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Therapeutic response and potential pitfalls in phase I clinical trials of anticancer agents conducted in Japan

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Abstract. The published reports of phase I clinical trials of anticancer agents conducted in Japan from 1981 to 1991 were reviewed. A total of 56 clinical studies that evaluated 38 different agents were reviewed. An average of five agents were studied each year. A total of 2200 patients had been recruited into the 56 clinical trials conducted during this period. A total of 91 patients (4.1%) responded to the treatment, with 23 showing a complete response (1.1%) and 48, a partial response (2.2%). In all, 62% of the responses were observed when patients were treated with doses ranging from 76% to 125% of the recommended doses for phase II studies. The response rates obtained for hematological malignancies were higher than those reported for other malignancies. The past status of phase I clinical trials in Japan can be summarized as follows. (1) A median of seven institutes participated in a single trial. The number of institutes participating correlated with the number of patients enrolled. However, too many institutes participated in a single phase I clinical trial in some studies. (2) The median duration of study for the clinical trials was 14 months. The duration of study was too long in some studies, considering the small number of patients enrolled. In conclusion, the methodology of phase I clinical trials of anticancer agents conducted in Japan should be improved in an efficient and scientific manner, especially for the testing of imported agents.

Key words: Phase I clinical trial – Anticancer agent – Response rate

Introduction

Clinical trial should be conducted in a safe, efficient, and scientific manner, especially those of anticancer agents. Although many anticancer agents, including imported agents as well as drugs developed in Japan, have been clinically tested in Japan for the last 20 years, to our knowledge, an investigation of the methodology and the results of clinical trials, especially phase I clinical trials of anticancer agents, has not been reported in Japan.

On the other hand, since patients do anticipate an antitumor effect of the new drug, even in the phase I study, the therapeutic response achieved in phase I clinical trials should be considered from the viewpoint of the patient's situation. However, there have been few reports concerning the response rate obtained in phase I clinical trials of anticancer agents in Japan.

The purpose of the present study was to examine the response rate on the basis of a review of phase I clinical studies of anticancer agents conducted in Japan from 1981 to 1991. In addition, the problems encountered in phase I clinical studies of anticancer agents conducted in Japan are discussed.

Materials and methods

All major journals published between 1981 and 1991 were searched for phase I clinical trials of anticancer agents conducted in Japan using the MEDLINE and JMEDICINE data bases. Only published reports of trials of cytotoxic agents were utilized. Studies on biological response modifiers and hormonal agents were excluded. A total of 56 phase I clinical studies that evaluated 38 different agents were reviewed.

The following parameters were collected for each study: (1) the number of patients enrolled, evaluable, and responding; (2) the dose of drug at which the responses were observed; (3) the type of tumor involved; (4) the number of institutes participating; and (5) the duration of study.

The patients in whom the toxicity of the anticancer agents was evaluated were classified as evaluable. Complete remission and partial remission were classified according to the description in the reports. The definition of response in many reports was almost the same as that of WHO [10], which is as follows: complete remission, the complete disappearance of all detectable disease and the absence of new lesions for at least 4 weeks; and partial remission, a decrease of $\geq 50\%$ in the size of all tumors as measured by the sum of the products of the diameters of measurable lesions and the absence of new lesions for at least 4 weeks. Cases that had been described only as "responded" or "effective" were classified into the category of "responded."

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Table 1. Drugs studied in phase I trials each year in Japan: 1981–1991

Year	Compounds	Year	Compounds
1981	GANU	1987	TA-077
	TAC-278		Carboplatin[a]
	Ranimustine[a]		Idarubicin
	Mitoxantrone[a]	1988	SM-5887
	Cisplatin[a]		Carboplatin[a]
	Vindesine[a]		
1982	TAC-278	1989	KRN-8602
	Neothramycin		SM-108
	KW-2083		5FU & leucovorin[a]
	CAM	1990	KRN-8602
	Amsacrine		CPT-11
	CDDP[a]		5FU[a]
1983	Tegafurl-Uracil-E[a]		1-OHP
	Pirarubicin[a]		Cytarabine ocfosfate[a]
	Ranimustine[a]		Sobuzoxane
	VP-16-213[a]		DWA-2114R
1984	FF-705	1991	Zinostatin stimalamer
	KW-2083		FK-973
	PL-AC		254-S
	4′-Epiadriamycin[a]		Etoposide & CDDP[a]
1985	NK-171 (etoposide)[a]		CPT-11
	Pirarubicin[a]		Tegafur[a]
	Doxifluridine[a]		Idarubicin
1986	Bestrabucil		Trimetrexate
	IgG-Melphalan		
	TA-077		
	Enocitabine[a]		
	VP-16-213[a]		

[a] Marketed in Japan

Table 2. Number of patients and responses in published phase I trials in Japan

Year	Number of patients		Number of patients		
	Registered	Evaluable	CR	PR	Responded[a]
1981	290	243	2	3	3
1982	287	287		1	6
1983	189	182	2	2	
1984	151	132		3	
1985	198	123	2	1	
1986	351	298	8	5	3
1987	56	55			
1988	73	55			
1989	100	100	2	5	
1990	189	158	4	11	5
1991	316	281	3	17	3
Total (%)	2200 (100)	1914 (87.0)	23 (1.1)	48 (2.2)	20 (0.9)
Mean number of patients/year	200	174			

CR, Complete remission; PR, partial remission
[a] Cases were described only as "responded" or "effective" in the reports

Results

The agents studied each year are listed in Table 1. Phase I clinical trials of 38 different agents were reported during this 11-year period; an average of 5 agents were studied each year (range, 2–8). The numbers of patients enrolled, evaluable, and responding are summarized by year in Table 2. A total of 2200 patients were treated in the 56 phase I clinical trials conducted during this period, with an average of 200 patients being enrolled into the phase I trials each year (range, 56–351). An average of 174 (range, 55–298) of these patients (87%) were evaluable for toxicity.

The overall response rate obtained in the phase I clinical trials in Japan was 4%. There were 23 complete remissions (1.1%) and 48 partial remissions (2.2%). The response rate by year ranged from 0 in 1987 and 1988 to 12.7% in 1990. In all, 62% of the patients who responded were treated with doses ranging from 76% to 125% of the recommended doses for phase II studies (Table 3). The types of tumors

Table 3. Number of clinical responses obtained at various dose levels used in phase I trials in Japan

% of Recommended dose for phase II study	Number of patients		
	CR	PR	Responded[a]
0%– 25%		2	
26%– 75%		5	4
76%–125%	10	25	6
≥126%	8	6	

CR, Complete remission; PR, partial remission
[a] Cases were described only as "responded" or "effective" in the reports

Table 4. Types of tumors that responded in phase I trials

Diagnosis	Number of patients[a]	CR	PR	Responded[b]	Response rate (%)
Acute nonlymphocytic leukemia	96	8	7		16
Acute lymphocytic leukemia	21	1	1		10
Atypical leukemia	3	2			67
Chronic myeloid leukemia	46	1	1	1	6.5
Malignant lymphoma	120	10	5	2	14
Hodgkin's disease	9	1	1		22
Non-Hodgkin's lymphoma	25	3	1		16
Lymphoma unspecified	86	6	3	2	13
Lung cancer	422		12	1	3.1
Non-small-cell	86		9		11
Small-cell	16		2		13
Lung unspecified	320		1	1	0.6
Gastric cancer	257		1	4	1.9
Colon cancer	118	1	7	3	9.3
Esophageal cancer	18		2	2	22
Hepatocellular carcinoma	63		2		3.2
Breast cancer	189		1	1	1.1
Renal-cell carcinoma	16		1		6.3
Urological cancer	23		1		4.3
Ovarian cancer	62		3		4.8
Uterus cancer	69		1	3	5.8
Thyroid cancer	10			1	10
Head and neck cancer	35			1	2.9
Melanoma	9			1	11
Soft-tissue sarcoma	35		3		8.6

CR, Complete remission; PR, partial remission
[a] Evaluable patients; if not available, enrolled patients were indicated
[b] Cases were described only as "responded" or "effective" in the reports

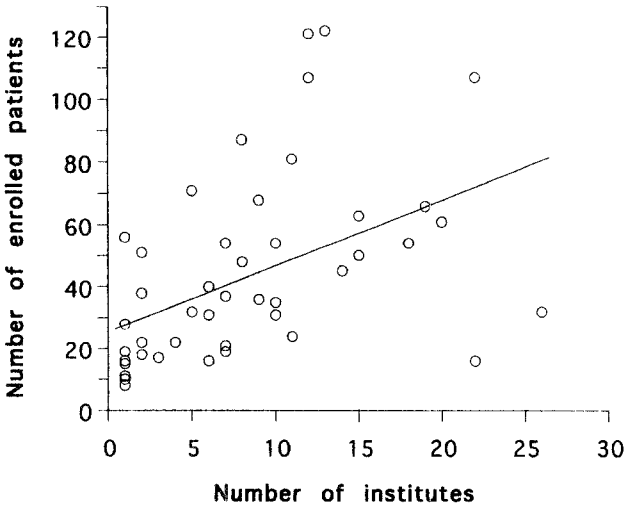

Fig. 1. Relationship between the number of institutes participating and the number of patients enrolled in phase I clinical trials conducted in Japan from 1981 to 1991. $n = 47$; $Y = 25.48+2.142X$; $r = 0.477$; $P < 0.001$

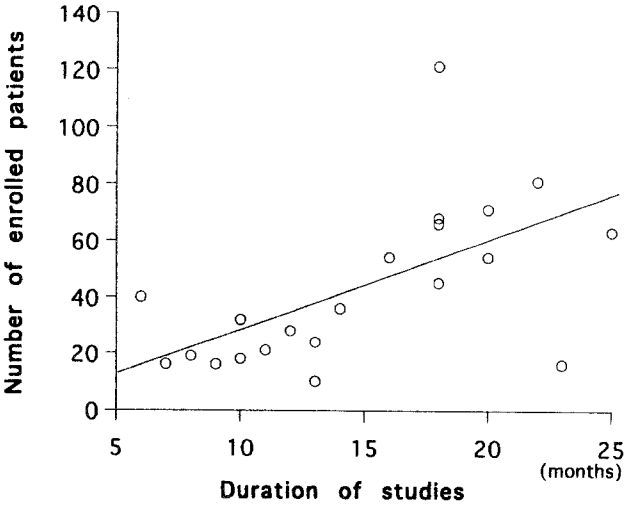

Fig. 2. Relationship between the duration of study and the number of patients enrolled in phase I clinical trials conducted in Japan from 1981 to 1991. $n = 21$; $Y = -1.535+2.994X$; $r = 0.589$; $P < 0.005$

that responded are shown in Table 4. The mean response rate obtained for hematological malignancies was 13.6% (range, 6.5%–67%). On the other hand, the mean response rate reported for nonhematological solid tumors was 3.9% (range, 0.6%–22%).

The relationship between the number of patients enrolled and the number of institutes participating in the studies is shown in Fig. 1. A median of 7 institutes participated in each phase I clinical trial (range, 1–26). The number of institutes participating correlated with the number of patients necessary for the study ($Y = 25.48 + 2.142X$; $r = 0.477$; $P < 0.001$). The relationship between the number of patients enrolled and the duration of study is shown in Fig. 2. The median duration of study in phase I clinical trials was 14 months (range, 6–25 months). The duration of study correlated with the number of patients enrolled ($Y = -1.535 + 2.994X$; $r = 0.589$; $P < 0.005$).

Discussion

The major goal of phase I clinical trials of anticancer agents is not only to determine the toxicity, the maximum tolerated dose, and the recommended dose for further study of the new drug but also to look for evidence of antitumor activity [6, 9].

According to the Japanese guidelines for the methodology of clinical evaluation of antineoplastic drugs, which was published in 1991, one of the objectives of phase I clinical trials is to observe the therapeutic activity [7]. All patients entered into phase I clinical studies have cancers that are refractory to chemotherapy or for which there is no standard chemotherapy. Therefore, it is important from an ethical point of view to know the response rates obtained in phase I clinical trials so that the patient can be aware of the possibility of therapeutic benefit. The overall response rate obtained in phase I clinical trials in Japan was 4% (1% for complete remission and 2% for partial remission). The actual response rate might be higher than 4% because of the inclusion of cases in which the response to the anticancer agents was unevaluable. The response rates by year ranged from 0 to 12.7%. In 1987 and 1988, in spite of the application of carboplatin, which has since been marketed in Japan, none of the heavily treated patients derived any therapeutic benefit from the treatment.

The overall response rate is considered a reasonable result because it was roughly the same as the 6% response rate reported by Von Hoff and Turner [8], the 4.2% reported by Estey et al. [3], the 4.5% reported by Decoster et al. [2], and the 2.6% reported by Penta et al. [5]. The response rates obtained for hematological malignancies were higher than those reported for other solid tumors. The same observation was made in several previous reports [2, 3, 8]. Moreover, the majority of responses occurred at 76%–125% of the doses recommended for phase II studies as reported by Von Hoff and Turner [8]. Therefore, a safe and more rapid schedule for increasing the dose to that recommended for phase II study might be needed from the viewpoint of the patient's chance of response. This might be achieved by the development of pharmacokinetically guided dose escalation [1].

Furthermore, many imported drugs undergo separate phase I testing in Japan after they have undergone phase II–III evaluation in other countries. In some instances, such "phase I" trials occurred after the drugs had been approved and had enjoyed widespread clinical use, e.g., cisplatin. A more rapid and simple dose-escalation schedule for imported agents should be established in Japan.

An additional interesting finding was that in several aspects, phase I clinical trials carried out in Japan differ from those conducted in Europe and the United States. Although phase I clinical trials should be conducted in a single institute or a limited number of institutes, in some studies performed in Japan, too many institutes participated in a single phase I clinical trial. Furthermore, an increase in

the number of participating institutes did not increase the number of patients enrolled in some studies. In the same way, the duration of study was too long in some trials, considering the small number of patients enrolled. These findings suggest that some institutes in Japan were not suitable to conduct phase I clinical trials, whereas others might have participated in too many clinical phase I trials as well as phase I/II studies. If an average of 200 patients are entered in phase I studies each year and a total of 25 patients are necessary for each phase I study, only 8 institutes will be sufficient to complete all phase I clinical trials in the single-institution setting in Japan.

In phase I clinical trials, a distinction should be made between patients with solid tumors and those with leukemia, as leukemic patients have a defective organ system (bone marrow) and can tolerate higher doses of drugs [9]. However, some reports in Japan did not distinguish between patients with solid tumors and those with leukemia. Furthermore, a definition of the maximum tolerated dose and the recommended dose for phase II study were not described in some reports. Therefore, the study design and the protocol for phase I clinical trials were not well described in some reports.

Although effective reporting of results is an integral part of good research, most reports of phase I clinical trials in Japan were published in commercial journals and all but eight papers were written in Japanese. Clinical trials of new drugs, especially those initially developed and clinically tested in Japan, should be reported in English for the benefit of foreign investigators.

The characteristics of the past phase I clinical studies of antineoplastic agents in Japan are described above. Recently, phase I clinical studies in Japan have improved due to the introduction of the Japanese guidelines for the methodology of clinical evaluation of antineoplastic drugs [4]. Phase I clinical studies of good quality, aiming at international harmonization, are anticipated to achieve data joining of phase I studies.

In conclusion, as there have been few reports concerning the methodology of phase I clinical trials of anticancer agents conducted in Japan, we carried out a critical review of such trials. The methodology of phase I clinical trials of anticancer agents conducted in Japan should be improved in an efficient and scientific manner in some aspects for example, the number of institutes participating and the duration of study. Especially for the testing of imported agents, a simple and more rapid dose-escalation schedule should be established in Japan.

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