Anti-Cancer Drug Development in Japan

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= Abstract =

일본의 항암제 개발 동향

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This survey is a sketchy description on anticancer drug development in Japan mainly focusing on pre-clinical development and phase I clinical trials.

Anticancer drug hunting in Japan is mainly pursued in pharmaceutical companies and the results are quite impressive. Several companies in Japan have been successful in developing many kinds of DNA-reacting anti-cancer agents like Mitomycin-C and its derivatives.

Drug screening

Traditionally, anticancer drug screening in Japan has been random natural product screening from fermentation products of microorganisms and recently the resources have been diversified to include marine products.

A recent breakthrough in anticancer drug development in Japan seems to be CPT-11, a semisynthetic analog of camptothecin, the DNA topoisomerase type I inhibitor isolated from the bark of Chinese tree *Camptotheca acuminata*. This drug has been developed by Yakult company and it is a very promising new drug which has efficacy on a variety of refractory

or multi-drug resistant cancers.

Likewise many other companies are trying to find a new drug acting on molecular targets other than DNA. For example, protein kinase C inhibitor UCN-01 and the ras oncoprotein inhibitor UCF-1 have been developed from Kyowa Hakko Company (Table 1, 2).

It is anticipated that more efforts will be given to mechanism-based drug screening as the advances in molecular oncology is bringing more light on the difference between normal and cancer cells.

Efficacy and Toxicity Evaluation

As for the efficacy evaluation of preclinical drug development, nude mouse xenograft model is widely used and the relevant techniques for toxicity evaluation in animal models are well established in most companies.

Some unresolved problems with animal models which the Japanese scientists face are 1) the heterogeneity of xenografts in nude mice may not be very representative of human tumor 2) with some anticancer agents the mouse pharmacokinetic parameters

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Table 1. Anticancer drug development from Kyowa-Hakko co

Classification	Agent	Target of Action	Origin	Clinical Trial	Comment
New drug	KW-2152	DNA, RNA	FP*	P-1 S [#]	
	KW-2189	DNA minor groove	SS**	P-1	
	KW-2401	PKC	FP	preclinical	
MMC	KW-2302	alkylator	SS	P-2 S	toxicity species difference
	KW-2083	alkylator	SS	P-2 S	BM ^{##} toxicity
	KW-2149	alkylator	SS	P-1	EORTC
Imported	KW-2307	mitosis	SS	P-1 A [@]	Navelbine
	EO-9	alkylator	S	P-2	EORTC
Approved	MMC	alkylator	FP	approved	Adriamycin
	ADM	intercalator	FP	approved	
	5-FU	antimetabolite	S	approved	
	MPA	hormone	S	approved	
	DTIC	alkylator	S	approved	
	FARM	intercalator	SS	approved	

* FP : fermentation product **SS : semisynthesis

[#]S : interrupted ^{##}BM : bone marrow [@] : in application

Table 2. New drugs screened from microorganisms at Kyowa-Hakko

A. Screening according to mechanism basis			
DNA target	DC 88/89	DC 52	DC 107
DNA topoisomerase	UCT 1003	UCT 4	UCE 1011
B. Screening by molecular biology of cancer cells			
Protein phosphorylation	UCN-01		
Ras blocker	UCF1		
Antiangiogenesis			

Table 3. Comparison of toxic dose of anticancer agents in animals and MTD in man(mg/m²)

Drug	Animal study		Clinic
	LD10 mouse	TDL dog	MTD
MMC	9.6	4.0	4—6
KW-2149	49.2	12.0	7.5
KW-2152	20.7	2.1	2.0
KW-2307	75.0	20.0	2.5

LD10 : lethal dose 10, TDL : toxic dose low,

MTD : max tolerated dose

were disordant from that of the human, so that it was very hard to predict toxicity in human trials from mouse data.

In the case of KW-2152, dose per kg body weight instead dose per m² body surface area was correlated with human pharmacokinetic parameters(Table 3).

So there seems to be a lack of scientific model to interpret the species difference in pharmacokinetics and future emphasis will be the introduction of similar route and schedule into animal models so that the preclinical evaluation might be more appropriate to that of human trial afterwards.

Research institutes like National Cancer Center Research Institute (Table 4) or Institute of Molecular and Cellular Biosciences of Tokyo University are pursuing research on drug resistance mechanisms or the elucidation of mechanism of action of potential new agents.

Clinical Drug Development in Japan

Phase I clinical trial of anticancer agents

Itoh et al reviewed the phase I clinical trials reported in Japan during the period of 1981—1991. Accord-

Table 4. Preclinical drug evaluation at pharmacology division, NCCRI

Compounds	Possible target	Collaboration/Company	
CPT-11	Topoisomerase I	Yakult	
NK 109	Topo II+ ?	Nihon Kayaku	Phase I
KT(indolcarbazole)	Topo I	Kyowa Hakko	
KW-2189	DNA alkylator	Kyowa Hakko	
	sequence specific binding		
	DNA repair inhibition		
Duocarmycin(DU86)	DNA ?	Kyowa Hakko	
KW-2149(MMC der)	DNA	Kyowa Hakko	
BMS(MMC der)	DNA	BMSquibb	
Adozelesin(CC1065)			Phase II
NB 506	Topo I	Banyu	Phase I
TAS 209	Topo I & II	Taiho	
TK	tubulin	Kyowa Hakko	
Anti-GM2 ab	GM2	Kyowa Hakko	
RZN	tubulin	Sankyo	
pRZN			
Leinamycin & der	DNA	Kyowa Hakko	
KRN 5500(spicamycin der) ?	Kirin		
Gnidimacrin	PKC activator	Tsumura	
Taxotere	tubulin	Rhone pleune	
Taxol	tubulin	BMSquibb	
Suramin	Top II ?	I. Gustave roussy	
8-cl-cAMP	PKA	Tonen	
Butyrolactone I	cdc 2	Banyu	
3-aminobenzamide	poly ADP ribose polymerase	Biochemical division	
DHA			
Trp-P1, Trp-P2		Shizuoka university	
Harman, Norharman		Bioche & Carcino. Div	
D 609	PC-PLC	Funakoshi	
Tamoxifen		Dr. Watanabe	

ding to his report 56 studies on 38 agents have been performed during the period of 11 years. 2,200 patients were enrolled to 56 studies and a median of 7 institutes participated in one phase I trial.

The median duration of study was 14 months. Overall, 4.1% (91 patients) obtained objective tumor responses. The responses in phase I trial were noted when 76–125% of drug dose recommended for phase II trial was given (Table 5, 6, 7).

When they analyzed the pharmacokinetics of im-

ported drugs there were no significant differences in AUCs or MTDs between people of western countries and Japanese. By the introduction of the concept of pharmacokinetically guided dose escalation schedule, the authors stress that some dose escalation steps could be saved.

Currently the following drugs are in clinical development in Japan (Table 8).

Multicenter randomized controlled clinical trial in Japan

Table 5. Drugs studied phase I trials each year in Japan : 1981—1991

Year Compounds	Year Compounds
1981 GANU	1987 TA-077
Ranimustine ^a	Idarubicin
Mitoxantone ^a	1988 SM-5887
Cisplatin ^a	Carboplatin ^a
Vindesine ^a	
1982 TAC-278	1989 KRN-8602
Neothramycin	SM-108
KW-2083	5FC & leucovorin ^a
CAM	1990 KRN-8602
Amsacrine	CPT-11
CDDP ^a	5FU ^a
1983 Tegafur-Uracil-E ^a	1-OHP
Pirarubicin ^a	Cytarabine ocfosfate ^a
Ranimustine ^a	Sobuzoxane
VP-16-213 ^a	DWA-21J4R
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 BHAC	
VP-16-213 ^a	

a : Marketed in Japan

b : Adapted from Itoh et al(8)

Since 1978, multicenter randomized controlled clinical trial was started with the grant support from Ministry of Health and Welfare. The study group consists of Japan Clinical Oncology Group(JCOG), a clinical trial review and monitoring committee, and a statistical center.

JCOG consists of 8 study groups(Fig. 1).

From 1978 till 1993, 6,340 patients were enrolled to 51 studies. 15 institutes accrued more than 100 patients to JCOG. Among the 51 studies 18 are completed, 21 are ongoing, 10 are ongoing but ended

Table 6. 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 200 174

number

of patients/year

CR, Complete remission ; PR, partial remission

a : Case were described only as "responded" or "effective" in the reports

b : Adapted from Itoh et al(8)

Table 7. 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%			
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

b : Adapted from Itoh et al(8)

new patient accrual and 2 have stopped.

Since 1991, guidelines for Good Clinical Practice in Clinical Trial was introduced and effective.

Such measures are promoting and enhancing the quality of anticancer drug clinical trial in Japan.

Future prospects and suggestions for collaborations

Table 8. Drugs currently undergoing clinical trial in japan*

Phase I trial	Phase II trial
TNP-351	BOF-A2
DMPC	SM-5887
IST-622	MX-2
NC-190	ME 2302
E 7010	DWA 2114R
KW-2189	NK 121
TRK-710	254-S
	CPT-11

* According to M.Ogawa and Ariyoshi Y.(9)

between korea and Japan

For the remaining part of the '90s, there seems to be following efforts to follow.

More efforts in identifying newer molecular targets for chemotherapy and in harmonization of preclinical animal efficacy and toxicity experiment with that of phase I clinical trial. This would mean construc-

tion of interpretational mechanism for the difference of pharmacologic parameters between animals and in man.

More close collaboration between scientists pursuing preclinical and clinical part of anticancer drug development might ensue.

There seems to occur ammendment in the strong preclinical requirements, from 2 species of animal acute toxicity data and 2 subacute toxicity data to that of 1 species of animal data each only.

The following level of collaboration in anticancer drug develeopment between Korea and Japan could be suggested. In view of the close collaboration of EC(european community) countries as in EORTC and the current networking of EORTC, Cancer Research Campaign of United Kingdom and the NCI of USA, such a manœuvre would be very constructive and worthwhile.

Fig. 1 Organization of study group of interdisciplinary treatment of solid tumors in japan.
JCOG : japan clinical oncology group.

Firstly, collaboration at the level of pharmaceutical industry for new drug hunting could be established.

Secondly, collaboration and exchange of scientists at the level of research institutes and academics could be more strengthened.

Lastly but not leastly, collaborative clinical trials of anticancer drugs could be started after due consensus are obtained through relevant seminars and meetings.

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