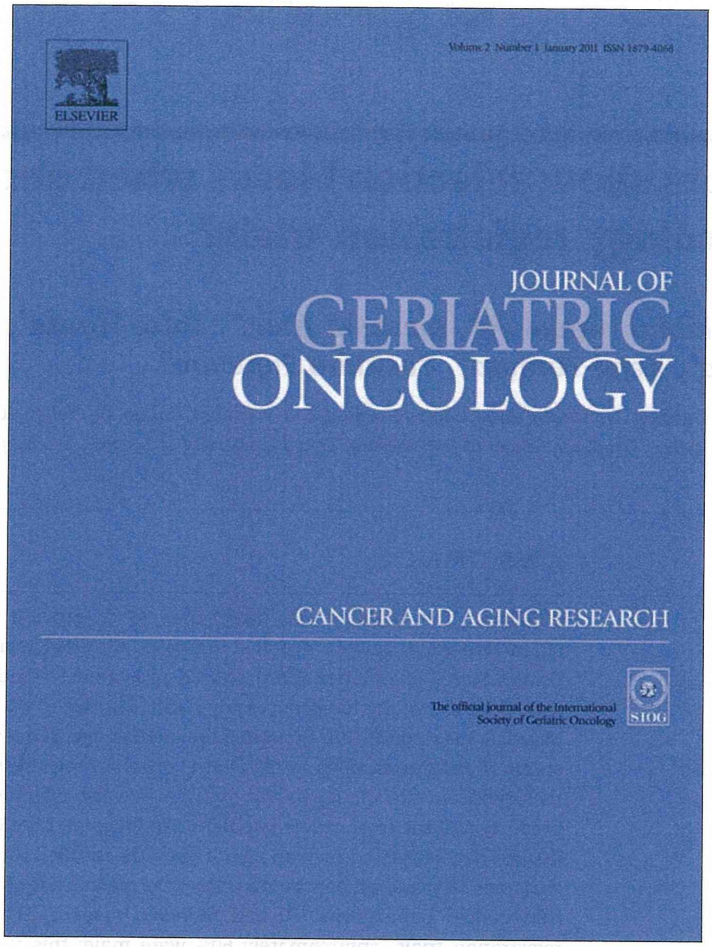
14. Ministry of Health Labor and Welfare. Annual Report on Health, Labour and Welfare 2003–2004. Tokyo: Gyosei 2004.
15. Surveillance, Epidemiology, and End Results http://seer.cancer.gov (last accessed 20 October 2009).
16. Kornblith AB, Kemeny MM, Peterson BL et al. Survey of oncologists' perceptions of barriers to accrual of older patients with breast carcinoma to clinical trials. Cancer 2002; 95: 959–996.
17. Lara PN, Higdon R, Lim N et al. Prospective evaluation of cancer clinical trial accrual patterns; identifying potential barriers to enrollment. J Clin Oncol 2001; 19: 1728–1733.
18. Townsley CA, Chan KK, Pond GR et al. Understanding the attitudes of the elderly towards enrollment into cancer clinical trials. BMC Cancer 2006; 6: 34.
19. The International Non-Hodgkin's Lymphoma Prognostic Factors Project: a predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med 1993; 329: 987–994.
20. Johnson PRE. Acute myeloid leukemia in the elderly: biology and treatment. Br J Haematol 1993; 83: 1–6.
21. Weick JK, Kopecky KJ, Appelbaum FR et al. A randomized investigation of high-dose versus standard-dose cytosine arabinoside with daunorubicin in patients with previously untreated acute myeloid leukemia: a southwest oncologist group study. Blood 1996; 88: 2841–2851.
22. Matsumura S, Fukuhara S, Kurokawa K. Nationwide survey of general population for clinical trials. Nihon-Iji-Shinpo 2000; 3962: 14–19 (in Japanese).
23. Ministry of Internal Affairs and Communications. Annual report of current population estimates (as of October 1st, 2008). http://www.e-stat.go.jp/SG1/estat/ListE.do?lid=000001054002 (last accessed 20 October 2009).
24. Ono K, Sugimachi K. The medical care system in Japan. Surgery 2002; 131: 341–342.
25. Morohashi Y. Controversial issues surrounding the case of HIV infections and AIDS through the use of unheated commercial blood products. Jpn Hosp 1997; 16: 1–3.
26. Shibutani Y. A preventive strategy for hepatitis C infection in Kobe city. Official announcement of medical facilities with past fibrinogen administration. Nippon Koshu Eisei Zasshi 2006; 53: 432–436 (in Japanese).
27. Ministry of Health, Labour and Welfare. Guidelines on methods of clinical evaluation of oncology drug Pharmaceutical and Food Safety Bureau Notification, No. 1101001, dated November 1, 2005 (in Japanese).

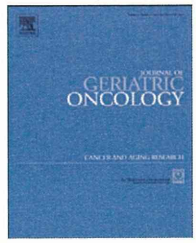


JOURNAL OF GERIATRIC ONCOLOGY 2 (2011) 25–30

available at www.sciencedirect.com

ScienceDirect

ELSEVIER



Do investigators show selection biases when enrolling patients in phase I oncology registration trials?

Kan Yonemori[a,*], *Akihiro Hirakawa*[b], *Masashi Ando*[a], *Taizo Hirata*[a], *Chikako Shimizu*[a], *Noriyuki Katsumata*[a], *Kenji Tamura*[a], *Yasuhiro Fujiwara*[a]

[a]*Breast and Medical Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Cuhuo-ku, Tokyo 103-0045, Japan*
[b]*Department of Management Science, Graduate School of Engineering, Tokyo University of Science, 1-3 Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan*

ARTICLE INFO

Article history:
Received 14 July 2010
Received in revised form
23 August 2010
Accepted 17 September 2010
Available online 13 October 2010

Keywords:
Oncology
Barrier
Elderly patients
Age
Performance status
Phase I
Registration trial

ABSTRACT

Objectives: The goals of this study are: (1) to provide a descriptive analysis of the characteristics of patients enrolled in phase I oncology registration trials in Japan and the United States of America (USA) and (2) to evaluate whether the trial populations were representative of the total cancer populations in these two countries.

Materials and methods: We examined the median age, gender distribution, and performance status of patients enrolled in 133 phase I oncology registration trials of 33 drugs. Data were included from trials in Japan and the USA. We also estimated the median age and gender proportion of the total cancer population in Japan and the USA.

Results: The estimated median age of patients enrolled into phase I oncology registration trials was 58 years, which was lower than the median age of patients in the Japanese and the USA cancer populations (70 and 66 years, respectively). Of the patients enrolled in registration trials, approximately 60% were male; this is higher than the proportion of males in the total cancer populations in both Japan and the USA (43% and 52%, respectively). The proportion of enrolled patients with a performance status of 0–1 was approximately 90%, in both Japanese and the USA cancer populations.

Conclusion: Investigators enroll a lower proportion of older cancer patients on phase I oncology registration trials.

1. Introduction

The development of new drugs requires many stages of scientific and objective evaluations. During preclinical trials, cell cultures or animal models are used for evaluating the efficacy and toxicology of the new drug as well as for determining the mechanism by which the proposed drug functions. Next, the drugs are administered to humans for the first time during phase I clinical trials, which are performed to generate safety profiles based on dose-limiting toxicity, in order to determine the recommended dose and treatment schedule. Later stages of drug development, including phase II and phase III clinical trials, are mainly used to evaluate the preliminary evidence of the efficacy and safety of the new agent, and comparing these values with those of conventional treatments.

The investigational agents used in cancer drug trials may work in a variety of ways, such as inhibiting cell proliferation and cell division. These agents may possess cytotoxicity, genetic toxicity, and reproductive toxicity. Therefore, while phase I trials for other medicines enroll healthy volunteers when possible, phase I trials for oncology drugs generally

* *Corresponding author*. Tel.: +81 3 3542 2511; fax: +81 3 3542 3815.
E-mail address: kyonemor@ncc.go.jp (K. Yonemori).

1879-4068/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jgo.2010.09.003

enroll only cancer patients whose diseases are refractory to standard treatments. Among phase I oncology drug trials, overall response rates have been demonstrated to be 4–10%. Severe toxicity rates and toxicity-related death rate were 14–42% and 0.5%, respectively.[1–7] Of new investigational drugs tested, approximately 0.0001% are eventually approved for use, and these require a median development period of 7–10 years.[8]

There is a unique ethical issue related to phase I oncology trials: because they target participants who have no standard treatment options, the trials may risk the safety of participants while possessing a potential efficacy against their diseases at the time of participation. However, of all patients who are refractory to conventional treatments and who have exhausted all standard treatment options, only a small proportion are eligible for participating in phase I oncology trials. Thus, investigators may find it difficult to accurately assess the risk/benefit balance of various investigational agents for various patients.

The present study was designed to investigate potential selection bias by investigating the demographics of patients enrolled in phase I oncology registration trials. A phase I registration trial is defined as a phase I trial that is conducted by a pharmaceutical company in order to submit a new drug application (NDA) or supplemental new drug application (sNDA) to a regulatory agency. Such a trial is required to satisfy the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice. Specifically, we collected information regarding the age, gender, and performance status (PS), of patients who enrolled in trials for 33 approved drugs (both NDA and sNDA) between 2000 and 2009. We investigated the distribution of demographic characteristics among the types of cancer, drug, administration, and region. Additionally, we compared the estimated median age and gender proportion of trial patients in Japan and the USA with the age and gender distributions of Japanese and US cancer populations. The results of the present study are expected to help investigators to enhance their understanding of participant backgrounds in phase I oncology registration trials and to accurately evaluate the results of such trials.

2. Materials and Methods

2.1. *Phase I Oncology Registration Trial Data Sources*

The Pharmaceuticals and Medical Devices Agency (PMDA) is a Japanese regulatory agency working in conjunction with the Ministry of Health, Labour and Welfare (MHLW).[9] The major role of the PMDA is to conduct drug and medical device reviews, evaluate post-marketing safety, and provide relief services with regard to adverse effects of drugs. The PMDA conducts scientific reviews of marketing authorization applications for pharmaceuticals and medical devices and also conducts registration trial consultations. On the basis of these reviews, the MHLW approves NDA or sNDA for Japan.

We extracted data from PMDA review reports and from documents submitted by pharmaceutical companies; these are available to the public on the websites of the PMDA and the Japan Pharmacists Education Center.[10,11] In particular, we focused on phase I oncology registration trials that had been reviewed by the PMDA between 2000 and 2009. These included trials conducted in Japan and the USA, for NDAs or sNDAs of oncology drugs and drugs for supportive care of cancer. However, data were excluded if the trials focused on limited patient populations (e.g., male-only, female-only, pediatric-only, etc.). Thus, of 149 phase I oncology registration trials that investigated 38 drugs, we excluded 16 trials for 5 drugs because they did not meet our criteria. Therefore, the present study focuses on 133 trials of 33 drugs (31 NDAs and 2 sNDAs) that included 3943 patients (Table 1).

For each oncology registration trial, the following data were collected: type of cancer (solid malignancy, hematologic malignancy), type of drug (cytotoxic; non-cytotoxic, including small molecular-targeted agents and antibody agents; and other, including supportive care agents and miscellaneous agents), type of administration (single or combination), region (Japan or USA), median age and age limits (upper and/or lower), gender distribution, and proportion of patients with each performance status based on the Eastern Cooperative Oncology Group (0, 1, or ≥2). In reports where the Karnofsky performance status was used, we converted it to the Eastern Cooperative Oncology Group performance status (ECOG PS) score.

2.2. *Age and Gender Distributions in Japanese and US Cancer Populations*

We estimated the median age and gender distributions of all Japanese cancer patients (regardless of cancer type) as follows. Age- and gender-specific incidences were obtained from Cancer Statistics in Japan 2003,[12] and were multiplied by age and gender population data provided by the Annual Report on MHLW 2003–2004.[13] This provided an estimate of newly diagnosed cancer patients in each age class and gender

Table 1 – Proportions of drug type, administration regime, type of cancer, and region of study across the 133 examined phase I oncology registration trials.

Variables		Number of trials	%
Drug type	Cytotoxic	53	39.9
	Antibody	17	12.8
	Small molecular targeted	50	37.6
	Others	13	9.8
Administration regime	Single	106	79.7
	Combination	27	20.3
Cancer type	Solid malignancy	103	77.4
	Hematologic malignancy	30	22.6
Region	US	50	37.6
	US/Others[a]	2	1.5
	US/UK	4	3.0
	UK	6	4.5
	UK/EU	1	0.8
	EU	12	9.0
	Regions excluding Japan	13	9.8
	Japan	45	33.8

[a] Others included Canada, Mexico, Brazil, and Israel.

category; this, in turn, allowed us to calculate the overall median age and gender distributions.

To obtain these values for patients comprising the total cancer population in USA, we used estimates provided by the Surveillance, Epidemiology, and End Results Program for the period from 2002 to 2006 (released by the National Cancer Institute).[14] These data were used to estimate the age and gender distributions of patients enrolled in the USA phase I registration trials.

2.3. *Evaluating demographics of patients in phase I registration trials*

Among the patients included in each of the focal phase I registration trials, we calculated the average median age and gender distributions and the proportion of patients in each PS. We then compared the distribution of these values across studies involving different types of cancer, drugs, administration regimes, and regions. For both the Japanese and the USA datasets, we also compared the average median age and gender distributions between the group of patients involved in registration trials and the total cancer population.

3. Results

3.1. *Demographics of patients in trials and in general cancer populations*

The average median age of trial participants was 58 years (range: 40–70 years), which was lower than the average age of patients in the Japanese and the USA general cancer populations (70 and 66 years, respectively). Although the gender ratio in Japanese and the USA trial groups, combined, was skewed toward males (61% males vs. 39% females), the cumulative cancer population of both Japan and the USA comprised approximately equal numbers of men and women (49% and 51%, respectively). The male proportion in Japanese and US cancer populations were 43% and 52%, respectively. In phase I oncology trials, 89% of patients had a PS of 0–1 (Table 2).

3.2. *Distribution of patient demographics according to the type of cancer, drug, administration, and region*

The average median age, gender distribution, and proportion of patients with an ECOG PS of 0–1 was approximately evenly distributed across trials, regardless of the type of drug, cancer, administration regime, or region (Table 3).

Table 2 – Average patient demographics among the examined studies.

	Number of trials	Average	Range
Number of patients, *n*	133	30	4–119
Median age, years	133	58	40–70
Proportion of males, %	132	61	5–100
Proportion of females, %	132	39	0–95
Proportion of patients with PS of 0, %	98	48	0–100
Proportion of patients with PS of 1, %	97	41	0–100
Proportion of patients with PS of ≥2, %	96	11	0–67

4. Discussion

Our analyses indicated that patients in phase I oncology registration trials in both Japan and the USA differed with respect to demographic characteristics from the general cancer population. The present study demonstrated that phase I oncology registration trials predominantly included younger patients, a disproportionately high number of males, and a disproportionate number of patients with PS<2. These trends suggest that investigators may avoid including potentially vulnerable patients (e.g., elderly patients or patients with poor PS) in the pool of potential participants in phase I oncology registration trials. This appears to occur irrespective of cancer type and the region.

A review of phase I oncology trials conducted from 1970 to 2005 (Table 4) indicated that the median age of trial participants was 54–58 years, suggesting that the tendency to include patients younger than the general cancer population (as reported here) is not a new one.[2–7,15–17] This may affect the broad applicability of results from these trials, as 60% of cancer patients are ≥65 years old.[18] Indeed, previous researchers have pointed out that elderly cancer patients are generally under-represented in cancer clinical trials.[19,20] The United States Food and Drug Administration has reported that only 36% of participants in oncology registration trials are ≥65 years old.[21] A number of trials with the eligibility criteria for age and performance status are shown in Table 5. In Table 5, most trials in the USA have no upper age limitation for patient enrollment, whereas most trials in Japan have an upper age limitation. Based on our results, we consider that investigators need to consciously enroll older eligible patients in phase 1 oncology registration trials. Additionally, upper age limitations in eligibility criteria for phase 1 oncology registration trials should be liberalized in Japan.

Prior to the 1990s, phase I trials included fairly equal proportions of patients with an ECOG PS of 0–1 (47–78% of the total) and PS≥2 (22–53% of the total). After the 1990s, the proportions were skewed toward patients with PS of 0–1 (85–94% vs. 6–12% for PS≥2) (Table 4). As shown in Table 5, most trials in both Japan and the USA enrolled patients with a PS≤2. The present study observed that Japanese trials contained a higher proportion of patients with PS 0 than did trials conducted in the USA (Table 3). One explanation could be that currently, cancer patients tend to have a better PS in general with early detection of malignancies, enhanced development of cancer treatments, and improvement in supportive care.

Several studies have used multivariate analyses to explore factors associated with prognosis in phase I oncology trials and have identified independent prognostic factors, including poor PS.[4,5,7,15,17] We found a greater number of patients with PS 0 enrolled in trials for hematologic malignancy than for solid malignancies; further, Japanese investigators appeared to preferentially recruit patients with PS 0 (Table 3). This may be because investigators hesitate to enroll individuals who are at risk of experiencing increased toxicity and who may not be able to survive through the trial.[22–24]

Table 3 – Average patient demographics in the examined studies, divided by type of malignancy and study region.

	Type of malignancy						Study region					
	Solid			Hematologic			USA			Japan		
	Number of trials	Average	Range	Number of trials	Average	Range	Number of trials	Average	Range	Number of trials	Average	Range
Number of patients, n	103	29	4–105	30	31	10–119	88	36	4–119	45	17	6–39
Median age, years	103	59	40–70	30	55	42–67	88	58	42–67	45	58	40–70
Proportion of males, %	103	59	5–100	29	64	42–91	87	61	27–100	45	60	5–100
Proportion of females, %	103	41	0–95	29	36	9–58	87	39	0–73	45	40	0–95
Proportion of patients with PS of 0, %	80	44	0–100	18	67	26–100	57	42	0–87	41	58	0–100
Proportion of patients with PS of 1, %	79	45	0–100	18	22	0–56	56	47	11–100	41	33	0–84
Proportion of patients with PS of 2, %	78	11	0–67	18	11	0–48	55	12	0–50	41	9	0–67

The gender distribution noted in most previous studies with large sample sizes was fairly similar to the actual gender distribution in the US cancer population (Table 4). However, the present study demonstrated that the overall male proportion in phase I oncology registration trials, in both Japan and USA regions, was higher than that in the respective general cancer populations. Particularly, the discrepancy in the proportion of males between phase I oncology phase I registration trials and the general cancer population in Japan is remarkable (60% vs. 43%). It is important to consider that, as of 2007, Japanese women have a considerably higher life expectancy at birth (86.0 years) than Japanese men (79.2 years).[25] Because increases in life span are associated with longer observation periods, it is possible that female patients will have an increasing incidence of cancer simply because of longer durations over which they can become ill. This may have also led to the discrepancy observed between the proportion of females in Japanese oncology phase I registration trials and the general Japanese cancer population.

Generally, older patients have certain co-morbidities, such as hearing loss and cardiovascular, renal, cognitive, and musculoskeletal system impairment. Phase I oncology registration trials often set eligibility criteria with respect to disease status, performance status, organ function, and co-morbidities. In fact, the inclusion criteria for both hepatic (serum total bilirubin) and renal function (serum creatinine) were set at approximately 1.0- to 1.5-fold higher than the normal limit in the analyzed trials (data not shown). These criteria are set in order to judge indications of chemotherapy; thus, inclusion criteria are not set to exclude older patients but rather to identify patients in whom toxicity may be evaluated appropriately and accurately. Further, exclusion criteria meant for increasing patient safety aim to exclude patients with severe or uncontrolled co-morbidities, such as cardiovascular disease, diabetes, infection, psychiatric illness, and multiple cancers. As a result, investigators potentially exclude older patients, who would have greater co-morbidity as compared to younger patients, from phase 1 oncology registration trials. Thus, selecting older patients for phase 1 oncology

Table 4 – Characteristics of participants in historical phase I oncology trials.

References	N	Study duration	Median age (range)	Male (%)	PS 0 (%)	PS 1 (%)	PS 2 (%)	PS>2 (%)
Decoster et al.[2]	6639	1972–1987	56 (2–93)	55%	–	–	–	–
Easty et al.[3]	6447	1974–1982	–	–	8%	39%	31%	22%
Bachelot et al.[4]	154	1986–1993	54 (21–74)	47%	20%	53%	25%	3%
Janisch et al.[15]	349	1987–1991	58 (27–87)	56%	25%	53%	22%	–
Han et al.[5]	420	1991–2000	56 (22–87)	50%	42%	43%	11%	1%
Roberts et al.[6]	6474	1991–2002	55	56%	89%	11%[a]	–	
Seidenfeld et al.[16]	9841	1991–2002	57	52%	93%	6%[a]	–	
Penel et al.[17]	156	1997–2002	54 (23–79)	40%	58%	30%	12%[a]	–
Arkenau et al.[7]	212	2005–2006	58 (19–86)	67%	28%	66%	6%	–
Current study	3943	2000–2009	58 (15–91)	61%	48%	41%	11%	–

Abbreviations: N, number; PS, performance status.
[a] Original data examined PS≥2.

Table 5 – Number of trials with age-specific and performance status criteria in Japan and the United States of America (USA).

Inclusion criteria		Japan		USA	
		Number of trials	%	Number of trials	%
Age	≤70	1	2.2	2	2.3
	≤75	32	71.1	3	3.4
	≤80	1	2.2	0	0.0
	No	8	17.8	70	79.5
	Unknown	3	6.7	13	14.8
PS	0–1	11	24.4	20	22.7
	0–2	28	62.2	50	56.8
	0–3	5	11.1	0	0
	Unknown	1	2.2	18	20.5

Abbreviations: PS, performance status.

registration trial based on current inclusion and exclusion criteria has certain inherent limitations. In the future, utilizing effective geriatric assessment to assess the individual risk-and-benefit balance would be important in phase I oncology trials in order to enroll appropriate elderly patients without potential selection biases.

Conflict of interest statement

Noriyuki Katsumata: Advisory Board: Astra-Zeneca; Honoraria: Sanofi-Aventis, Chugai-Pharmaceutical, Daiichi Sankyo, Novartis, Kyowa-Kirin, and Ono Pharmaceuticals.

Yasuhiro Fujiwara: Research Funding: Pfizer, GlaxoSmithKline, Chugai-Pharmaceutical, Eisai, Daiichi Sankyo, Taiho Pharmaceutical, and Nihon Kayaku.

The other authors declare no conflict of interest.

Contribution for the study

Conception and Design: Yonemori K, Hirakawa A, Ando M, Fujiwara Y.

Data Collection: Yonemori K, Hirakawa A, Hirata T, Ando M, Fujiwara Y.

Analysis and Interpretation of Data: Yonemori K, Hirakawa A, Ando M, Fujiwara Y.

Manuscript Writing and Approval: Yonemori K, Hirakawa A, Ando M, Hirata T, Shimizu C, Katsumata N, Tamura K, Fujiwara Y.

Acknowledgments

This study was supported by science research grants (Grant number: H21-rinken-ippan-005, research on clinical infrastructure development) from the Ministry of Health, Labour and Welfare.

REFERENCES

1. Horstmann E, McCabe MS, Grochow L, Yamamoto S, Rubinstein L, Budd T, et al. Risks and benefits of phase 1 oncology trials, 1991 through 2002. *N Engl J Med* 2005;**352**:895–904.
2. Decoster G, Stein G, Holdener EE. Responses and toxic deaths in phase I clinical trials. *Ann Oncol* 1990;**1**:175–181.
3. Estey E, Hoth D, Simon R, Marsoni S, Leyland-Jones B, Wittes R. Therapeutic response in phase I trials of antineoplastic agents. *Cancer Treat Rep* 1986;**70**:1105–1115.
4. Bachelot T, Ray-Coquard I, Catimel G, Ardiet C, Guastalla JP, Dumortier A, et al. Multivariable analysis of prognostic factors for toxicity and survival for patients enrolled in phase I clinical trials. *Ann Oncol* 2000;**11**:151–156.
5. Han C, Braybrooke JP, Deplanque G, Taylor M, Mackintosh D, Kaur K, et al. Comparison of prognostic factors in patients in phase I trials of cytotoxic drugs vs. new noncytotoxic agents. *Br J Cancer* 2003;**89**:1166–1171.
6. Roberts Jr TG, Goulart BH, Squitieri L, Stallings SC, Halpern EF, Chabner BA, et al. Trends in the risks and benefits to patients with cancer participating in phase 1 clinical trials. *JAMA* 2004;**292**:2130–2140.
7. Arkenau HT, Olmos D, Ang JE, de Bono J, Judson I, Kaye S. Clinical outcome and prognostic factors for patients treated within the context of a phase I study: the Royal Marsden Hospital experience. *Br J Cancer* 2008;**98**:1029–1033.
8. Japan pharmaceutical manufactures association. Pharmaceutical research and development. Data book. Tokyo: Japan Pharmaceutical Manufacture Association; 2010. p. 37–55.
9. Farrell AT, Papadouli I, Hori A, Harczy M, Harrison B, Asakura W, et al. The advisory process for anticancer drug regulation: a global perspective. *Ann Oncol* 2006;**17**:889–896.
10. Pharmaceuticals and Medical Devices Agency: Public assessment report. http://www.info.pmda.go.jp/shinyaku/shinyaku_index.html (last accessed on 1 March 2010).
11. Japan Pharmacists Education Center: Public assessment report. http://www.jpec.or.jp/contents/c01/link.html (last accessed on 20 October 2009).
12. Nomura K. Cancer Statistics in Japan 2003. Tokyo: Foundation for Promotion Cancer Research; 2003.
13. Ministry of Health Labor and Welfare. Annual Report on Health. Labour and Welfare 2003–2004. Tokyo: Gyosei; 2004.
14. Surveillance, Epidemiology, and End Results: http://www.seer.cancer.gov (last accessed on 1 March 2010).
15. Janisch L, Mick R, Schilsky RL, Vogelzang NJ, O'Brien S, Kut M, et al. Prognostic factors for survival in patients treated in phase I clinical trials. *Cancer* 1994;**74**:1965–1973.
16. Seidenfeld J, Horstmann E, Emanuel EJ, Grady C. Participants in phase 1 oncology research trials: are they vulnerable? *Arch Intern Med* 2008;**168**:16–20.
17. Penel N, Vanseymortier M, Bonneterre ME, Clisant S, Dansin E, Vendel Y, et al. Prognostic factors among cancer patients with good performance status screened for phase I trials. *Invest New Drugs* 2008;**26**:53–58.
18. Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics. *CA Cancer J Clin* 2000;**50**:7–33.
19. Ford JG, Howerton MW, Lai GY, Gary TL, Bolen S, Gibbons MC, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. *Cancer* 2008;**112**:228–242.
20. Townsley CA, Selby R, Siu LL. Systemic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol* 2005;**23**:3112–3124.
21. Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trial for cancer drug registration: a 7-year experience by the US Food and Drug Administration. *J Clin Oncol* 2004;**22**:4626–4631.

22. Shipp MA, Harrington DP, Klatt MM, Jochelson MS, Pinkus GS, Marshall JL, et al. Identification of major prognostic subgroups of patients with large-cell lymphoma treated with m-BACOD or M-BACOD. *Ann Intern Med* 1986;**104**:757–765.
23. Tam CS, Wolf MM, Januszewicz EH, Grigg AP, Prince HM, Westerman D, et al. A new model for predicting infectious complications during fludarabine-based combination chemotherapy among patients with indolent lymphoid malignancies. *Cancer* 2004;**101**:2042–2049.
24. Janssen-Heijnen ML, van Spronsen DJ, Lemmens VE, Houterman S, Verheij KD, Coebergh JW. A population-based study of severity of comorbidity among patients with non-Hodgkin's lymphoma: prognostic impact independent of International Prognostic Index. *Br J Haematol* 2005;**129**:597–606.
25. Cabinet Office Director-general for Policies on Cohesive Society. White paper on aging society 2009. Tokyo: Cabinet Office; 2009.

Biography: **Kan Yonemori, MD.**
1999.3. MD: Tsukuba University, Japan
1999.5-2001.4. Resident of Internal Medicine, International Medical Center of Japan (IMCJ)
2001.5-2002.5. Clinical Fellow of Respiratory Medicine, IMCJ
2002.6-2005.3. Clinical Fellow of Medical Oncology, National Cancer Center, Tokyo, Japan (NCCH)
2005.4-2007.3. Chief Clinical Fellow of Breast and Medical Oncology Division, NCCH
2007.4-2007.8. Staff Clinician of Breast and Medical Oncology Division, NCCH
2007.9-2010.8:
1) Medical reviewer of Pharmaceuticals and Medical Devices Agency
2) Medical Oncologist of Breast and Medical Oncology Division, NCCH
2010.9-present. Medical Oncologist of Breast and Medical Oncology Division, NCCH
Board Certifications:
Certificated Doctor of Japanese Society of Internal Medicine
Certificated Doctor of Japanese Society of Respiratory Medicine
Certificated Doctor of Japanese Society of Medical Oncology
Certificated Doctor of Japanese Board of Cancer Therapy
Certificated Attending Doctor for Clinical Training of Ministry of Health, Labour and Welfare in Japan
Member of Academic Society:
Japanese Society of Internal Medicine
Japanese Society of Respiratory Medicine
Japanese Society of Cancer Association
Japanese Society of Clinical Oncology
Japanese Society of Medical Oncology
Japanese Society of Breast Cancer
Japanese Society of Lung Cancer
Japanese Society of Medical Education
American Society of Clinical Oncology
Awards:
Incitement Award of Japanese Cancer Association (2008.10)

Annals of Oncology Advance Access published November 30, 2010

original article

Annals of Oncology
doi:10.1093/annonc/mdq594

Compliance with Good Clinical Practice in oncology registration trials in Japan

K. Yonemori[1]*, A. Hirakawa[2], M. Ando[1,3], T. Hirata[1], C. Shimizu[1], N. Katsumata[1], K. Tamura[1] & Y. Fujiwara[1,3]

[1]Department of Breast and Medical Oncology, National Cancer Center Hospital; [2]Department of Management Science, Graduate School of Engineering, Tokyo University of Science; [3]Department of Clinical Trial Coordination and Developmental Therapeutics, National Cancer Center Hospital, Tokyo, Japan

Received 18 June 2010; revised 26 August 2010; accepted 27 August 2010

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

original article

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

*Correspondence to: Dr K. Yonemori, Breast and Medical Oncology Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 103-0045, Japan. Tel: +81-3-3542-2511; Fax: +81-3-3542-3815; E-mail: kyonemor@ncc.go.jp

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.

Table 3. Frequencies of audits in each deficiency ascribed to each responsible participant in 42 approvals judged as conformation with proviso

Responsible participants	Deficiencies	*n* (%)
Institution	Qualification requirements of hospitals were not met	6 (14.3)
	Lack of appropriate SOP	0 (0.0)
	All investigators were not identified in the contract	0 (0.0)
	Inappropriate contract	6 (14.3)
	Inappropriate informed consent	11 (26.2)
	CRFs filled incorrectly/and or insufficiently	8 (19.1)
	Problems related to archives	19 (45.2)
	Delay in communication of safety information	3 (7.1)
	Others	6 (14.3)
Investigator	Eligibility criteria were not met	13 (31.0)
	Prohibited concomitant therapies	7 (16.7)
	Laboratory tests were not performed according to the defined protocol	9 (21.4)
	Nonobservance of dose and/or schedule provided by the protocol	8 (19.1)
	Others	8 (19.1)
Sponsor	Inappropriate monitoring	24 (57.1)
	Delay in communication of safety information to institution	4 (9.5)
	Others	2 (4.8)
IRB	Qualification requirements of IRB were not met	2 (4.8)
	Lack of appropriate SOP	1 (2.4)
	Insufficient review	4 (9.5)
	Insufficient minutes of meetings	2 (4.8)
	Others	7 (16.7)

IRB, institutional review board; SOP, standard operational procedure; CRFs, case report forms.

Table 4. Frequencies of audits in which one or more deficiencies ascribed to the responsible participants were found by GCP inspection in oncology and other registered trials [*n* (%)]

Responsible participants	Medicinal type		Total	*P* value[a]
	Oncology	Others		
Institution				0.184
Yes	15 (37.5)	168 (49.0)	183 (47.8)	
No	25 (62.5)	175 (51.0)	200 (52.2)	
Investigator				0.309
Yes	13 (32.5)	145 (42.3)	158 (41.3)	
No	27 (67.5)	198 (57.7)	225 (58.8)	
IRB				0.696
Yes	10 (25.0)	78 (22.7)	88 (23.0)	
No	30 (75.0)	265 (77.3)	295 (77.0)	
Sponsor				0.740
Yes	21 (52.5)	169 (49.3)	190 (49.6)	
No	19 (47.5)	174 (50.7)	193 (50.4)	

[a]Fisher's exact test for contingency table of the presence of deficiencies ascribed to each responsible participant and medicinal types.
GCP, Good Clinical Practice; IRB, institutional review board.

Drug development generally takes considerably long due to the on-site GCP audit in response to a trial application. However, problems related to archives would essentially relate to the reliability of the registration trial regarding the existing subjects, ethics, and science. We noted no problems related to archives in the oncology drug registration trials; the frequency of this deficiency was clearly lower for oncology drugs as compared with other drugs. Thus, the compliance with GCP regarding archives was satisfactory in oncology drug registration trials.

The frequency of protocol deviation in oncology fields is lower than that for other medicinal classifications; however, protocol deviations for eligibility criteria or use of prohibited concomitant therapies would influence subject safety in registration trials. Therefore, investigators, clinical research coordinators (CRC), and other health care professionals who support registration trials should make an effort to have sufficient knowledge regarding the target disease and treatment and keep track of details regarding the protocol and GCP. The incidence of deficiencies at domestic investigational sites with CRC was 21% (N = 270/1260), which was lower than that of deficiencies at domestic investigational sites without CRC, i.e. 58% (N = 188/325) [7, 18]. Therefore, an effective approach for reducing deficiencies associated with protocol deviation would entail the careful selection of trial institutions with sufficient numbers of well-trained CRCs and suitable conditions for carrying out monitoring.

In the present study, deficiencies in monitoring were most frequent both overall and in sponsor deviations. Monitoring of the medical institution by the sponsor is enforced by GCP in order to ensure appropriate operation of the registration trial according to trial protocol and GCP. A previous study indicated that typical monitoring issues associated with sponsors in the fiscal year 2005 were as follows: operation of monitoring associated with standard operation procedure and source document verification (41%), timing of monitoring (9.5%), taking appropriate precautions to prevent deviation by monitoring report (8.5%), submission of monitoring report (5.5%), and other (35.5%) [18]. Appropriate monitoring for registration trial by a monitor who has been specifically trained and possesses scientific and clinical knowledge is important for ensuring quality control and quality assurance of registration trials. For further improvement in reducing deficiencies in monitoring, the monitor in the sponsor organization or contract research organization (CRO) should be sufficiently familiar with the protocol and GCP. Improved performance of various parties in the registration trial would not only facilitate operation of the registration trial by the sponsor but also the operation of investigator-initiated registration-directed clinical trials by the investigator, according to the revised GCP enforced from July 2003 [19].

Another major item of deficiency related to the sponsor is a delay in communicating information regarding adverse drug reactions; this is related to subject safety, ethics, and operation of the registration trial. A seamless communication system for delivering critical information is important for ensuring subject safety and appropriate operation of the registration trial. In

Table 5. Frequencies of audits in which each deficiency was found by GCP inspection in oncology drug and other drug applications [*n* (%)]

Responsible participants	Deficiencies	Oncology	Others	Total	*P* value[a]
Institution	Qualification requirements of hospitals were not met	1 (2.5)	6 (1.8)	7 (1.8)	0.541
	Lack of appropriate SOP	0 (0.0)	0 (0.0)	0 (0.0)	–
	All investigators were not identified in the contract	0 (0.0)	3 (0.9)	3 (0.8)	1.000
	Inappropriate contract	2 (5.0)	17 (5.0)	19 (5.0)	1.000
	Inappropriate informed consent	3 (7.5)	26 (7.6)	29 (7.6)	1.000
	CRFs filled incorrectly/and or insufficiently	8 (20.0)	81 (23.6)	89 (23.2)	0.696
	Problems related to archives	1 (2.5)	47 (13.7)	48 (12.5)	0.043
	Delay in communication of safety information	2 (5.0)	21 (6.1)	23 (6.0)	1.000
	Others	4 (10.0)	36 (10.5)	40 (10.4)	1.000
Investigator	Eligibility criteria were not met	2 (5.0)	43 (12.5)	45 (11.8)	0.201
	Prohibited concomitant therapies	0 (0.0)	28 (8.2)	28 (7.3)	0.099
	Laboratory tests were not carried out according to the defined protocol	6 (15.0)	59 (17.2)	65 (17.0)	0.823
	Nonobservance of dose and/or schedule provided by the protocol	5 (12.5)	23 (6.7)	28 (7.3)	0.195
	Others	5 (12.5)	48 (14.0)	53 (13.8)	1.000
IRB	Qualification requirements of IRB were not met	1 (2.5)	5 (1.5)	6 (1.6)	0.487
	Lack of appropriate SOP	0 (0.0)	2 (0.6)	2 (0.5)	1.000
	Insufficient review	7 (17.5)	19 (5.5)	26 (6.8)	0.012
	Insufficient minutes of meetings	0 (0.0)	12 (3.5)	12 (3.1)	0.623
	Others	2 (5.0)	49 (14.3)	51 (13.3)	0.138
Sponsor	Inappropriate monitoring	19 (47.5)	136 (39.7)	155 (40.5)	0.395
	Delay in communication of safety information to institution	5 (12.5)	50 (14.6)	55 (14.4)	1.000
	Others	1 (2.5)	13 (3.8)	14 (3.7)	1.000

[a]Fisher's exact test for contingency table of the presence of each deficiency and medicinal types.
GCP, Good Clinical Practice; IRB, institutional review board; SOP, standard operational procedure.

recent drug development protocols, registration trials such as randomized clinical trials are carried out globally in various trial institutions; in such a scenario, worldwide regional offices of the sponsor would be ideal for improving communication systems and ensuring smooth and timely communication.

There have been various approaches for improving social and scientific infrastructure for clinical research in Japan by academia, industry, and the government. In 2003, the MHLW drew up and published the nationwide 3-year clinical trial activation plan, under which it promoted various measures, including the creation of clinical trial networks and fostering of CRC. Subsequently, the MHLW created the office of clinical trial promotion, research, and development and launched the new 5 yearly clinical trial activation plan in 2007, which was expected to reinforce clinical research infrastructure to ensure patient safety and to secure access to new drugs and devices [20]. Furthermore, the MHLW science research grants 'research on clinical trials infrastructure development' were inaugurated to support framework development for promoting clinical trials (comprising grants to 10 leading academic medical centers). Thus, a study on 'the development of individual health care institution infrastructure models aimed at equally sharing cancer research infrastructure development' was started, and it became possible to pursue favorable institutional infrastructure development and human resources training concerning the ethical aspects of clinical research and methods of new drug development in the National Cancer Center Hospital [21, 22]. Furthermore, the Japanese Ministry of Education, Culture, Sports, Science and Technology provided grants to five universities and a clinical research organization named 'Coordination, Support and Training Program for Translational Research' in 2007 and onward [22, 23]. These various approaches promoted the establishment of a clinical trial infrastructure; we believe that an adequate infrastructure would be the optimal influence for ensuring compliance with GCP in registration trials.

Our study had certain limitations. We were not able to use the full data of on-site GCP audits for a number of trial institutions—such as the trial institution background, i.e. scale (university hospital, national hospital, private hospital, and clinic), region (Japan or other countries), number of subjects under on-site GCP audit, presence of supporting system for registered trial (CRC, site management organization, CRO, etc.)—because the PMDA review reports for on-site GCP audit are the only available data source and these do not have detailed data. Therefore, it is difficult to directly compare the results of the present study with those of previous studies. Because there

are few reports of on-site GCP audits by regulatory agencies, the present study described differences in deficiencies from on-site GCP audits between Japan and other countries. For further improving global compliance with GCP, we consider that each regulatory agency should disclose detailed results of on-site GCP audits on a regular basis.

GCP inspections have indicated certain deficiencies in the data of registration trials and the operation systems of registration trials; these were evaluated in the regulatory reviews of NDA or sNDA. However, the most important purpose of GCP inspection is to prevent a recurrence of GCP deficiencies for establishing higher quality in drug development. In 2009, the European Medicines Agency (EMEA) and the Food and Drug Administration (FDA), USA, initiated the EMEA–FDA GCP initiative that focuses upon enhanced and systematic GCP-related information exchanges between the EMEA and FDA combined with collaboration in the conduct of GCP inspections of registration trials [24]. The results of the present study suggest that the principle of compliance with GCP for registration trials has reached Japanese investigators and trial institutions, and high-quality GCP inspections are thereby being carried out by the PMDA. The clinical development of medicines is a global undertaking. Therefore, in the future, we consider it important that all regulatory agencies work in a collaborative and synergistic manner in order to achieve a system for the optimal use of GCP inspection resources and results and implement information exchanges.

funding

This study was supported by science research grants (H21-rinken-ippan-005, research on clinical infrastructure development) from the Ministry of Health, Labour and Welfare.

disclosure

NK: advisory board: Astra-Zeneca; honoraria: Sanofi-Aventis, Chugai-Pharmaceutical, Daiichi Sankyo, Novartis, Kyowa-Kirin, Ono pharmaceutical. YF: research funding: Pfizer, GlaxoSmithkline, Chugai-Pharmaceutical, Eisai, Daiichi Sankyo, Taiho Pharmaceutical, Nihon Kayaku. The other authors declare no conflict of interest. The research funding had no involvement in the study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

references

1. Rickham PP. Human experimentation. Code of ethics of the world medical association. Declaration of Helsinki. Br Med J 1964; 2: 177.
2. Ministry of Health and Welfare. Pharmaceutical Affairs Bureau Notification. No. 874 dated October 2 1989 (in Japanese).
3. Ministry of Health and Welfare. Ministerial Ordinance. No. 28 dated March 27 1997 (in Japanese).
4. International Conference on Harmonization Harmonized Tripartite Guidelines (step 4) Guideline for Good Clinical Practice. Geneva, Switzerland: ICH-secretariat 1996.
5. Mori K. Results of the forum for anticancer drug development: two years performance of the review team. Pharm Regul Sci 2008; 39: 803–806 (in Japanese).
6. Yamada M. Current trend in review of PMDA. Pharm Regul Sci 2008; 39(12): 781–795 (in Japanese).
7. Akiyama T, Furuta M, Yamada H. In order to perform clinical efficiently in Japan. Nihon Kokyuki Gakkai Zasshi 2006; 44: 541–549 (in Japanese).
8. Ministry of Health, Labour and Welfare. Pharmaceutical and Food Safety Bureau Notification. No. 0131006 dated January 31,2006 (in Japanese).
9. Pharmaceuticals and Medical Devices Agency. Public Assessment Report. http://www.info.pmda.go.jp/shinyaku/shinyaku_index.html (9 December 2009, date last accessed) (in Japanese).
10. Farrell AT, Papadouli I, Hori A et al. The advisory process for anticancer drug regulation: a global perspective. Ann Oncol 2006; 17: 889–896.
11. Ono S, Kodama Y, Nagao T, Toyoshima S. The quality of conduct in Japanese clinical trials: deficiencies found in GCP inspections. Control Clin Trials 2002; 23: 29–41.
12. Saito K, Kodama Y, Ono S, Fujimura A. Recent changes in quality in Japanese clinical trials. Ann Pharmacother 2004; 38: 151–155.
13. Saito K, Kodama Y, Ono S et al. Current status of quality in Japanese clinical trials. Contemp Clin Trials 2005; 26: 503–509.
14. Saito K, Kodama Y, Ono S et al. Quality of Japanese clinical trials estimated from good clinical practice audit findings. Am J Ther 2006; 13: 127–133.
15. Saito K, Kodama Y, Ono S et al. Reliability of Japanese clinical trials estimated from GCP audit findings. Int J Clin Pharmacol Ther 2008; 46: 415–420.
16. Nishimura T. improving clinical trials in Japan by GCP audit at the office of conformity audit of PMDA. Pharm Regul Sci 2005; 36: 249–257 (in Japanese).
17. Nishimura T. Methods to ensure GCP compliance in clinical trials: findings generated by GCP audit of the office of conformity audit of PMDA. Pharm Regul Sci 2008; 39: 388–395(in Japanese).
18. Kaichi S, Oda T, Goto K, Sato K. In order to perform clinical trials efficiently in Japan: important issues regarding monitoring by sponsors. Nihon Kokyuki Gakkai Zasshi 2007; 45: 829–835 (in Japanese).
19. Ando M, Fujiwara Y. Changes to the clinical trial system in Japan. ASCO News and Forum. Alexandria, Egypt: USA, ASCO Publications 2005; 35–37.
20. Hayashi Y. New 5 yearly clinical trial action plan. Pharm Regul Sci 2007; 38: 658–663 (in Japanese).
21. Fujiwara Y. Infrastructure development and human resources training for clinical trials. The national cancer center hospital as an example. Pharm Regul Sci 2007; 38: 646–650 (in Japanese).
22. Fujiwara Y. Current environment of clinical drug development/research in Japan. 20th International Congress on Anti-cancer Treatment. 3–6 February 2009. Abstract book, 2009; 93–95.
23. Arakawa Y. Improvement of clinical trial environment: activities of University Tokyo Hospital and University Hospital clinical trial alliance. Pharm Regul Sci 2007; 38: 639–645 (in Japanese).
24. EMEA-FDA GCP Initiative. Terms of Engagement and Procedures for Participating Authorities. http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/EuropeanUnion/EuropeanUnion/EuropeanCommission/ucm189508.htm (9 December 2009, date last accessed).

Invest New Drugs
DOI 10.1007/s10637-011-9638-0

PHASE III STUDIES

The notorious "drug lag" for oncology drugs in Japan

Kan Yonemori · Akihiro Hirakawa · Masashi Ando · Taizo Hirata · Mayu Yunokawa · Chikako Shimizu · Noriyuki Katsumata · Kenji Tamura · Yasuhiro Fujiwara

Received: 19 December 2010 / Accepted: 24 January 2011

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

K. Yonemori (✉) · M. Ando · T. Hirata · M. Yunokawa · C. Shimizu · N. Katsumata · K. Tamura · Y. Fujiwara
Breast and Medical Oncology Division,
National Cancer Center Hospital,
5-1-1 Tsukiji, Chuo-ku,
Tokyo 103-0045, Japan
e-mail: kyonemor@ncc.go.jp

A. Hirakawa
Department of Management Science, Graduate School of Engineering, Tokyo University of Science,
1-3 Kagurazaka, Shinjuku-ku,
Tokyo 162-8601, Japan

Published online: 01 February 2011

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).

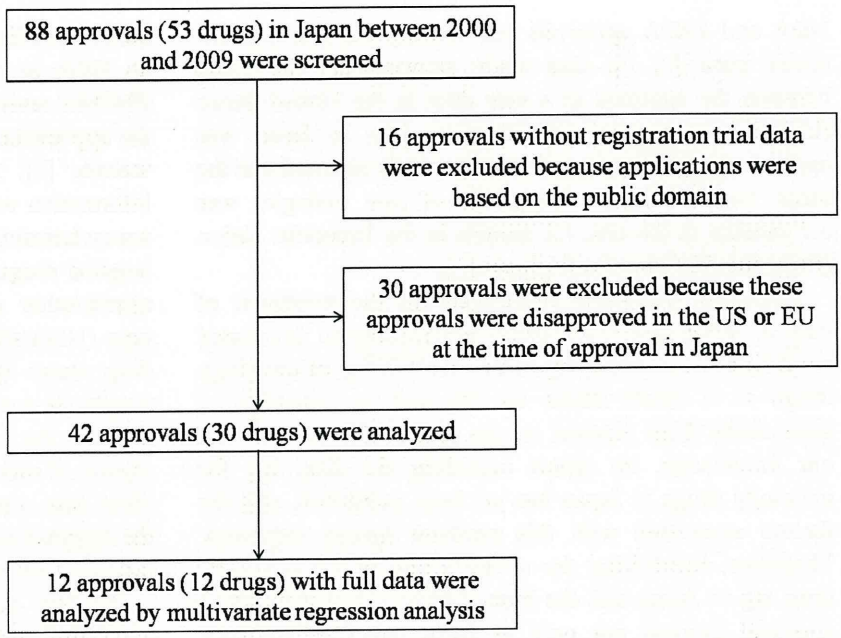


Fig. 1 Diagram of selection of study objects

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

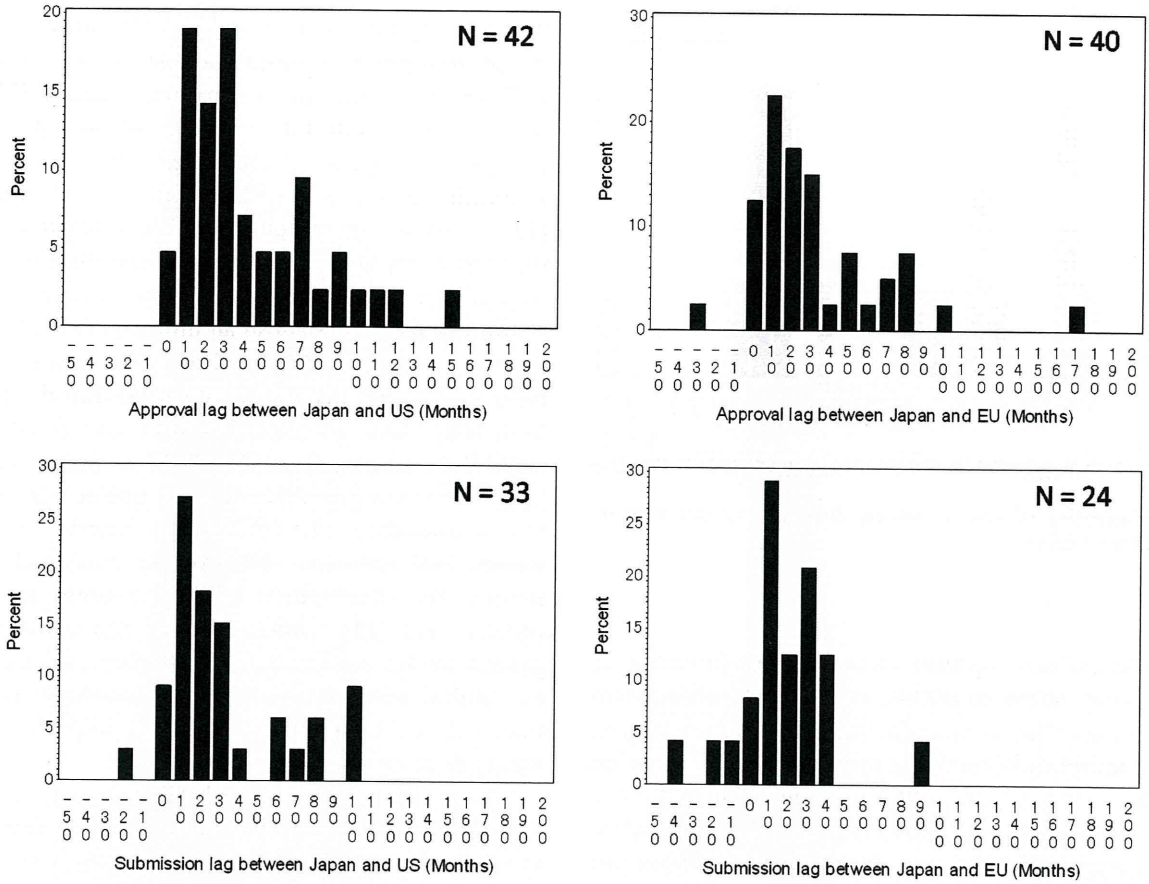


Fig. 2 Histograms of approval lags and submission lags between Japan and the US/EU

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

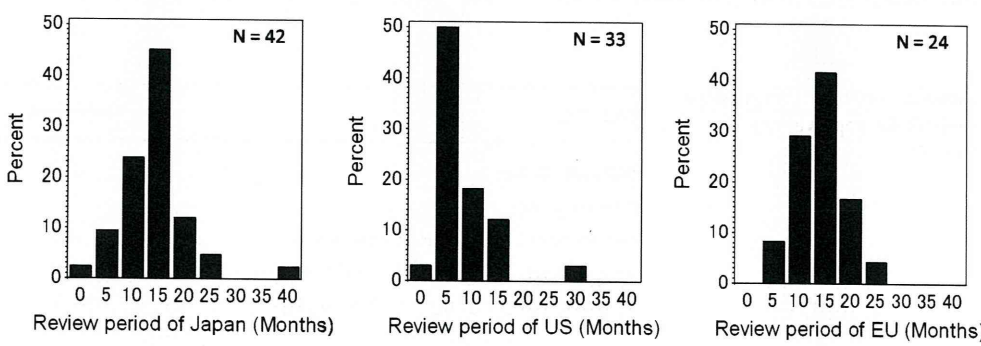


Fig. 3 Histograms of review periods in Japan, the US, and EU

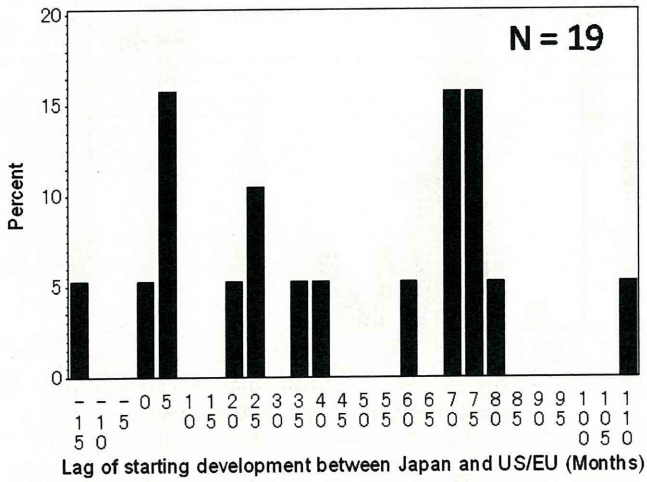


Fig. 4 Histograms of lags in starting drug development between Japan and the US/EU

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.