The anticancer activity of the transcription inhibitor terameprocol (meso-tetra-*O*-methyl nordihydroguaiaretic acid) formulated for systemic administration

Rocio A. Lopez, Amanda B. Goodman, Melissa Rhodes, Jessica A.L. Blomberg and Jonathan Heller

Terameprocol (meso-tetra-*O*-methyl nordihydroguaiaretic acid, formerly known as EM-1421 and M4N) is a semi-synthetic small molecule with antitumor activity occurring via selective targeting of Sp1-regulated proteins, including survivin and cdc2 that control cell cycle and apoptosis. Terameprocol is in clinical development as a site-specific transcription inhibitor in solid refractory tumors. The present studies were designed to investigate the in-vitro and in-vivo anticancer activity of terameprocol in a novel hydroxypropyl β-cyclodextrin and polyethylene glycol solvent formulation (designated CPE) designed for safe parenteral administration. Terameprocol powder was dissolved in CPE (20% hydroxypropyl β-cyclodextrin and 50% polyethylene glycol 300 or 30% hydroxypropyl β-cyclodextrin and 25% polyethylene glycol 300) or dimethyl sulfoxide and used for in-vitro cell proliferation assays, and in human carcinoma xenograft studies using female athymic nude mice injected with SW-780 human bladder cells. Terameprocol (50 and 100 mg/kg), paclitaxel (5 mg/kg), terameprocol and paclitaxel or vehicle was administered intraperitoneally daily for 21 days. Stock solutions of the CPE formulation were stable for up to 12 months. Terameprocol CPE formulation showed concentration-dependent inhibition of HeLa and C33A cell proliferation, and was less toxic than terameprocol dimethyl sulfoxide formulation. The terameprocol CPE formulation showed no overt toxicities in tumor-bearing mice. Terameprocol alone reduced the rate of tumor growth, and a combination of terameprocol/paclitaxel reduced both the rate and extent of tumor growth. These preclinical results confirm the tumoricidal activity of terameprocol formulated in a solvent suitable for parenteral administration and suggest that terameprocol has improved efficacy when coadministered with paclitaxel. *Anti-Cancer Drugs* 18:933–939 © 2007 Lippincott Williams & Wilkins.

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Erimos Pharmaceuticals, Raleigh, North Carolina, USA

Correspondence to Dr Rocio A. Lopez, Erimos Pharmaceuticals, 930 Main Campus Dr, Ste. 100, Raleigh, NC 27606, USA
Tel: +1 919 821 5204 (ext) 2808; e-mail: ralopez@erimos.com

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Introduction

Meso-tetra-*O*-methyl nordihydroguaiaretic acid (terameprocol, EM-1421, M4N) is a semisynthetic derivative of meso-nordihydroguaiaretic acid, a naturally occurring plant lignan. Terameprocol blocks cell cycle progression by inhibiting expression of the Sp1-dependent gene coding for cyclin-dependent kinase 1 (cdk1, also known as cdc2 and cyclin B kinase) and promotes apoptosis by inhibiting expression of the survivin gene [1,2]. Cdc2 is one of several kinases controlling mitosis and is deregulated in cancer cells [3,4]. Survivin is an inhibitor of apoptosis protein overexpressed in many cancers [5]. Tumor cells that overexpress survivin are prevented from entering the caspase-induced cell-death pathway that would lead to their destruction [6]. Terameprocol represents a novel site-specific transcription inhibitor that can potentially regulate the function of cell cycle and apoptosis genes aberrantly expressed in many types of human cancers.

Several studies have examined the anticancer activity of terameprocol. Terameprocol inhibits cancer cell growth *in vitro* [1,7–10] and exhibits tumoricidal activity *in vivo* in human tumor cell xenografts in mice [1,8–10]. The safety of terameprocol has been assessed in phase I studies using intratumoral administration in solid tumors using a dimethyl sulfoxide (DMSO) formulation [11–13]. Intratumoral doses of terameprocol of up to 100 mg (20 mg/day) in oral squamous carcinoma patients and up to 495 mg (20 mg/cm^3/day) in head and neck cancer patients were well tolerated with no acute or deferred toxicity [11,12]. Terameprocol also inhibited cdc2 and survivin expression, induced apoptosis, and improved relapse-free 5-year survival rates [12,14]. In a phase I dose-escalation study in patients with cervical intraepithelial neoplasia, intravaginal administration of terameprocol was well tolerated and there were no serious or treatment-related adverse events [13].

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In addition to direct effects on genes regulating cancer cell growth, terameprocol may also modulate the effectiveness of other chemotherapeutic drugs. Terameprocol showed synergistic effects with doxorubicin and paclitaxel on inhibition of cell growth in culture, and also increased the effectiveness of these drugs *in vivo* [9].

Terameprocol is a nonionic hydrophobic compound that is insoluble in aqueous solutions. In previous in-vitro and in-vivo studies, terameprocol was dissolved in DMSO or Cremophore EL [1,2,7–9]. Concerns over the safety of DMSO and Cremophore EL have arisen, including hypersensitivity reactions and interference with cancer drug pharmacokinetics [15,16]. Therefore, alternative solvents are needed for hydrophobic compounds to ensure safety and to control pharmacological interactions when used systemically.

Cyclodextrins are a family of cyclic oligosaccharides with a hydrophilic outer surface and a lipophilic central cavity [17]. Various natural cyclodextrins as well as hydrophilic derivatives have been used in the formulation of poorly water-soluble drugs to improve drug solubility and/or dissolution [18]. Over 30 different marketed pharmaceutical products are present worldwide containing drug/cyclodextrin complexes, and hydroxypropyl β-cyclodextrin (HPβCD) is included in the database for inactive ingredients in Food and Drug administration-approved drugs. The hydrophilic, amorphous cyclodextrin derivative HPβCD has been widely investigated for oral and parenteral use owing to its high aqueous solubility and minimal toxicity [18]. Hydrophylic polymers such as polytheylene glycol (PEG) have been shown to enhance complexation and solubilizing efficiencies of cyclodextrins, including HPβCD [19,20].

The present studies were designed to investigate the in-vitro and in-vivo anticancer activity of terameprocol in a novel HPβCD and PEG formulation (designated CPE) designed for parenteral administration. Terameprocol (CPE formulation) is currently being administered as an intravenous infusion at doses up to 3300 mg/day in a phase 1 trial in patients with refractory solid tumors.

Methods

Terameprocol CPE preparation

Terameprocol was synthesized as previously described [21]. Terameprocol powder was dissolved in CPE (20% HPβCD and 50% PEG 300 in water for injection, or 30% HPβCD and 25% PEG 300 in water for injection) using a cosolvent technique or in Hybri-max DMSO (Sigma, St. Louis, Missouri, USA). Stock solutions of terameprocol were further diluted with the appropriate vehicle (CPE or DMSO) before addition to the cell culture medium for a final solvent concentration of 1%. Controls included CPE solvent or DMSO without terameprocol and untreated cells.

Formulations of terameprocol in 30% HPβCD and 25% PEG 300 at 10 mg/ml and terameprocol/paclitaxel coformulated in 30% HPβCD and 25% PEG 300 at 10 mg/ml terameprocol and 0.5 mg/ml paclitaxel were used for xenograft studies.

Terameprocol formulations were stored at 2–8°C. Stability studies assessed biological activity of terameprocol in CPE solutions up to 12 months old.

Cell culture

All cell lines were cultured in 5% CO_2 and > 70% air at 36–38°C using standard culture conditions. HeLa human cervical cancer cells [American Type Culture Collection (ATCC) no. CCL-2] were cultured in Eagle's Minimal Essential Medium (MEM) with 10 mmol/l sodium pyruvate, 10 mmol/l nonessential amino acids, antibiotic cocktail (1000 units penicillin/1000 µg streptomycin) and 10% fetal bovine serum. The C33a–human papilloma virus-negative human cervical cancer cell (ATCC no. HTB-31) was grown and maintained in MEM supplemented with 10% fetal calf serum, nonessential amino acids, sodium pyruvate and antibiotic cocktail. The human bladder carcinoma cell line, SW-780 (ATCC no. CRL-2169), was cultured in Dulbecco's Modified Eagles Medium (DMEM), supplemented with 4 mmol/l L-glutamine, 0.1 mmol/l nonessential amino acids and 10% fetal bovine serum.

Cell proliferation assays

Cells were plated (10^5 cells per well) in six-well culture dishes. After 18–24 h incubation, growth media was removed and replaced with media containing 0, 20, 40, 60 and 80 µmol/l terameprocol in 1% DMSO or CPE. Control cells were grown under the same conditions and left untreated. After 72 h, the cell proliferation rate and the percentage of dead cells in each sample were determined by the Trypan blue exclusion assay and/or the CellTiter 96 Aqueous Non-Radioactive Cell Proliferation Assay (Promega, Madison, Wisconsin, USA) according to the manufacturer's instructions using a microplate reader for absorbance detection.

In-vivo implantation of SW-780 cells and efficacy studies

Cells to be implanted in mice were harvested from cell culture flasks during exponential growth, washed twice in phosphate-buffered saline, counted and suspended in Hanks balanced salt solution for injections. Female athymic, nude mice, *Crl: NU-Foxn1^{nu}* aged 7–9 weeks were used for xenograft studies carried out at Charles River Laboratories (Willmington, Massachusetts, USA) with the approval of the Institutional Animal Care and

Table 1 Terameprocol treatment groups and dosing in the mouse xenograft model

Group number ($N=10$)	Treatment	Dose (mg/kg)
1	Untreated	–
2	CPE vehicle	–
3	Paclitaxel	5
4	LD terameprocol	50
5	HD terameprocol	100
6	Terameprocol/paclitaxel	100/5

Intraperitoneal injections of all treatments were administered daily for 21 days in a volume of 10 or 20 ml/kg.
HD, high dose; LD, low dose.

Use Committee in an American Association for Accreditation of Laboratory Animal Care-accredited vivarium and in accordance with the Institute of Laboratory Animal Research (Guide for the Care and Use of Laboratory Animals, National Institutes of Health, Bethesda, Maryland, USA).

Mice received subcutaneous injections into the right lateral thorax with 1×10^7 viable SW-780 human bladder cells in 0.2 ml of Hanks balanced salt solution. Animals with established tumors (100–196 mg, determined as described below) were randomized into six treatment groups of 10 mice each. Terameprocol, paclitaxel, terameprocol and paclitaxel or vehicle was administered intraperitoneally daily for 21 days at the doses indicated in Table 1. Treatment group 6 (terameprocol/paclitaxel) was coadministered the two compounds simultaneously following the same dosing schedule as other treatment groups. Tumor growth was measured twice weekly using vernier calipers. Individual animal weights were recorded three times per week during dosing. Animals were monitored daily for signs of toxicity and morbidity.

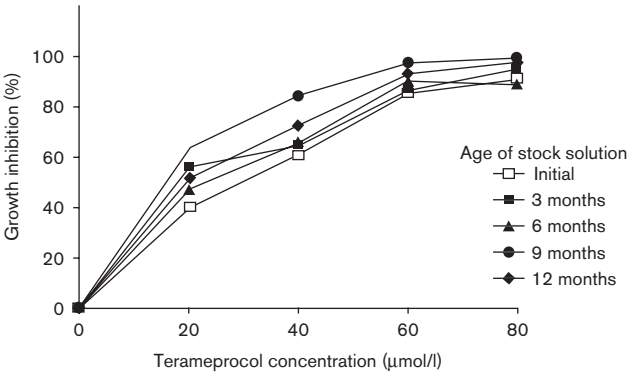
Tumor weights (M) in milligrams were calculated by using the formula associated with a prolate ellipsoid: $M = (L \times W^2)/2$, where L = length and W = width of any tumor developed and L is the longer of the two dimensions. Descriptive statistics included means and standard deviations.

Results

Terameprocol is biologically stable in the CPE formulation

To determine the continuous biological activity over time of terameprocol in the CPE formulation, the effect of terameprocol on proliferation of HeLa cells was assessed over a 12-month time course. Terameprocol stock solutions were prepared and added to cell culture media for 72 h for final concentrations of 20, 40, 60 and 80 µmol/l terameprocol as described in Methods. Results are shown in Fig. 1. HeLa cell proliferation was inhibited by terameprocol in a concentration-dependent manner, with IC_{50} values in the 20–40 µmol/l range. Inhibition of cell proliferation was comparable at all time points evaluated (0, 3, 6, 9 and 12 months).

Fig. 1



Stability study of terameprocol CPE formulation. Terameprocol CPE stock solutions that were stored at 2–8°C for up to 12 months were used in HeLa cell proliferation assays as described in Methods.

Terameprocol CPE formulation inhibits proliferation of HeLa and C33A cell lines with reduced toxicity compared with dimethyl sulfoxide

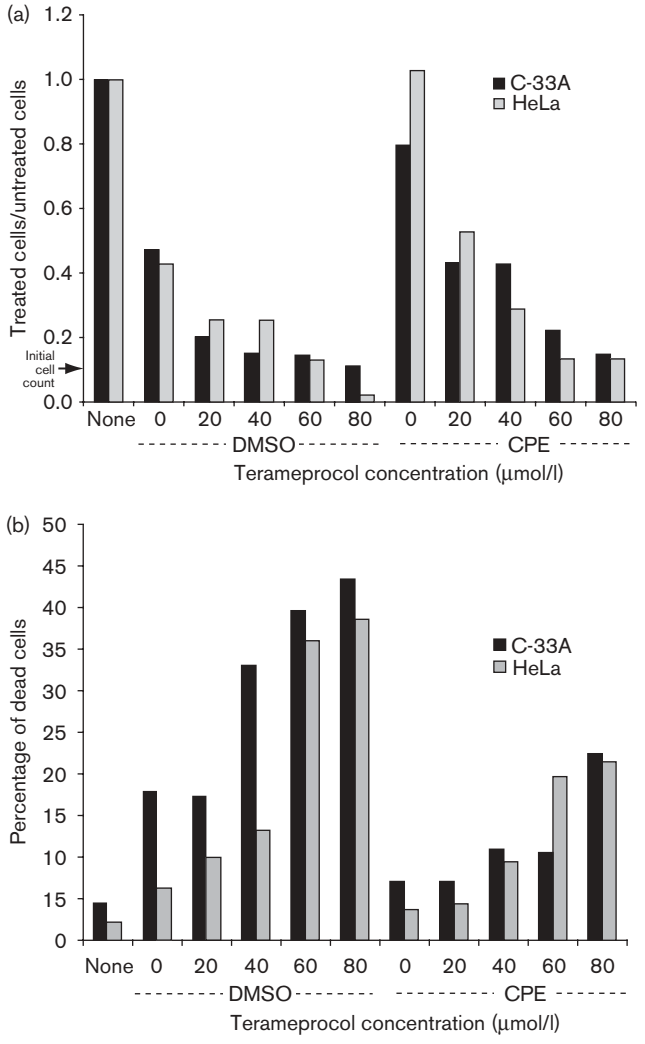
Previous cell proliferation and tumor xenograft studies of terameprocol used DMSO as solvent. Therefore, the effects of terameprocol on cell proliferation and cell death were compared when formulated in DMSO and CPE. The cell proliferation rate was reduced in both HeLa and C33A cell lines after treatment with terameprocol formulated in both vehicles when compared with untreated cells (Fig. 2a). The percentage of dead cells in culture increased with increasing concentrations of both terameprocol formulations (Fig. 2b). The DMSO formulation, however, was more toxic to cells than the CPE formulation. The highest concentration of terameprocol (80 µmol/l) tested in the DMSO formulation induced death in 40% of the cell population, while the same concentration of terameprocol in the CPE formulation was associated with 20% cell death. These data indicate that the CPE formulation of terameprocol can arrest cell proliferation with less cellular toxicity than the DMSO formulation in the test cell lines. As results may be cell line and/or culture-condition-specific, they cannot be extrapolated to all cell lines.

The terameprocol CPE formulation prepared for in-vivo xenograft studies with SW-780 cells was used for in-vitro cell proliferation assays. Increasing concentrations of terameprocol inhibited cell proliferation with an IC_{50} in the 20–40 µmol/l range (data not shown).

Terameprocol CPE formulation inhibits tumor growth *in vivo*

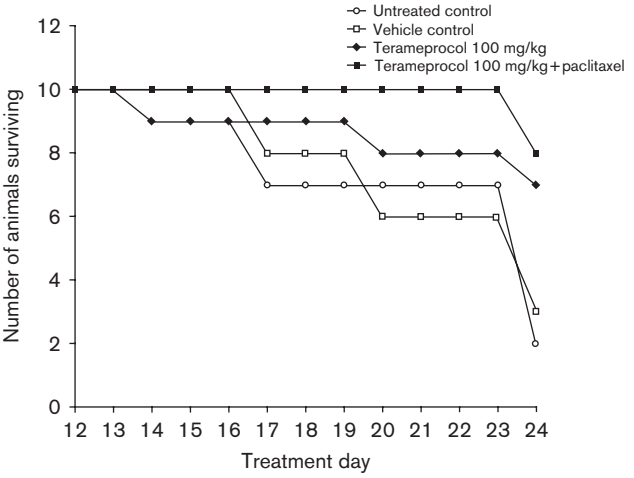
All mice injected with SW-780 human bladder cancer cells were confirmed to have tumors consistent with

Fig. 2



Cell proliferation (a) and cell death (b) in C-33A and HeLa cell lines following incubation with different concentrations of terameprocol in DMSO or CPE. The cell proliferation rate and the percentage of dead cells in each sample were determined 72 h after addition of terameprocol to cell cultures. DMSO, dimethyl sulfoxide.

Fig. 3



Survival in control and terameprocol treatment groups. Nude mice with xenografts of human bladder tumor cell line SW-780 were treated on study days 1–21 with daily intraperitoneal injections of vehicle, terameprocol or terameprocol/paclitaxel. All groups had 10 animals through day 13.

Table 2 Mean tumor weights (mg) for nude mice with SW-780 human tumor xenografts treated for 3 weeks (study days 1–21) with daily intraperitoneal injections of vehicle, paclitaxel, terameprocol or terameprocol plus paclitaxel

Study day	Treatment groups					
	Untreated	Vehicle control	Paclitaxel	Terameprocol		Terameprocol/paclitaxel
			5 mg/kg	50 mg/kg	100 mg/kg	100 mg/kg/5 mg/kg
4	151	156	124	181	146	164
5	157	162	155	161	158	158
7	178	193	187	160	170	164
11	369	395	360	249	306	282
14	719	760	539	377	509	453
18	1193	1358	993	767	730	698
21	1255	1350	1286	979	1070	817
25	2020[a]	1359[a]	1757	1143	1289	955

[a]Number of animals/group ≤ 3.

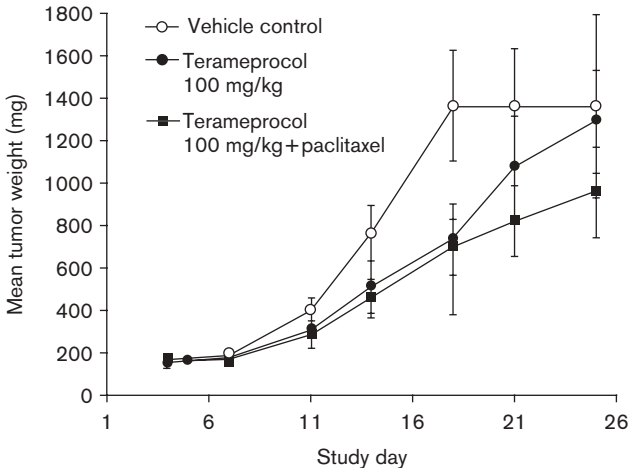
implanted carcinomas. Animal weights continued to increase throughout the study (days 1–21) and were comparable across treatment groups. No overt toxicity was observed in animals in any of the treatment groups. All treatment groups had 10 animals through day 13 of the study. After day 13, the numbers of animals surviving per group decreased; there were greater numbers of animal deaths in both control groups compared with the terameprocol, terameprocol/paclitaxel and paclitaxel treatment groups. Survival data for the control, terameprocol (100 mg/kg) and terameprocol/paclitaxel (100 mg/kg/5 mg/kg) treatment groups from day 12 through 24 are shown in Fig. 3. Survival was greatest in the terameprocol/paclitaxel group with all 10 animals surviving through day 23 and lowest for the two control groups. Survival was similar in the terameprocol and the paclitaxel groups (not shown).

Mean tumor weights for all groups are shown in Table 2. Weights in the untreated or vehicle control groups reached 1000 mg by day 18. Mean tumor weight in the paclitaxel-treated group (Group 3) was slightly lower than the control groups at each time point during treatment days (up to study day 21). The mean tumor weights in the low- and high-dose terameprocol groups (Groups 4 and 5) were similar at each time point and were reduced compared with control groups. Mean tumor weights in the terameprocol groups never exceeded those in the negative control groups (on study day 25 maximum mean weights of 1143, 1289, 2020 and 1359 mg in the

low-dose, high-dose, untreated and vehicle control groups, respectively).

Tumor growth in the terameprocol/paclitaxel-treated group (Group 6) was delayed compared with the other dose groups. Mean tumor weight in this group reached 500 mg by study day 21; a growth delay of approximately 7 days compared with the control groups. Tumor weights in this group did not exceed 1000 mg by the end of the study (maximum of 985 mg). Mean tumor weights (± SEM) for animals in the vehicle control, 100 mg/kg terameprocol and the terameprocol/paclitaxel groups are shown in Fig. 4. The lack of increase in mean tumor weight and the increase in the standard error of the means in the vehicle control group at study days 21–25 reflects the decrease in the number of animals remaining alive in that group (see Fig. 3).

Fig. 4



Effect of systemic terameprocol treatment on the growth of human xenograft tumors in nude mice. Nude mice with xenografts of human bladder tumor cell line SW-780 were treated on study days 1–21 with daily intraperitoneal injections of vehicle, terameprocol or terameprocol/paclitaxel. Measurements of tumor size were made twice weekly and the mean tumor weight ± the SEM is plotted as a function of time. The lack of increase in mean tumor weight in the vehicle control group at study days 21–25 is due to the decrease in the number of animals remaining alive in that group.

These data demonstrate that at the dosing concentrations and schedule used in this study, the high and low doses of terameprocol alone reduce the rate of tumor growth, and the combination terameprocol/paclitaxel reduces both the rate and extent of tumor growth of human bladder xenografts.

Discussion

Terameprocol is a semisynthetic small molecule with antitumor activity via selective targeting of Sp1-regulated genes overexpressed in cancer cells [22]. Terameprocol arrests growth of a variety of human cells *in vitro*, the majority of which are part of the National Cancer Institute panel of 60 cancer cell lines, including solid tumors cell lines (breast, colon, prostate, colorectal, liver and cervical carcinomas) and erythroleukemia cells (Table 3). *In vivo*, terameprocol also decreases tumor cell growth and exhibits antitumor activity in a large number

Table 3 In-vitro anticancer activity of terameprocol formulations

Tumor cell line	Solvent formulation	Results	References
HeLa human cervical carcinoma C33A human cervical cancer SW-780 human bladder carcinoma	CPE	Inhibition of cell proliferation with IC_{50}values between 20 and 40 μmol/l	Present study
MCF7 human breast cancer NCI/ADR-RES (multidrug resistant ovarian cancer cell)	DMSO	Terameprocol (M4N) acts synergistically with doxorubicin and paclitaxel in inhibiting cell growth. Terameprocol IC_{50} (9 μmol/l) reduced 30–60% when used in combination with doxorubicin or paclitaxel.	Chang *et al.* [9]
Hep 3B hepatocellular carcinoma MCF7 human breast cancer HT-29 human colorectal carcinoma LNCaP human prostate carcinoma K-562 human erythroleukemia	Cremophore EL	Cell growth is arrested in concentration dependent manner	Park *et al.* [10]
BIC1, SEG1 esophageal adenocarcinoma cell lines	DMSO	Dose-dependent decrease in cell growth with complete inhibition between 20 and 40 μmol/l	Hansel *et al.* [7]
A375 human melanoma A549 human nonsmall cell lung MCF7 human breast cancer SW480 human colon cancer ACC375 human melanoma	DMSO	Inhibition of cell proliferation with IC_{50} values between 1 and 20 μmol/l	Lambert *et al.* [8]
HPV-16/ras-transformed C3 cells HPV-16 E6/E7/ras-transformed TC-1 cells C33A human cervical cancer CEM-T4 human leukemia	DMSO	Cell growth is arrested in concentration-dependent manner	Heller *et al.* [1]

Cell culture test models for terameprocol.
DMSO, dimethyl sulfoxide.

Table 4 In-vivo anticancer activity of terameprocol formulations

Tumor cell line	Solvent formulation	Efficacy results	Safety results	Reference
SW-780 human bladder carcinoma	CPE	Inhibition of tumor growth with 50 and 100 mg/kg intraperitoneally; increased effect when combined with paclitaxel	No signs of treatment-related toxicities (e.g. reduction in animal weights or mortalities)	Present study
NCI/ADR-RES (multidrug-resistant ovarian cancer cell)	Cremophore EL	160 and 320 μmol/m^2 intraperitoneally inhibited the growth of human tumor xenografts, and increased effectiveness of doxorubicin and paclitaxel	No signs of treatment-related toxicities (e.g. reduction in animal weights or mortalities)	Chang *et al.* [9]
Hep 3B hepatocellular carcinoma MCF7 human breast cancer HT-29 human colorectal carcinoma LNCaP human prostate carcinoma K-562 human erythroleukemia	Cremophore EL	2 mg intraperitoneally or 300 mg oral doses decreased tumor volumes in xenografts	No signs of treatment-related toxicities (e.g. reduction in animal weights or mortalities)	Park *et al.* [10]
A375 human melanoma SW480 human colon cancer	Cremophore EL	Up to 300 mg/kg intraperitoneally slowed tumor growth	No signs of treatment-related toxicities (e.g. reduction in animal weights or mortalities)	Lambert *et al.* [8]
HPV-16/ras-transformed C3 cells	DMSO	Reduction in tumor mass with 20 mg intratumoral injections	No signs of treatment-related toxicities (e.g. reduction in animal weights or mortalities)	Heller *et al.* [1]

Xenografts in athymic nude mice were implanted with the following tumor cell lines and animals were injected with terameprocol.
DMSO, dimethyl sulfoxide.

of tumor xenograft models, including human breast, colon and cervical carcinomas (Table 4), without apparent toxicity.

The hydrophobicity of terameprocol necessitates use of synthetic solvents. Preclinical studies used DMSO or Cremophore EL as terameprocol solvents [1,8–10]. Initial clinical studies of terameprocol using DMSO were limited to intratumoral administration owing to the lack of a suitable solvent compatible with systemic administration [12,14]. Both DMSO and Cremophore EL can be associated with side effects that make them undesirable for use in systemic applications [15,16]. The objectives of this study were to assess the in-vitro and in-vivo tumoricidal activity of a new formulation of terameprocol consisting of the solubilizing excipients HPβCD and PEG that is suitable for parenteral administration (CPE).

HPβCD is a relatively new excipient developed as a modified, hydrophilic β-cyclodextrin without the associated nephrotoxicity observed in the parent molecule (β-cyclodextrin). HPβCD was also found to be superior to DMSO in the intrathecal and intracerebral drug delivery of cyclic peptide opiates in rats [23]. Toxicological studies demonstrate the safety of HPβCD for use in intravenous delivery. No clinical toxicities have been observed in subchronic studies in rats, rabbits, dogs or monkeys, receiving high concentrations of HPβCD (up to 1 g/kg) by the intravenous route [24–26]. Reversible histological changes have been associated with HPβCD at the highest dose (1 g/kg) in dogs, including vacuolar degeneration of renal epithelial cells and alveolar histiocytosis of the lung. In humans, no adverse effects and no evidence of renal impairment have been observed in individuals receiving 500 mg/kg/day for 3 days or 470 mg/kg/day for 4 days [25,27].

Using human cancer cell lines *in vitro*, we found that the terameprocol CPE formulation inhibits cell proliferation and is less toxic than the DMSO formulation in two cell lines tested. Although responses may be different in other cell lines and are likely influenced by the formulation of the cell culture media, the level of inhibition of cell proliferation with the terameprocol CPE solvent is comparable to that seen with DMSO or Cremophore EL formulations tested on other human cancer cell lines [1,8,10]. Table 3 shows the different in-vitro cell culture systems that have been used to test terameprocol formulations. The pharmacological properties *in vitro* are similar (IC_{50} values range from 10 to 40 μmol/l) for the different terameprocol formulations.

The terameprocol CPE formulation has in-vivo antitumor effects against human bladder carcinoma xenografts in nude mice. Terameprocol appeared to inhibit the rate of tumor growth and shows potential for synergism with paclitaxel. Survival was highest in the group of animals treated with 100 mg/kg terameprocol per 5 mg/kg paclitaxel. The combination of terameprocol and paclitaxel decreased both the rate and magnitude of bladder tumor growth. These results are likely owing to the mechanisms of paclitaxel in preventing cell division and of terameprocol in inducing cell death via survivin inhibition, resulting in a synergistic effect against cancer cells. Paclitaxel was used at a reduced dose of 5 mg/kg in the bladder cancer xenograft model in this in-vivo study; effective doses normally range from 20 to 25 mg/kg. This observation also supports previous results showing that the terameprocol Cremophore EL formulation in combination with doxorubicin or paclitaxel has increased efficacy and allows significant reductions in the concentrations required for maximal cell growth inhibition *in vitro* [9]. Table 4 summarizes the in-vivo xenograft

studies using different tumor cell lines and different terameprocol formulations. The three formulations used have been effective in reducing growth of a variety of human tumor xenografts in nude mice, including bladder, melanoma, colon, breast and liver cancer.

Administration of the terameprocol CPE formulation showed no overt toxicities in treated animals. The number of animal deaths was highest in the untreated and vehicle control groups. Previous studies have shown that repeated dosing of mice with at least 300 mg/kg terameprocol (intraperitoneally) in DMSO or Cremophore EL formulations was nonlethal [1,8,10].

The preclinical results presented in this paper confirm the tumoricidal activity of terameprocol formulated in a solvent suitable for parenteral administration. These results suggest that terameprocol has improved efficacy when coadministered with paclitaxel. The terameprocol CPE formulation administered intravenously is currently in clinical trials for solid tumor malignancies refractory to surgery, radiation therapy and/or chemotherapy.

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