[S3-4] *[4/21/2000 (Fri) 16:10~16:50/Byulkwan Auditorium, Bldg 26]*

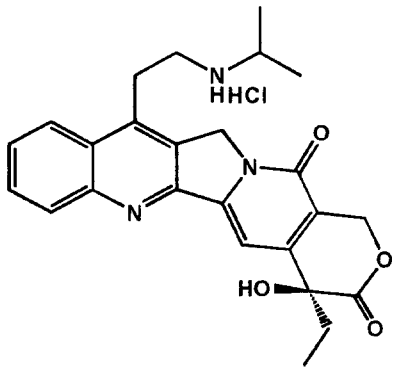
Development of CKD-602, a novel camptothecin derivative, for anticancer agent

Chung Il Hong

Chong Kun Dang Research Institute, Chong Kun Dang Pharmaceutical Corporation

Camptothecin is an alkaloid isolated from *Camptotheca acuminata*, and has shown a potent S-phase specific cytotoxicity by inhibiting topoisomerase I. However, the development of camptothecin was terminated at preclinical stage due to its water insolubility and the toxicities in late 1960s. Due to its unique mode of action on topoisomerase I, a variety of camptothecin derivatives with improved water solubility and reduced toxicities was synthesized and tested for their antitumor activities. Among them Irinotecan in 1994 and Topotecan in 1995 have been approved for clinical use.

In 1994 CKD Research Institute started to synthesize more than 100 camptothecin derivatives in order to find more potent one with less side effect and broader therapeutic range than Irinotecan and Topotecan. Among them CKD-602, 7-[2-(N-isopropyl-amino)ethyl]-(20S)-camptothecin was selected due to its potent cytotoxicity and water solubility. CKD-602 was synthesized by both semi- and total synthesis in good yield.[1] CKD-602 is topoisomerase I inhibitor like other camptothecin derivatives and causes apoptosis to the tumor cells.



Structure of CKD-602

CKD-602 showed superior *in vivo* antitumor activities to a clinical camptothecin derivative, Topotecan, against animal tumor models including L1210 leukemia, P388 leukemia, B16 melanoma, Lewis lung carcinoma, and B16 melanoma with a broader safety margin.[2,3] Preliminary studies showed that the intermittent dosing schedule showed the superior antitumor activity to the single. In the studies of CKD-602 against a panel of human tumor xenografts comprised of colon and breast carcinomas, greater activities and higher [R/E]max values than those of Topotecan were obtained.[2,3](Table 1).

Table 1. Antitumor activity of CKD-602 in human tumors bearing athymic nude mice

Tumor	[R/E]max[a]	Total dose[b] (mg/kg)	IR%[c]	BW loss (%)[d]
CX-1	3.48	30	44.6	
		60	64.2	5.8
		80	68.9	10.8
		100	75.8	17.5
HT-29		15	58.3	9.9
		30	65.5	6.2
		60	79.8	10.3
WIDR	6.68	15	45.1	8.7
		30	70.3	12.4
		60	90.8	11.0
		80	93.6	17.4
LX-1	2.17	15	53.3	1.9
		60	64	14.5
		100	66.7	14.1
MX-1	3.8	15	39.7	2.0
		60	76.5	9.8
		100	87	35.2
SKOV-3	3.8	15	40.8	
		60	88.0	14.2
		100	88.6	24.5
HepG2	2.2	30	47.5	
		60	71.5	8.4
		100	85.1	9.1
KATO-III	2.5	15	38.6	
		60	82.1	12.1
		100	89.9	43.4

[a] Therapeutic index (MTD/ED), MTD: maximum tolerated dose, ED: effective dose.
[b] Total dose given for the treatment schedule, Q4dx4.
[c] Inhibition rate = (1-TWt/TWc)x100, TWt: the mean tumor weight of the treated group, TWc: the mean tumor weight of the control group.
[d] Maximal body weight change, relative to the body weight of the day 1.

The CKD-602 treatments resulted in tumor regressions, extensive tumor growth delays including highly resistant CX-1 human colon tumor: inhibition rate (IR%) of CKD-602 was 76 whereas that of Topotecan was 41, and more broad therapeutic dosage range than Topotecan, [R/E]max value was 3.48 and 1.33, respectively.

The pharmacokinetics studies on CKD-602 were performed in rats. In single i.v. administration, CKD-602 showed a linear pharmacokinetics with mean half-lives of 9.5-11.7. The AUCs were increased dose-dependently. In 5 daily administrations, the pharmacokinetic parameters were not significantly different to those in the single. The AUCs of lactone form were 52.1, 56.8, and 50.5% of total CKD-602 at 5, 10, and 20 mg/kg dose, respectively, and also pharmacokinetic parameters at 5 day repeated doses were not significantly different to those at single dose.[4]

The *ex vivo* antitumor activity of CKD-602 in beagle dogs was assessed against 10 human tumor cell lines by MTT assay and compared with that of topotecan using antitumor index (ATI) determined from the *ex vivo* pharmacodynamics results of inhibition rates (%) versus time curve. The mean ATI values recorded for CKD-602 was significantly ($p<0.05$) higher than that of Topotecan.[3] (Table 2)

Table 2. *Ex vivo* pharmacodynamics of CKD-602 and Topotecan.

	ATI (Antitumor Index)	
Cell line	CKD-602	Topotecan
Colon	8860 ± 1645	6555 ± 1180
Ovary	10361 ± 2336	4257 ± 1378
Lung	10040 ± 544	2107 ± 416
Breast	7249 ± 3273	3782 ± 557
Liver	8699 ± 1035	5861 ± 1505
Total	**9137 ± 2186**	**4662 ± 1899**

The cell-killing kinetics showed that the toxicity was dependent on exposure time rather than concentration. And the hematological toxicities and the histological

changes were more noticeable in 24-hour continuous infusion than in a single injection. From these results, CKD-602 was found to have a characteristic of cell-cycle (S-phase) specific agent and exposure time of the drug was a determinant of toxicity.[4]

The phase I clinical trials of CKD-602 was performed on a total of 16 cancer patients with the progressive solid tumors. The patients were given CKD-602 intravenously for 30 minutes with a daily dose of 0.5 – 0.9 mg/m^2 for 5 consecutive days every 3 weeks. The maximum tolerated dose (MTD) was 0.7 mg/m^2/day. Dose limiting toxicity (DLT) was found to be neutropenia, and other severe toxicity such as diarrhea was not observed. In spite of the progressive disease partial responses (PR: >50% reduction of tumor) were observed each in stomach and ovarian cancer patients. (Table 3).

Table 3. CKD-602 Dose Escalations and Responses

Dose (mg/m^2/day×5)	New Patients	Response*	Total patients	Accessible courses
0.9	4		4	5
0.68	0	1PR (ovary) 1SD(esophageal)	2	9
0.5	6		6	16
0.7	6	1PR (stomach)	6	13
Total	16			43

* PR: Partial response (>50% reduction of tumor)
SD: Stable disease

The phase II clinical trials with gastric, ovarian, colon, and small cell lung cancer patients are now ready to be performed.

References

1. Patent: PCT WO96-2166. Granted in U.S. and Japan.
2. Lee, J.-H., et al., *Arch. Pharm. Res.*, **22**, 581-590 (1988).
3. Lee, J.-H., et al., *Proceedings of AACR* **39**, 1988, Abstract Nos. 2071 and 3544.
4. Lee, J.-H., et al., *Proceedings of AACR* **40**, 1988, Abstract No 716.