Lags in the approval and submission process, review period, and initiation of drug development between Japan and the US/EU

The characteristics of the 42 approvals studied are shown in Table 1. The median submission and approval lags were 20.0 (N=33) and 29.9 (N=42) months, respectively, between Japan and the US, while those between Japan and the EU were 14.9 (N=24) and 21.3 (N=40) months (Fig. 2).

The median review periods for Japan, the US, and the EU were 14.3 (N=42), 6.0 (N=33), and 13.2 (N=24) months, respectively (Fig. 3). In many cases, drug development in the US and EU was initiated in parallel, so we calculated the lag time in drug development initiation between Japan and the US/EU. The median delay in the initiation of drug development for oncology drugs between Japan and the US/EU was found to be 38.9 months (N=19) (Fig. 4).

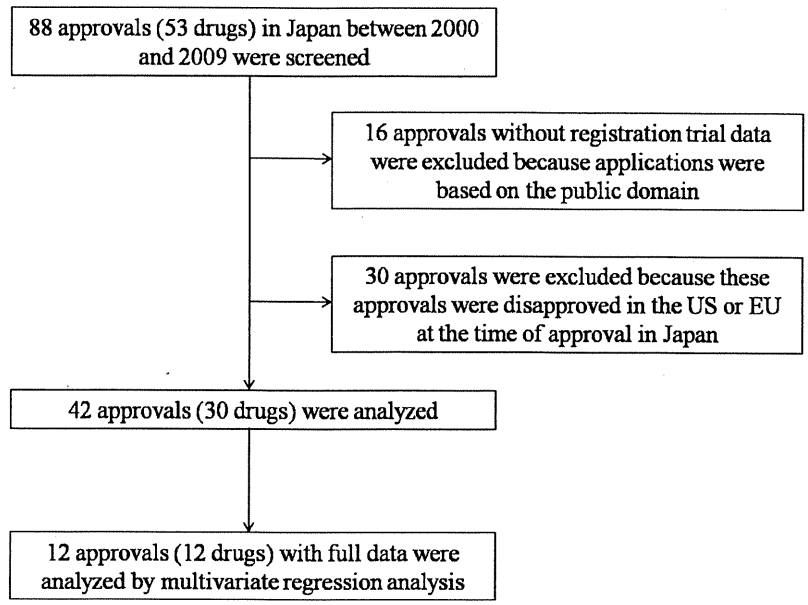

Fig. 1 Diagram of selection of study objects

Factors associated with approval lags between Japan and the US/EU

For 12 approvals of 12 drugs for which all data were completely collected, we used multivariate regression analysis to examine the impact of submission lag, review period duration, targeted cancer type (solid vs. hematologic malignancy), and drug type (molecular-targeted vs. non-molecular-targeted drugs) on the approval lag between Japan and the US/EU. The results are shown in Table 2. All of the variables, excluding submission lag, were significantly associated with the approval lag.

Additionally, the development status of drugs in the US and EU at the start date of Phase I oncology trials in Japan is shown in Table 3. The number of drug approvals for which Japanese Phase I registration trials started after the drug had been submitted for approval in the US was 13 out of 33 (39%); in the EU, this number was 16 out of 34 (47%).

Discussion

Our study indicated that several factors are significantly associated with the oncology drug lag in Japan. We observed that the initiation of drug development in Japan for many oncology pharmaceuticals began after the NDA/sNDA for these same drugs had already been submitted or approved in the US or EU. Therefore, Japanese pharmaceutical companies should coordinate oncology drug development with pharmaceutical development in other countries in order to reduce duplication of effort and minimize drug development delays. The review period required by the Japanese regulatory agency needs to be reduced in order to minimize the drug lag for oncology drugs, and this can occur only with the concerted efforts of the pharmaceutical companies, the PMDA, and concerned academia. Oncology drugs classified as "drugs for hematologic malignancy" and "non-molecular-targeted drugs" were associated with increased drug lag. This may be

Table 1 Characteristics of 42 approvals for 30 drugs approved in Japan, the US, and EU

Variables		Number of drugs (%)
Submission	NDA	24 (57.1)
	sNDA	18 (42.9)
Malignancy	Solid	29 (69.1)
	Hematologic	13 (30.1)
Drug type	Molecular-targeted drug	20 (47.6)
	Non-molecular- targeted drug	22 (52.4)
Orphan	Yes	17 (40.5)
	No	25 (59.5)
Review	Standard	9 (21.4)
	Priority	33 (78.6)

NDA new drug application; *sNDA* supplemental new drug application

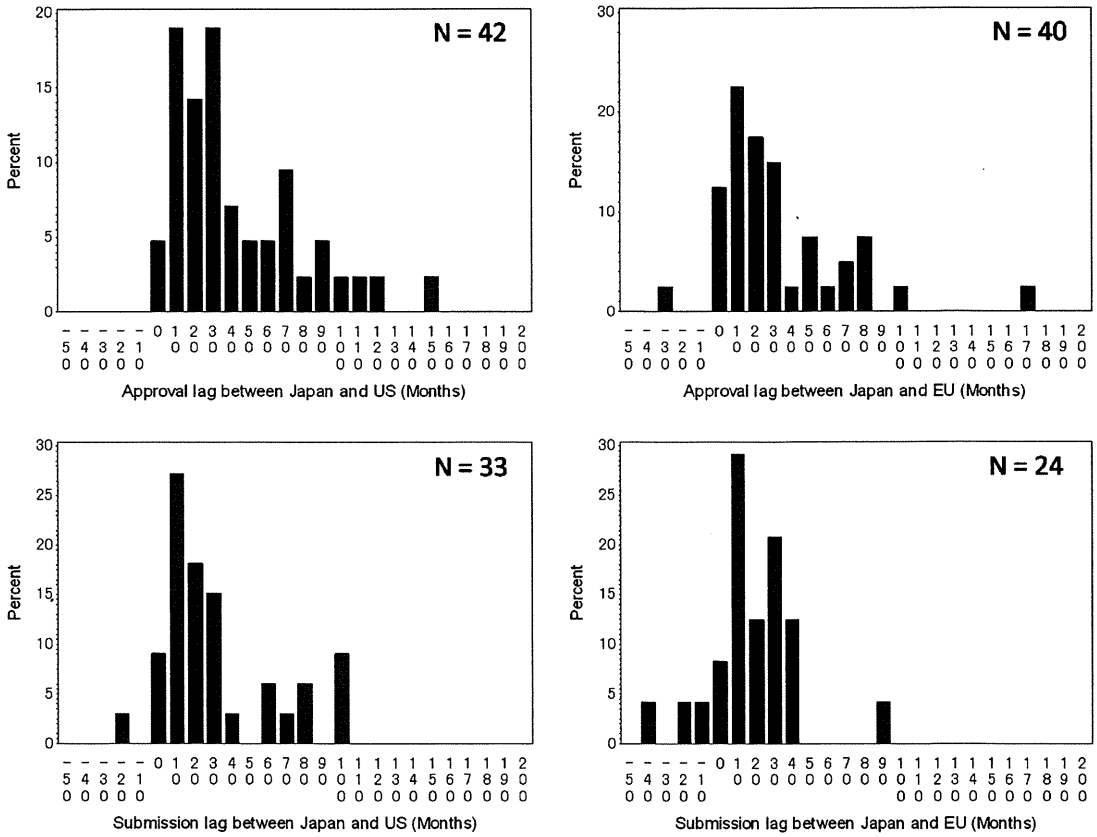

Fig. 2 Histograms of approval lags and submission lags between Japan and the US/EU

because hematologic malignancy is generally a rare disease associated with slow enrollment of patients in registration trials as compared with solid malignancy. Further, NDAs/sNDAs for molecular-targeted drugs may tend to achieve priority review status as compared to non-molecular-targeted drugs. Based on our results, both factors contributed to delays in the initiation of oncology drug development in Japan.

Drug lag is closely affected by pharmaceutical regulation. The regulatory standards for registration trials and evaluation procedures for oncology drugs in Japan have dramatically changed over the last decade following publication by the MHLW of two important notifications related to global oncology registration trials in Japan [10, 11]. "Guidelines on Methods of Clinical Evaluation of Oncology," published in November 2006, included important revisions that required evidence from confirmatory Phase III trials of survival prolongation in major cancers such as lung, breast, gastric, and colorectal cancers. "Basic Principles on Global Clinical Trials," published in September 2007, allowed the submission of clinical data from international trials with or without Japanese patients for NDAs or sNDAs. However, Japanese regulations require the submission of registration trials involving Japanese

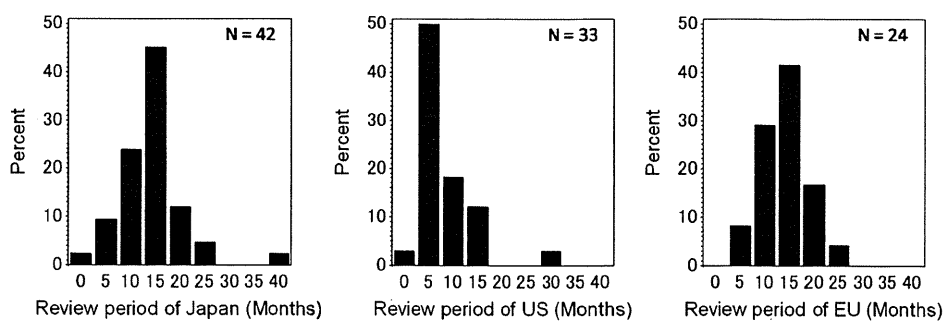

Fig. 3 Histograms of review periods in Japan, the US, and EU

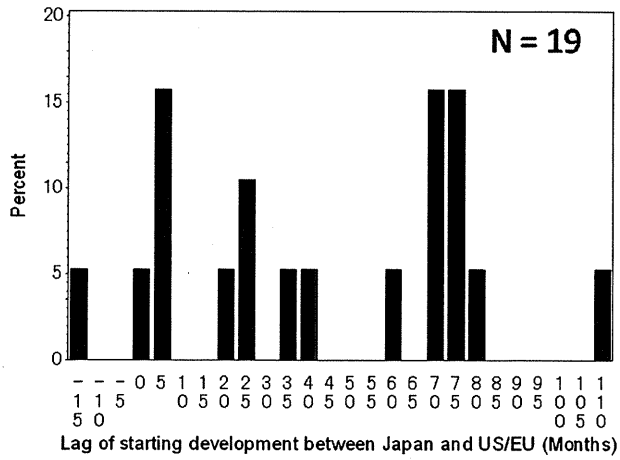

Fig. 4 Histograms of lags in starting drug development between Japan and the US/EU

patients to evaluate Japanese safety profiles. Therefore, at present, most NDAs or sNDAs must include clinical data from Japanese registration trials, which is more information than is required by NDA/sNDA submission packages in the US or EU. Thus, the current Japanese guidelines will have limited impact on resolving the oncology drug lag in Japan.

The Japanese government has initiated various direct and indirect measures for resolving and reducing drug lag. As a direct measure, in order to expand the indications of oncology drugs used in combination chemotherapy, the MHLW set up a transient special committee in 2004 that evaluated evidence of efficacy and safety for several drugs based on publications, textbooks, guidelines, and reviews. Accordingly, sNDAs for 27 drugs for use in 20 chemotherapy combinations were approved between November 2004 and September 2005 without clinical data from registration trials [12].

As an indirect measure, the MHLW set up an expert review committee for examining unapproved drugs between January 2005 and October 2009; this committee evaluated drugs that had been approved in the US or EU and additionally considered the opinions of academia and patient groups regarding the need and appropriateness of the unapproved drugs in clinical practice [1]. Thus, by incorporating these measures, the MHLW aimed to encourage pharmaceutical companies to conduct registration trials in Japan. A revision of the Pharmaceuticals Affairs Law, which came into effect in July 2003, allowed companies to perform investigator-initiated registration trials for the submission of NDAs or sNDAs that required clinical data [13]. To ensure the smooth operation of registration trials, the MHLW set up an expert review committee for defining registrations that functioned between March 2005 and September 2007 to establish an infrastructure for operating registration trials in Japan and to reduce excess responsibility on the managers of investigator-initiated registration trials [14]. Thus, the MHLW issued several notifications related to investigator-initiated trials based on Good Clinical Practice guidelines and the opinions of the expert review committee. The MHLW also launched nationwide clinical trial activation initiatives in 2003 and 2007 to support the development of a framework to promote clinical trials [15]. Continuation of this investment and support for the establishment of an adequate infrastructure for clinical trials would serve to encourage registration trials and could represent an important factor in the future reduction of the drug lag in Japan.

The present study suggests that the oncology drug lag is associated with delays in the initiation of drug development in Japan. One possible reason for the delays may be that pharmaceutical companies believe that simultaneously conducting early-phase registration trials in Japan and in the US/EU is a major financial risk. To resolve delays in the initiation of drug development in Japan, pharmaceutical companies should make an effort to enroll Japanese patients in international registration trials. Although participation in international Phase I trials would be ideal, it is imperative that pharmaceutical companies start drug development in Japan in time for participation in confirmatory-phase global trials.

The results of the present study also suggest that decreased review times by the Japanese regulatory agency would directly contribute to resolving the oncology drug lag. According to a report by Japan's Council for Science and Technology Policy, the PMDA has doubled its staff over a period of approximately 3 years to reduce submission lag and review time by 1.5 years and 1 year,

Table 2 Multivariate regression analysis for approval lag (N=12)

Variables	Coefficient	95% confidence interval		P value
Submission lag	0.1	−0.1	0.2	0.478
Review period	1.3	0.8	1.9	<0.001
Lag in initiation of drug development	0.6	0.4	0.7	<0.001
Hematologic malignancy vs. solid malignancy	−15.3	−26.7	−3.8	0.009
Molecular-targeted drug vs. Non-molecular-targeted	−34.0	−46.2	−21.8	<0.001

Table 3 Development status in the US and EU at the time of starting phase I oncology trials in Japan

Status	US	EU
Post approval, n (%)	9 (27.3)	6 (17.7)
Submitted for approval, n (%)	4 (12.1)	10 (29.4)
Starting pivotal study to submission, n (%)	12 (36.4)	10 (29.4)
Starting Phase I study to starting pivotal study, n (%)	8 (24.2)	8 (23.5)

respectively, by 2011 [16]. Between October 2006 and July 2007, an expert review committee set up by the MHLW worked to clarify the review policy, discussed post-marketing safety controls and infrastructure for consultation of registration trials, and evaluated the review system. The PMDA then released "Points to be Considered by the Review Staff Involved in the Evaluation Process of New Drug" to promote an understanding of the reviewers' standard policies and evaluation process among those in industry and academia [17]. Increasing human resources in the review system and further improving the transparency of the review process at the PMDA would further contribute to reducing review time. During the review process, the PMDA and the pharmaceutical company that developed the drug repeatedly discuss the NDA/sNDA submission until a decision regarding final approval is made by the MHLW. Therefore, both the PMDA and the pharmaceutical company are central players and have a major responsibility for reducing review time.

In Japan, every citizen is required to join universal health insurance program (i.e., employees' health insurance programs or the National Health Insurance program) and the cost of medical drugs is reimbursed by universal health insurance programs according to the indications and dosages that have been approved by the Health Insurance Bureau of the MHLW and the Central Social Insurance Medical Council. Therefore, all pharmaceutical companies have necessary to obtain pharmaceutical approval by submitting an NDA or sNDA to the PMDA in order to sell drugs under Japan's universal health insurance system. Additionally, submitting published data from non registration trials for an NDA or sNDA is not acceptable, even if the trial provides highly significant clinical evidence for treatment guidelines. The drug lag in Japan may also be a result of the relationship between pharmaceutical and medical insurance approval [18]. Thus, resolving drug lag may require changes in the health insurance approval system. A government infrastructure for the evaluation of medical insurance approval independent of pharmaceutical approval, as is embodied in the US compendia, is necessary [19]. Ideally, the PMDA would review all NDAs only that are required to evaluate the risk/benefit balance as drug with new active ingredients; this would make all additional insurance approval process to undertaken by the Health Insurance Bureau. Further, eliminating sNDA submissions for the PMDA would allow the PMDA to reduce its workload and improve the quality of the reviews, thus helping to resolve the drug lag.

In light of the realities of the drug lag in Japan, the MHLW set up a transient expert review committee in February 2010 to evaluate unapproved drugs for unmet medical needs. Although this committee is similar to the transient special committee set up in 2004, the new committee targeted all medicinal classifications of drugs rather than a specific class [20]. The 2010 committee issued three approvals for three oncology drugs without registration trial data because the applications were eligible for inclusion in the public domain [20]. Although this committee successfully led an effort to reduce temporarily unapproved drugs in Japan, its transient nature is not a long-term solution. Therefore, it is imperative that the entire regulatory system for drug and health insurance approval in Japan be reformed in order to better address the needs of Japan's patient population [21].

This study had some limitations. The number of examined approvals varied depending on region (i.e., Japan, the US, and the EU) in Figs. 2, 3, and 4, and the number of approvals examined by multivariate regression analysis was only 12. Specifically, since the imbalance of the examined approvals between Japan and the US/EU could lead to a bias of the summary statistics, the median values shown in the Results section should be carefully interpreted. Furthermore, the coefficients for the parameters shown in Table 2 may include a bias due to the small number of examined approvals, although the multivariate regression analysis showed that all variables, excluding submission lag, were significantly associated with approval lag.

In conclusion, our analysis suggests that delays in drug development initiation and the extended length of the regulatory review period in Japan may contribute to the longer oncology drug lag observed in Japan compared with that in the US/EU. To reduce this lag, the review period required by the Japanese regulatory agency should be reduced; however, this can only occur through the combined efforts of pharmaceutical companies, the PMDA, and concerned academia. We also recommend that Japanese pharmaceutical companies coordinate oncology drug development with development initiatives in other countries to reduce duplicative development efforts as well as delays.

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Compliance with Good Clinical Practice in oncology registration trials in Japan

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Background: This study aimed to examine the quality in oncology registration trials for new drug application (NDA) or supplemental new drug application (sNDA) as extensions of the indications for use in Japan based on Good Clinical Practice (GCP) audit findings.

Materials and methods: We collected audit reports of on-site GCP inspections for registration trials in 383 NDAs or sNDAs that were reviewed by the Pharmaceuticals and Medical Devices Agency between the fiscal years 2004 and 2009.

Results: Among the 40 audits for oncology drug applications, the frequencies at which one or more deficiencies ascribed to institution, investigator, sponsor, and institutional review board were found to be 15 (37.5%), 13 (32.5%), 21 (52.5%), and 10 (25.0%), respectively. The exclusion of patients from the review objective due to serious violations of GCP in 40 audits for oncology drug applications was observed in 2 (5.0%) cases, whereas that in the remaining 343 audits for other drug applications was observed in 40 (11.7%) cases.

Conclusion: The overall compliance of GCP in oncology registration trials was moderately better than that in registration trials for other diseases, although there was no statistically significant difference between them.

Key words: audit, cancer, compliance, Good Clinical Practice, inspection, registration trial

introduction

Approval of new drug applications (NDA) or supplemental new drug applications (sNDA) for extension of the range of indication and/or posology as well as the method of administration is based on collecting evidential materials from registration trials that are strictly managed in terms of quality control and quality assurance. The registration trials for applications are conducted in conformity with Good Clinical Practice (GCP) that provides corroboration of both ethics and science. The purpose of GCP is to protect the human rights and safety of the subjects and is based on the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subject in order to ensure accurate data and reliability in registration trials [1]. The Ministry of Health and Welfare [currently Ministry of Health, Labour and Welfare (MHLW)] of Japan had issued instructions regarding the old GCP guideline in October 1990, which was not legally binding [2]. In April 1997, a new GCP guideline was enforced in response to the implementation of the GCP released by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use for all Japanese registration trials that began from April 1998 onward [3, 4]. Major differences between the old and new GCP guidelines are related to the acquisition of written informed consent documents, intensification of the responsibility of the sponsor, clarification of the responsibility and role of the principal investigator, and improvements in the function of the institutional review board (IRB) and supports for registration trials [2, 3].

In Japan, the number of clinical trial protocol notifications for oncology drug applications is rapidly increasing with each passing year; oncology drug applications comprised ~15% of all clinical trial protocol notifications in the fiscal year 2007 [5]. The number of clinical trial protocol notifications among global registration trials has been increasing substantially; moreover, clinical trial protocol notifications for oncology drugs comprised 59% of global clinical trial protocol notifications, making it the largest field in drug applications in the fiscal year 2007 [6]. It appears that clinical development in the oncology drug field became both active and stable in Japan around this time. These conditions have also made it easier to carry oncology registration trials with sufficient quality according to GCP as compared with that in other drug fields.

Clinical trials for oncology drugs have many differentiating features as compared with those for other drugs. In oncology clinical trials, complicated inclusion/exclusion criteria, frequent dose modifications caused by toxic effects, numerous

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prohibited concomitant medications, tight schedules of clinical assessments, and long follow-up periods are required. In addition, since the pharmacological effects of oncology drugs generally influence cell proliferation or cell division, a large number of adverse events are frequently reported in oncology clinical trials as compared with clinical trials for other drugs. Thus, enormous effort and responsibility are imposed on trial participants, such as institutions, investigator, IRBs, and sponsors.

In this study, we examined GCP compliance in oncology registration trials in order to ensure high-quality clinical trials in Japan. The GCP compliance of the registration trials for NDA and sNDA was examined based on the Pharmaceuticals and Medical Devices Agency's (PMDA) judgment on recent overall results of on-site GCP audits. We have discussed the quality of oncology registration trials through a comparison of the deficiencies found in GCP inspections that were ascribed to the institution, investigator, sponsor, and IRB between 40 oncology drugs applications and 343 drug applications for other diseases.

materials and methods

GCP inspection of PMDA in Japan

The Office of Conformity Audit of PMDA carried out GCP inspections that consisted of document-based conformity audit at the PMDA along with on-site GCP audits [7]. The document-based conformity audit exhaustively inspects the consistency between application materials attached to the application form for approval and all evidential materials of all institutions retained by study sponsors (e.g. case report forms, monitoring records, etc.) from the viewpoint of Good Laboratory Practice, GCP, and conformity criteria of the application materials. The on-site GCP audit inspects the consistency between raw data (e.g. medical records, examination slips, and patient diaries) as evidential materials of surveyed medical institutions and evidential documents of surveyed institutions held by study sponsors (e.g., case report forms). In addition, the on-site GCP audit inspects the general institutional structure for registration trials at the institution (e.g. administration of the medical institution, IRB, maintenance of essential archives, and investigational drug accountability of the pharmacy). The objectives of on-site GCP audits in trial applications have been previously defined [8]. On-site GCP audits are generally carried out for four institutions in NDA and two institutions in sNDA. An institution in Japan or another country enrolling many patients into a pivotal registration trial of application is selected for on-site GCP audit. The PMDA finally judges GCP compliance as follows: conformation, conformation with proviso, or nonconformation. The results are sent to both the sponsor and the institution.

Conformation indicates complete compliance with the GCP in the registration trial for the application. Conformation with proviso means that the PMDA imposes the exclusion of patients from the review objective due to serious violations of the GCP and evaluates the registration trial comprising the remaining patients. If a critical GCP violation concerning ethics and/or science in the registration trial is found, the PMDA judges that all the materials in the registration trial related to GCP nonconformation should be deleted from the application for NDA or sNDA. In this case, the PMDA generally concludes in favor of rejection of the application. It should be noted that when the PMDA's judgment is nonconformation, these results are not publicly released; therefore, the frequency of nonconformations is not investigated.

data sources

In Japan, for each application, on-site GCP inspection for the registration trials—including trials conducted in Japan and overseas for the drugs—are conducted, and their comprehensive audit results are publicly released with exposures of the deficiencies found in GCP inspections that are ascribed to the institution, investigator, sponsor, and IRB [9]. In this study, 344 audits, which were reviewed by the PMDA and approved by the MHLW of Japan between April 2004 and March 2010 (fiscal years 2004 to 2009), were examined, excluding public domain approvals and audits without on-site GCP inspections [10]. For each audit, the following data were collected: medicinal classification of the approved drug, approval year, the PMDA's judgment on GCP compliance (conformation with/without proviso), the number of patients excluded due to serious violations of GCP, GCP deficiencies, and responsible participants of deficiencies (institution, investigator, sponsor, and IRB).

Fisher's exact test was used to compare the frequency distributions with respect to the deficiencies between the audits for anticancer drugs and those for other diseases. A two-sided $P \leq 0.05$ was considered to be statistically significant. All the analyses were carried out using the SAS software (version 9.1; SAS Institute Inc., Cary, NC).

results

conformation with/without proviso

The approval years and medicinal classifications for 383 audits are shown in Table 1. The audits for oncology drug applications comprised 40 (10.4%) of the 383 audits.

Table 2 shows the proportions of conformation with/without proviso overall and for each medicinal classification. Overall, 89.6% of conformation and 10.4% of conformation with proviso were observed. Among the 42 audits judged as conformation with proviso, the frequencies of audits with ≥1 deficiencies ascribed to the institution, investigator, IRB, and sponsor were 34 (81.0%), 23 (54.8%), 12 (28.6%), and 25 (59.5%), respectively. Additionally, the frequencies of audits in each deficiency ascribed to each responsible participant are shown in Table 3.

Conformation with proviso in 40 audits for anticancer drug applications were observed in 2 (5.0%) cases, whereas that in the remaining 343 audits for the other disease applications was observed in 40 (11.7%) ($P = 0.286$). The proportion of conformation with proviso in cancer registration trials tended to be smaller than that in the registration trials for other disease applications, although the number of audits varied depending upon the medicinal classification. Furthermore, although the number of excluded patients was unknown in 9 audits, among the 42 audits judged as conformation with proviso, the median number of excluded patients was 3 (range 1–182) in the remaining 33 audits.

responsible participants due to deficiencies

Table 4 shows the distributions of audits in which one or more deficiencies were ascribed to the responsible participants overall and in each medicinal classification. The proportion of approvals with ≥1 deficiencies ascribed to the institution, investigator, IRB, and sponsor were 15 (37.5%), 13 (32.5%), 10 (25.0%), and 21 (52.5%) in 40 audits, respectively, for oncology drug applications and 168 (49.0%), 145 (42.3%), 78 (22.7%), and 169 (49.3%),

Table 1. Summary of 383 registration trial approvals [*n* (%)]

Medicinal classification	Approval year, fiscal year						Total
	2004	2005	2006	2007	2008	2009	
Neurological	1 (4.2)	3 (7.3)	8 (12.3)	10 (10.9)	8 (11.0)	17 (19.3)	47 (12.3)
Metabolic	1 (4.2)	6 (14.6)	12 (18.5)	15 (16.3)	18 (24.7)	17 (19.3)	69 (18.0)
Oncology	2 (8.3)	7 (17.1)	6 (9.2)	8 (8.7)	9 (12.3)	8 (9.1)	40 (10.4)
Cardiovascular	3 (12.5)	3 (7.3)	4 (6.2)	7 (7.6)	10 (13.7)	9 (10.2)	36 (9.4)
Respiratory	1 (4.2)	1 (2.4)	1 (1.5)	2 (2.2)	0 (0.0)	5 (5.7)	10 (2.6)
Gastrointestinal	0 (0.0)	1 (2.4)	3 (4.6)	10 (10.9)	2 (2.7)	6 (6.8)	22 (5.7)
Hormonal	2 (8.3)	3 (7.3)	7 (10.8)	6 (6.5)	8 (11.0)	7 (8.0)	33 (8.6)
Urological	2 (8.3)	1 (2.4)	4 (6.2)	5 (5.4)	3 (4.1)	1 (1.1)	16 (4.2)
Antimicrobial	7 (29.2)	7 (17.1)	10 (15.4)	16 (17.4)	4 (5.5)	9 (10.2)	53 (13.8)
Biologics	2 (8.3)	4 (9.8)	5 (7.7)	6 86.5)	5 (6.8)	7 8.0)	29 (7.6)
Others	3 (12.5)	5 (12.1)	5 (7.7)	7 (7.6)	6 (8.2)	2 (2.3)	28 (7.3)
Total	24 (100)	41 (100)	65 (100)	92 (100)	73 (100)	88 (100)	383 (100)

Table 2. PMDA's judgment on GCP compliance in oncology and other drug audits [*n* (%)]

Judgments	Medicinal types		Total
	Oncology	Others	
Conformation (without proviso)	38 (95.0)	303 (88.3)	341 (89.6)
Conformation with proviso	2 (5.0)	40 (11.7)	42 (10.4)

Fisher's exact test for contingency table of judgments and medicinal types: $P = 0.286$.

GCP, Good Clinical Practice; PMDA, Pharmaceuticals and Medical Devices Agency.

respectively, in the remaining 343 audits for other drug applications. The deficiencies ascribed to the institution and investigator in the cancer registration trials tended to be lesser than those in the registration trials for other diseases ($P = 0.184$ for institution and $P = 0.309$ for investigator).

deficiencies ascribed to responsible participants

Table 5 shows the frequencies of audits in each deficiency ascribed to each responsible participant overall and in each medicinal classification. The deficiencies related to archives, eligibility criteria, and prohibited concomitant therapies in 40 audits for oncology drug applications were 1 (2.5%), 2 (5.0%), and 0 (0.0%), respectively, whereas those in the 308 other drug audits were 47 (13.7%), 43 (12.5%), and 28 (8.2%), respectively ($P = 0.043$ for archives, $P = 0.201$ for eligibility criteria, and $P = 0.099$ for prohibited concomitant therapies). On the other hand, the deficiency of 'insufficient review' by the IRB in 40 audits for oncology drug applications was higher than that in the 343 other drug audits (17.5% versus 5.5%, $P = 0.012$).

discussion

The results of the present study indicated that the overall compliance of GCP in oncology registration trials was passably better than that in registration trials for other diseases, although there was no statistically significant difference between them. According to Table 5, the problems related to archives in institutions were lesser but insufficient reviews by the IRB were more frequent in the oncology drug applications when compared with those for other diseases. Therefore, completeness of IRB reviews would enhance quality of drug applications in the oncology field.

Previous studies have analyzed a number of GCP deficiencies in registration trials for NDA or sNDA, approved by the MHLW of Japan, from the fiscal year 1997 to 2006 [11–18]. Since a white paper or annual report regarding the overall results of on-site GCP audit has not been officially published, these studies have repeatedly used the same data that were partly released by the PMDA, workshops, or symposiums. In addition, most of these studies examined GCP deficiencies immediately after the enforcement of the new GCP guidelines [11–15]. The examination of compliance with GCP in registration trials for NDA or sNDA in recent times is required.

Our study demonstrated 10.4% of conformations with proviso in registration trials overall in the past 5 years. Previous studies have reported that conformations with proviso comprised 17.6% of registration trials during the fiscal years 2001 and 2003 [16]. Based on the results of the present study and those of previous studies, compliance with GCP in Japanese registration trials has generally been improving [16, 17]. Furthermore, the present study revealed the overall GCP compliance of oncology registration trials tended to be better than that of registration trials for other drugs.

The present study revealed trial institution deviations, investigator deviations, and sponsor deviations in 40%–50% of the audits. The frequencies of deviations related to the trial institution or investigator were lower in the oncology registration trials as compared with those in the other drug registration trials. This may be because the development of oncology drugs is highly specialized; therefore, research sources—including the trial institution, investigator, and other health care professionals—for the registration trials of oncology drugs have much greater experience and can carry registration trials with greater compliance.