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Preclinical and phase I trials of topoisomerase I inhibitors

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Abstract. A total of three topoisomerase I inhibitors, including topotecan, CPT-11 (irinotecan), and intoplicine, have been studied in both preclinical and clinical/clinical pharmacology studies. In in vitro testing against human tumor colony-forming units, all three compounds were significantly more effective when tested as a continuous exposure as compared with a 1-h exposure. The dose-limiting toxicities were different for all three of the agents, with neutropenia and thrombocytopenia being dose-limiting for topotecan; diarrhea, for CPT-11; and hepatotoxicity, for intoplicine. In these phase I studies a number of marginal responses were noted with topotecan; partial and marginal responses, with CPT-11 (particularly in patients with colon cancer); and no response, with intoplicine. The detailed pharmacology of all three agents documented a very short half-life for topotecan, an intermediate half-life for CPT-11, and a prolonged half-life for intoplicine. Based on our experience to date, these compounds (particularly CPT-11) have promise as useful additions to our tremendous therapeutic armamentarium.

Key words: CPT-11 – Topotecan – Intoplicine – Topoisomerase I

Introduction

Our group in San Antonio has been involved in preclinical and clinical studies with several topoisomerase I inhibitors. In this report we summarize the ongoing work with three topoisomerase I inhibitors, including topotecan, CPT-11 (irinotecan), and intoplicine. Table 1 outlines the preclinical effort with the topoisomerase I inhibitors. The major emphasis has been evaluating each of the agents in a human tumor-cloning assay [16, 18, 20]. The preclinical work in the cloning assay was performed to (1) determine the optimal concentrations and exposure times that need to be achieved with trials of the agent in patients, (2) pinpoint tumor types against which each compound will have activity, and (3) identify patients who might be sensitive to each agent and might benefit from receiving it in a phase I clinical trial. The work measuring carboxylesterase (CE) levels in patients tumors was conducted on the basis of the hypothesis that the CE family is responsible for metabolism of CPT-11 into its more potent metabolite SN38 (7-ethyl-10-hydroxy camptothecin). Table 2 describes the San Antonio clinical efforts with topoisomerase I inhibitors. As can be seen in that table, we have had the most extensive experience with topotecan followed by CPT-11. Only one phase I trial has been performed with intoplicine. Our experience with each of the compounds is presented below.

Table 1. San Antonio preclinical efforts with topoisomerase I inhibitors

1) Evaluated the following compounds in a human tumor-cloning assay
Topotecan
CPT-11 (irinotecan)
Intoplicine
2) Measured carboxylesterase (CE) levels in patients' tumors (CE converts CPT-11 to SN38)

SN38, 7-Ethyl-10-hydroxy camptothecin

Materials and methods

Human tumor-cloning assay. Our human tumor-cloning assay (HTCA) utilized a modification of the technology of Salmon and Hamburger [16]. We previously used this technique both for preclinical testing and for in vitro-in vivo correlative studies [18, 20–22].

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Table 2. San Antonio clinical efforts with topoisomerase I inhibitors

1) Topotecan
Single-dose phase I study
120-h continuous-infusion phase I study
72-h continuous-infusion phase I study
Topotecan + etoposide phase I study
Topotecan + cisplatin phase I study (in patients with non-small-cell lung cancer)
Oral topotecan-bioavailability phase I study
2) CPT-11
Weekly ×4 repeated every 6 weeks phase I trial
Weekly ×4 repeated every 6 weeks phase II trial in patients with colon cancer refractory to 5-fluorouracil
3) Intoplicine
Single dose repeated every 3 weeks phase I trial

CE assays. Single-cell suspensions of tumors taken directly from patients were lysed by three cycles of freeze-thawing. The activity of CE was measured spectrophotometrically using conversion of the substrate *p*-nitrophenyl acetate to the product (*p*-nitrophenyl). The technique has been reported in detail by Chen and colleagues [5].

Phase I trial methods. The phase I clinical trial methods are outlined under each of the individual studies. Criteria for toxicity and response are those used by the Southwest Oncology Group [8].

Results

Topotecan

In vitro activity. The in vitro activity of topotecan against primary human tumor colony-forming units has previously been reported by Burris and colleagues [3]. Table 3 provides an update of the activity of topotecan against primary human tumor colony-forming units growing in an HTCA. As can be seen in that table, topotecan has substantially more in vitro activity when continuous exposure to the compound is used.

Table 4 details the tumor-specific activity for topotecan. In that table we compare 1.0 μg of topotecan/ml as a 1-h exposure with 0.1 μg of topotecan/ml as a continuous exposure. The continuous exposure gives tumor-specific activity (defined as ≤50% survival) against breast, colon, kidney, non-small-cell lung, and ovarian tumor colony-forming units (where enough patients tumors have been tested). As can also be seen in Table 4, topotecan demonstrates in vitro activity against other types of human tumor colony-forming units (HTCFUs) such as lymphoma, stomach, and sarcoma HTCFUs. If concentrations of at least 0.1 μg/ml can be achieved for prolonged periods in patients, then topotecan should have activity in the clinical setting.

San Antonio clinical trial results. Table 5 lists the one ongoing and three completed clinical trials of topotecan conducted in San Antonio. A total of 87 patients have received 244 courses of the drug. As can be seen in Table 6, the amount of drug that constitutes a maximally tolerated dose (MTD) was highly dependent on the schedule. Continuous-infusion schedules created much lower MTDs. With the single dose of topotecan the dose-limiting toxicity (DLT) was neutropenia (without the use of colony-stimulating factors), whereas with continuous infusion of topotecan the DLTs included both neutropenia and thrombocytopenia. Other toxicities that were not dose-limiting (grade 1–2) included anemia (25% of patients), nausea and vomiting (50% of patients), fever to >101° F (20% of patients), rash (14% of patients), and alopecia (common only at the highest dose of topotecan). Overall, in our experience, topotecan has been fairly well tolerated by patients. It is our impression that if a growth factor for platelets could be identified, doses of the agent could be further escalated.

Table 3. Overview of the in vitro activity of topotecan

Concentration (μg/ml)	Exposure	Responses[a]/evaluable (%)		
1.0	1 hour	27/207	(13%)	$P = 0.001$
10.0	1 hour	69/205	(34%)	
0.1	continuous	29/ 84	(35%)	
1.0	continuous	61/ 80	(76%)	

[a] Response is defined as ≤50% survival of tumor colony-forming units

Table 4. Tumor-specific in vitro activity of topotecan

	1 h 1.0 μg/ml	Continuous 0.1 μg/ml	
Breast	5/39	4/13	(31%)
Colon	2/26	3/13	(23%)
Head and neck	0/2	0/1	(0%)
Kidney	1/9	5/11	(45%)
Lung (non-small-cell)	4/40	8/23	(35%)
Lung (small-cell)	1/3	1/1	(100%)
Lymphoma	1/1	1/1	(100%)
Ovary	3/48	7/18	(39%)
Pancreas	1/5	0/1	(0%)
Mesothelioma	0/2	0/1	(0%)
Sarcoma	1/3	1/2	(50%)
Stomach	1/7	1/2	(50%)
Thyroid	0/2	0/1	(0%)
Unknown primary	1/7	0/3	(0%)

Table 5. Phase I trials of topotecan in San Antonio

Schedule	Number of patients	Number of courses
Single 30-min infusion every 3 weeks (1st time in patients)	42	107
120-h (5-day) continuous infusion (continuous exposure more active in vitro)	14	41
72-h (3-day) continuous infusion (NCI animal model)	31	96
Single oral dose vs i.v. bioavailability	–	–
Totals	87	244

Table 6. Maximally tolerated doses and dose-limiting toxicities of topotecan

Schedule	MTD		DLT	References
	mg/m² per dose	total dose (mg/m²)		
Single 30-min	22.5	22.5	Neutropenia	Wall et al. 1992 [23]
120-h CI	0.68	3.4	Neutropenia, thrombocytopenia	Burris et al. 1992 [4]
72-h CI	1.6	4.8	Neutropenia, thrombocytopenia	Burris et al. 1992 [4]
Oral	–	–	–	–

DLT, Dose-limiting toxicity; CI, continuous infusion

Of note in our studies to date has been the absence of any complete or partial response to topotecan. Marginal responses have been seen in patients with non-small-cell lung cancer, ovarian cancer, and renal cell carcinoma.

Topotecan plus other agents. Rothenberg and colleagues [15] have explored the combination of topotecan plus cisplatin using an escalating dose of topotecan (0.75 and then 1.0 mg/m² per day ×5) given after a single dose of cisplatin (75 mg/m² on day 1), with the course being repeated every 21 days. The combination has been reasonably well tolerated with dose escalation of topotecan up to 1.0 mg/m² per day ×5. This ongoing study has been confined to patients with non-small-cell lung cancer. Partial responses have been noted, but it is too early to determine the actual response rate.

Our group is also studying the combination of the topoisomerase I inhibitor topotecan (used to up-regulate the expression of topoisomerase II) with the topoisomerase II inhibitor etoposide given in a subsequent treatment [6]. The topotecan is given as a 72-h infusion on days 1–3 and the etoposide, at a dose of 100 mg/m² on days 7–9. The study includes measurement of protein levels of topoisomerase I and II in tumor cells. To date, dose-limiting neutropenia has been seen with topotecan doses of 1.05 mg/m² per day ×3 for good-risk patients and 0.5 mg/m² per day ×3 for poor-risk patients.

Future San Antonio studies with topotecan. Future studies with the agent will be aimed at maximizing the exposure to the drug. To accomplish this, the ongoing phase I trial is using oral topotecan.

CPT-11

Activity in the HTCA. Table 7 describes the in vitro activity of CPT-11 in the HTCA using information updated after our previous publication on that activity [17]. As can be seen in that table, CPT-11 has good in vitro activity against breast, colon, non-small-cell lung, ovarian, and mesothelioma HTCFUs. Although there are too few of the other tumor types to draw any conclusions, it is clear that CPT-11 has a broad spectrum of in vitro activity.

CE in patients tumors. Our group has studied CE levels in patients tumors, reasoning that high CE levels could cause more rapid conversion of CPT-11 to its more cytotoxic metabolite SN38. Work by Chen et al. [5] in our group has documented variable levels of CE even within a particular histologic type of tumor (e.g., colon cancer). CE levels ranged from 0.009 to 1.274 μmol min⁻¹ mg protein⁻¹ (median, 0.125 μmol min⁻¹ mg protein⁻¹). However, tumors with the highest median level of CE (with at least six tumors being examined) include small-cell lung, endometrial, gastric, mesothelioma, breast, melanoma, ovarian, colon, and non-small-cell lung cancer (in descending order of CE level).

San Antonio clinical trials with CPT-11. We have conducted a weekly ×4 dosing schedule with a 2-week rest using a 90-min infusion of CPT-11 [14]. In that study, the dose-limiting toxicity was diarrhea noted at a dose of 180 mg/m² per week ×4. Other toxicities consisted of leukopenia, nausea and vomiting, malaise, stomatitis, possible pneumonitis, and a syndrome of acute gastrointestinal cramping with diarrhea. Partial responses were noted in two patients with colorectal cancer.

In addition to this phase I trial, we have initiated a phase II trial of CPT-11 using the same schedule of drug administration in patients with advanced colorectal cancer who have failed (and indeed have progressed) on one prior 5-fluorouracil (5 FU)-containing regimen. This trial is ongoing, but responses have clearly been documented.

Diarrhea has severely limited the dose intensity with which CPT-11 can be given. Researchers have tried multiple regimens to prevent and treat this diarrhea, including loperamide, diphenoxylate, scopalomine, atropine and somastatin analogs. However, an important report by Abigerges and colleagues [1] noted that if two capsules of loperamide were given at the very beginning of the diarrhea and were followed by one capsule given every 2 h around the clock, severe diarrhea could be avoided. These investigators were capable of achieving a very high dose (>650 mg/m² every 3 weeks) using that technique. It is our initial impression that the every-2-h loperamide schedule also works to prevent/treat the diarrhea associated with the weekly administration of CPT-11.

Table 7. Activity of CPT-11 in the HTCA

Tumor type	Responses/evaluable		
	0.3 μg/ml	1.5 μg/ml	3.0 μg/ml
Breast	1/8	3/9	5/8
Cervix	1/2	1/2	1/2
Colon	1/20	2/20	5/20
Renal	0/2	0/2	0/2
Hepatoma	0/1	0/1	0/1
Lung (non-small-cell)	1/11	4/11	6/11
Melanoma	0/4	1/5	1/5
Ovary	2/22	3/22	5/21
Pancreas	0/2	1/2	1/2
Mesothelioma	1/10	2/11	4/11
Prostate	0/1	0/1	1/1
Sarcoma	0/2	1/2	2/2
Stomach	0/1	1/1	1/1

Table 8. Dose intensity for CPT-11

Schedule	MTD (mg/m^2)	Dose intensity per week[a]
Weekly ×6 (Japan)	120	120
Weekly ×4 (USA)	180	120
Single (Japan)	240	83
Single (USA)	240	80
Single[b] (France)	750	**250**

[a] 6-week period
[b] Drug given with loperamide every 2 h beginning at the onset of diarrhea

Table 9. Summary of the activity of intoplicine in the HTCA

Concentration (μg/ml)	Exposure time	Responses/evaluable	(%)
0.25	1 h	5/93	(5%)
2.5	1 h	25/92	(27%)
10.0	1 h	50/93	(54%)
0.25	Continuous	16/87	(18%)
2.5	Continuous	60/87	(69%)
10.0	Continuous	77/87	(89%)

Table 8 delineates the dose intensity of CPT-11 achieved by using the loperamide technique. As can be seen in that table, an impressive increase in dose intensity is possible when loperamide is used to alleviate the CPT-11-induced diarrhea.

Future work with CPT-11. Even though CPT-11 is undergoing phase II trials in multiple institutions, it is our feeling that we should now try to intensify the doses of CPT-11 that can be given on the other schedules (daily ×3, weekly, every 2 weeks) by using the loperamide technique. Additional phase II trials of CPT-11 should proceed only when a real MTD is reached by using loperamide. A recently described, more potent analog of CPT-11 will soon be entering the market [10].

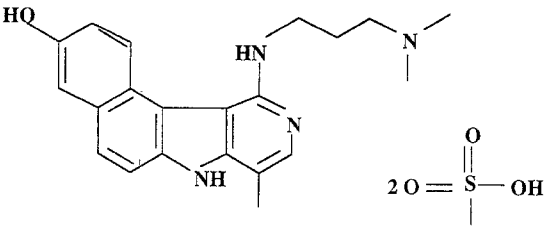

Fig. 1. Structure of intoplicine

Intoplicine

Preclinical background and work. Intoplicine (RP 60475, NSC 645008) is a member of a new class of topoisomerase inhibitors [11, 12] (see Fig. 1). Intoplicine has excellent antitumor activity in a number of in vitro and in vivo systems [2]. The compound is unique because it appears to inhibit both topoisomerase I and II [13].

Activity in the HTCA. Table 9 provides a summary of the activity of intoplicine in the HTCA. As can be seen in that table, intoplicine is considerably more active when used as a continuous exposure. This information is an update of the data published by Eckardt and colleagues [7].

Table 10 details the tumor-specific activity of intoplicine as a 1-h and as a continuous exposure. Based on the preliminary pharmacokinetic data for intoplicine obtained in patients given a 30-min infusion of the drug [9], the concentration of 2.5 μg/ml for 1 h appears to be achievable. At that concentration, activity (≥25%) for intoplicine was found against non-small-cell lung cancer, small-cell lung cancer, and adenocarcinoma of unknown primary site.

Clinical trials. In San Antonio, a phase I/pharmacokinetics study was performed using a 30-min infusion repeated every 21 days [9]. A total of 30 patients were entered on study, and the dose-limiting toxicity was hepatotoxicity with elevation of SGOT, SGPT, and alkaline phosphatase.

Table 10. Tumor-specific activity of intoplicine

Tumor type	Responses/evaluable					
	1-h exposure			Continuous exposure		
	0.25 μg/ml	2.5 μg/ml	10.0 μg/ml	0.25 μg/ml	2.5 μg/ml	10.0 μg/ml
Breast	0/7	2/6	5/7	1/6	5/6	5/6
Cervix	0/1	0/1	0/1	0/1	1/1	1/1
Colon	1/13	3/13	5/13	3/12	7/12	10/12
Kidney	0/12	2/12	4/12	1/12	9/12	11/12
Lung (non-small-cell)	3/18	5/18	11/18	3/18	11/18	16/18
Lung (small-cell)	1/2	2/2	2/2	1/2	1/2	2/2
Melanoma	0/6	1/6	4/6	2/7	4/7	6/7
Ovary	0/20	4/20	9/20	2/18	14/18	16/18
Pancreas	0/1	1/1	1/1	1/1	1/1	1/1
Mesothelioma	0/5	1/5	3/5	1/5	3/5	5/5
Prostate	0/3	0/3	1/3	0/2	1/2	1/2
Stomach	0/1	1/1	1/1	0/1	1/1	1/1
Unknown primary	0/4	3/4	3/4	1/1	2/2	2/2
Totals	5/93 (5%)	25/92 (27%)	49/93 (53%)	16/86 (19%)	60/87 (69%)	77/87 (88%)

Other toxicities (grade 1–2) included prolongation of the QT interval, nausea (7%), anorexia (30%), phlebitis (20%), fatigue (13%), hypotension (10%), and fever (7%). No antitumor response was noted.

Pharmacology studies using a high-performance liquid chromatography (HPLC) assay, with mitoxantrone serving as an internal standard, revealed that plasma levels declined in a triphasic manner with a half-life of 61.4 h. At 425 mg/m^2 the maximal plasma concentration was 10.96 μg/ml, whereas at 283 mg/m^2 it was 7.65 μg/ml. The plasma clearance was 18.7 l h^{-1} m^{-2}, and the volume of distribution at steady state was 1583 l/m^2.

At present, the future of intoplicine is uncertain until a schedule that avoids hepatotoxicity can be found. A phase I study by Strauss et al. [19] using a daily ×5 schedule of intoplicine has not reached a maximally tolerated dose up to and including 270 mg/m^2. It is possible that such a schedule is preferable to avoid serious hepatotoxicity.

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References

1. Abigerges D, Armand JP, Chabot GG, Cote C, Rougier P, Concalves E, Fadel E, Herait P, Gandia D (1993) High dose intensity of CPT-11 administered as a single dose every 3 weeks: the Institut Gustave Roussy experience. Proc Am Soc Clin Oncol 12: 133
2. Bissery MC, Nguyen CH, Bisagni E, Lavelle F (1990) Preclinical evaluation of RP 60475, a pyrido-benzo-indole antitumor agent. Proc Am Assoc Cancer Res 31: 2747
3. Burris HA III, Hanauske A-R, Marshall MH, Kuhn JG, Hilsenbeck SG, Von Hoff DD (1992) Activity of topotecan, a new topoisomerase I inhibitor, against human tumor colony-forming units in vitro. J Natl Cancer Inst 84: 1816
4. Burris H, Kuhn J, Wall J, Eckardt J, Rodriguez G, Johnson R, Weiss G, Shaffer D, Von Hoff D (1992) Early clinical trials of topotecan, a new topoisomerase I inhibitor. Ann Oncol 3 [Suppl 1]: 118
5. Chen S-F, Rothenberg ML, Clark G, Degen D, Wajima M, Barton D, Von Hoff DD (1994) Human tumor carboxylesterase activity correlates with CPT-11 cytotoxicity in vitro. Proc Am Assoc Cancer Res 35: 2174
6. Eckardt JR, Burris HA, Rodriguez GI, Fields SM, Rothenberg ML, Moore TD, Smith SC, Ganapathi R, Weiss GR, Johnson RK, Kuhn JG, Von Hoff DD (1993) A phase I study of the topoisomerase I and II inhibitors topotecan (T) and etoposide (E). Proc Am Soc Clin Oncol 12: 137
7. Eckardt JR, Burris HA III, Kuhn JG, Bissery MC, Klink-Alakl M, Clark GM, Von Hoff DD (1994) Activity of intoplicine (RP60475), a new topoisomerase I and II inhibitor, against human tumor colony-forming units in vitro. J Natl Cancer Inst 86: 30
8. Green S, Weiss GR (1992) Southwest Oncology Group standard response criteria, endpoint definition, and toxicity criteria. Invest New Drugs 10: 239
9. Kane BJ, Eckardt JR, Burris HA, Rodriguez GI, Rothenberg ML, Weiss GR, Smith L, Fields SM, Cook G, Klink-Alakl M, Bayssas M, Von Hoff DD, Kuhn JG (1993) Phase I clinical and pharmacokinetic trials of intoplicine (RP 60475). Proc Am Soc Clin Oncol 12: 156
10. Mitsui I, Kumazawa E, Hirota Y, Sugimori M, Ohsuki S, Uoto K, Terassura H, Sato K (1993) Antitumor activity of DX8951, a new camptothecin derivative. Proc Am Assoc Cancer Res 34: 421
11. Nguyen CH, Lhoste JM, Lavelle F, Bissery MC, Bisagni E (1990) Synthesis and antitumor activity of 1-[(dialkylamino)alkyl]amino-4-methyl-5H-pyrido-[4,3-*b*]-benzo(*e*)- and benzo(9)-indoles. A new class of antineoplastic agents. J Med Chem 33: 1519
12. Nguyen CH, Lavelle F, Riou JF, Bissery MC, Huel C, Bisagni E (1992) Further SAR in the new antitumor 1-amino-substituted-carbolines and 5H-benzo(*e*)pyrido-(4,3)-indoles series. Anticancer Drug Design 7: 239
13. Riou JF, Fossé I, Bissery MC, Larsen A, Nguyen CM, Grondard L, Saucier JM, Bisagni E, Lavelle F (1992) RP60475 and derivatives, a new class of antitumor agents inhibiting both topoisomerase I and II activities. Proc Am Assoc Cancer Res 33: 2611
14. Rothenberg ML, Kuhn J, Burris HA, Morales MT, Nelson J, Eckardt JR, Rock MK, Terada K, Von Hoff DD (1992) A phase I and pharmacokinetic trial of CPT-11 in patients with refractory solid tumors. Proc Am Soc Clin Oncol 11: 113
15. Rothenberg ML, Burris HA III, Eckardt JR, Rinaldi DA, Weiss GR, Smith S, Jones K, Johnson RK, Von Hoff DD (1993) Phase I/II study of topotecan + cisplatin in patients with non-small-cell lung cancer (NSCLC). Proc Am Soc Clin Oncol 12: 156
16. Salmon SE, Hamburger AW (1977) Primary bioassay of human tumor stem cells. Science 197: 461
17. Shimada Y, Rothenberg M, Hilsenbeck SG, Burris HA III, Degen D, Von Hoff DD (1994) Activity of CPT-11 (irinotecan hydrochloride), a topoisomerase I inhibitor, against human tumor colony-forming units. Anticancer Drugs (in press)
18. Shoemaker RH, Wolpert-Defillipes MK, Kern DH, Lieber MM, Makuch RW, Melnick NR, Miller WT, Salmon SE, Simon RM, Venditti JM, Von Hoff DD (1985) Application of a human tumor colony-forming assay to new drug screening. Cancer Res 45: 2145
19. Strauss G, Pagiani O, Sessa C, Lund B, Caralli F, Hansen HH (1993) A phase I study of intoplicine (RP60475F, NSC D645008) administered on a daily ×5 schedule. Proc Am Assoc Cancer Res 34: 231
20. Von Hoff DD (1990) He's not going to talk about in vitro predictive assays again, is he? J Natl Cancer Inst 82: 96
21. Von Hoff DD, Clark GM, Stogdill BJ, Sarosdy MF, O'Brien MT, Casper JT, Mattox DE, Page CP, Cruz AB, Sandbach JF (1983) Prospective clinical trial of a human tumor cloning system. Cancer Res 43: 1926
22. Von Hoff DD, Sandbach JF, Clark GM, Turner JN, Forseth BF, Piccart MJ, Colombo N, Muggia FM (1990) Selection of cancer chemotherapy for a patient by an in vitro assay versus a clinician. J Natl Cancer Inst 82: 110
23. Wall JG, Burris HA III, Von Hoff DD, Rodriguez G, Kneuper-Hall R, Shaffer D, O'Rourke T, Brown T, Weiss G, Clark G, McVea S, Brown J, Johnson R, Friedman C, Smith B, Mann W, Kuhn J (1992) A phase I clinical and pharmacokinetic study of the topoisomerase I inhibitor topotecan (SK&F 104864) given as an intravenous bolus every twenty-one days. Anticancer drugs 3: 337