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Canfosfamide Hydrochloride

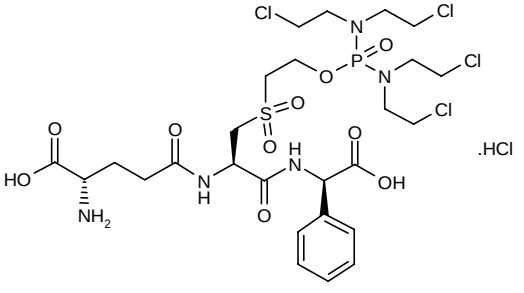
USAN

Oncolytic
DNA Alkylating Drug

TER-286
TLK-286
Telcyta™

2(*R*)-[2-[4(*S*)-Amino-4-carboxybutyramido]-3-[2(*R*)-[bis[*N*,*N*-bis(2-chloroethyl)amino]phosphoryloxy]ethylsulfonyl]propionamido]-2-phenylacetic acid hydrochloride

L-γ-Glutamyl-3-[2-[bis[bis(2-chloroethyl)amino]phosphinyloxy]ethylsulfonyl]-L-alanyl-2(*R*)-phenylglycine monohydrochloride



$C_{26}H_{40}Cl_4N_5O_{10}PS.HCl$
Mol wt: 823.9399
CAS: 439943-59-6
CAS: 158382-37-7 (as free base)
EN: 219471

Abstract

A targeted approach to the treatment of solid tumors involves the development of potent alkylating agents activated by glutathione *S*-transferase P1-1 (GST P1-1). The novel nitrogen mustard prodrug canfosfamide is one such compound. Preclinical studies demonstrated the increased sensitivity of tumors expressing high levels of GST P1-1 to the cytotoxic effects of canfosfamide. In multiple human cancer cell lines, synergy or marked enhancement of cytotoxicity was observed when canfosfamide was combined with a variety of other chemotherapeutic agents. Phase I studies in patients with solid tumors supported the administration of a dose of 960 mg/m^2 given weekly or once every 3 weeks in disease-specific phase II studies. In patients with ovarian, colorectal, non-small cell lung (NSCLC) and breast cancer, canfosfamide was well tolerated and exerted antitumor activity when given alone. Phase II studies in combination with other cytotoxic agents provided further evidence of the activity of canfosfamide and phase III studies in ovarian cancer and NSCLC have been initiated.

Synthesis

Debenzylation of known L-γ-glutamyl-(*S*-benzyl)-L-cysteinyl-(*R*)-(–)-phenylglycine (I) (1) by means of sodium in liquid ammonia gives the corresponding thiol (II), which by subsequent *S*-alkylation with 2-bromoethyl *N*,*N*,*N*',*N*'-tetrakis(2-chloroethyl)phosphorodiamidate (III) provides the thioether (IV). Finally, this thioether (IV) is oxidized with H_2O_2 in acetic acid (2, 3). Scheme 1.

2-Bromoethyl *N*,*N*,*N*',*N*'-tetrakis(2-chloroethyl)phosphorodiamidate (III) is prepared by addition of phosphoryl chloride to 2-bromoethanol (V) in the presence of Et_3N, followed by *in situ* treatment of the resulting intermediate (VI) with bis(2-chloroethyl)amine (VII) (2, 3). Scheme 1.

Introduction

Targeted approaches to cancer treatment involve the identification of agents that are tumor-selective in their toxicity with relatively little effect upon normal tissues. They are also designed to have improved tolerability over conventional cytotoxic agents. Glutathione *S*-transferase P1-1 (GST P1-1) is a detoxification enzyme that has been shown to be elevated in a number of tumor types, including lung, colon and stomach cancers. Compared with matched normal tissues, the average levels of the enzyme in tumors are increased by approximately 100%. Overexpression of GST P1-1 in human tumors is associated with a poor prognosis and the development of drug resistance. The design and synthesis of alkylating agents activated by GST P1-1 therefore represents a targeted approach against these tumor types (4-6).

One such compound is the novel nitrogen mustard prodrug canfosfamide (TER-286, TLK-286, Telcyta™), which was discovered at Telik using the company's proprietary Target-Related Affinity Profiling (TRAP™) tech-

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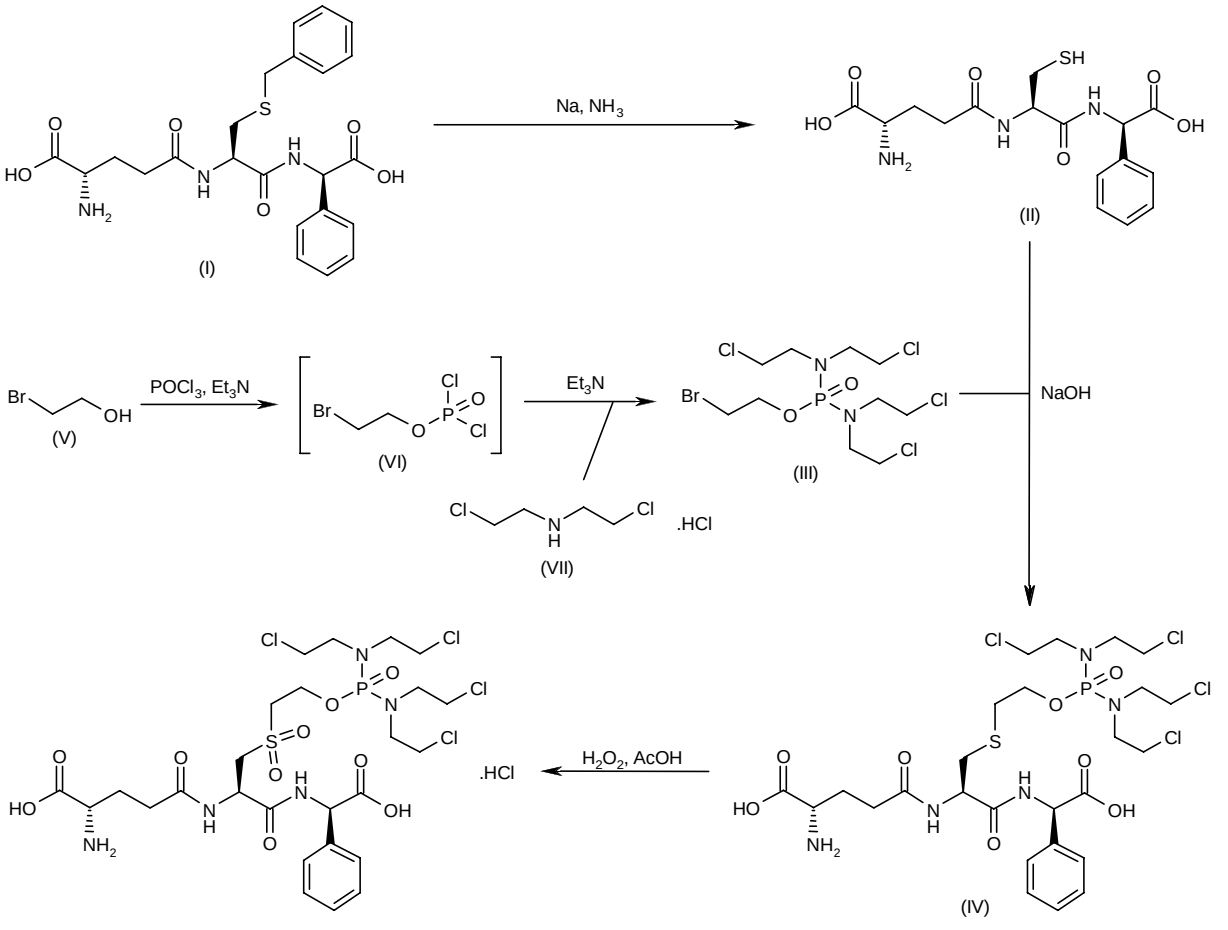
Scheme 1: Synthesis of Canfosfamide Hydrochloride



nology. The metabolism of the compound results in the generation of a potent alkylating agent and a glutathione analogue fragment, with subsequent blockade of the enzyme (7, 8).

Pharmacological Actions

Mechanistic studies on the enzyme-catalyzed decomposition of canfosfamide have provided evidence of the breakdown of the prodrug into the active cytotoxic mustard component and reactive components. The alkylating nature of the decomposition products was also demonstrated. Cell culture studies indicated that elevated levels of GST P1-1 would result in increased toxicity of canfosfamide. Canfosfamide was toxic against MCF7 breast cancer cells (IC_{50} = 37.5 μM). When MCF7 cells were transfected to overexpress GST P1-1, they showed a 4-fold increase in sensitivity to canfosfamide (IC_{50} = 9.5 μM) (2, 9).

The cellular response to canfosfamide was also studied in cell lines with acquired drug resistance. Chronic, long-term exposure to the prodrug resulted in a human promyelocytic leukemia cell line resistant to canfosfamide. The cell line exhibited a significant decrease in the expression and enzymatic activity of GST P1-1, as well as other changes reflecting the alkylating properties of the drug. NIH/3T3 cells transfected with γ-glutamylcysteine synthetase (γ-GCS) and multidrug resistance protein-1 (MRP-1) showed 6-fold resistance to canfosfamide. However, cotransfection with GST P1-1 reduced the degree of resistance to 3.7-fold. This may represent an alteration in the cellular kinetics of canfosfamide, and a shift between drug activation and detoxification. Overall, the data supported the rationale that tumors expressing high levels of GST P1-1 would be more sensitive to the cytotoxic effects of canfosfamide (10-13).

The cytotoxic activity of canfosfamide was further demonstrated in cell cultures and in clonogenic assays using primary tumor biopsies. Human breast cancer MCF7 cells selected for resistance to cyclophosphamide

and human colon carcinoma M7609 cells selected for resistance to doxorubicin showed increased sensitivity to canfosfamide compared with their parental lines, concomitant with increased expression of GST P1-1. Lung and breast tumor specimens were examined using a primary tumor clonogenic assay. Specimens from both previously treated and chemotherapy-naïve patients were exposed to concentrations of canfosfamide of 1, 10 and 50 μM for 1 h or continuously. Tumor specimens responded to canfosfamide with a clear concentration-response effect, with a positive response observed in approximately 50% of the 41 samples. Based on individual tumor types, following continuous exposure to canfosfamide, a 50% response was observed in breast tumors, a 70% response in NSCLC and a 100% (1/1) response in small cell lung tumors. The assays indicated that canfosfamide has a novel and broad spectrum of activity compared to other drugs tested in the same assays. It showed improved cytotoxic activity in terms of individual specimen response over cisplatin in lung tumor specimens and over cyclophosphamide in breast tumor specimens. There was no significant difference in activity between specimens from patients who had received prior therapy compared with those who had not. In clinical leukemia samples, a strong response to canfosfamide 50 μM was observed. Concentrations of 10 and 50 μM resulted in growth suppression greater than that obtained in a parallel treatment with melphalan 5 μM or daunorubicin 0.2 μM (14-17).

Mice implanted with human tumor M7609 xenografts were treated with either a single i.v. dose of canfosfamide of 150 mg/kg or with 5 daily i.p. doses of 200 mg/kg. The xenografts were engineered to have variable GST P1-1 levels, and response to canfosfamide in terms of percentage tumor growth inhibition was positively correlated with the level of GST P1-1. Human breast tumor MX-1 xenografts were highly responsive to the 5-day regimen, with significant growth inhibition or tumor regression in nearly all tumors. The bone marrow suppression observed with the 5-day i.p. regimen of canfosfamide was similar to that observed following a single i.v. dose, and was consistent with mild bone marrow toxicity at therapeutic doses in mice (14, 17).

The molecular mechanism of canfosfamide-induced apoptosis was investigated in human leukemic T-cells. Apoptosis was induced in a concentration- and time-dependent manner, with concomitant concentration- and time-dependent activation of c-jun *N*-terminal kinase (JNK). Activation of intracellular caspase 3 and the mitogen-activated protein kinase MEK4 was also observed. The sequential activation of kinases in the stress response pathway indicated that canfosfamide-induced programmed cell death is at least in part mediated by the stress response signaling pathway (18-20).

The mechanism of action of canfosfamide was further investigated in platinum-resistant ovarian cancer C70 and C200 cell lines. An altered expression of the DNA-dependent protein kinase (DNA-PK) complex was found. Canfosfamide, either as the parental form or in the activated form, inhibited the catalytic activity of purified DNA-PK with an IC_{50} value of approximately 1 μM (21, 22).

Canfosfamide has been investigated in combination with a variety of other chemotherapeutic agents in multiple human cancer cell lines *in vitro*. The ovarian cancer cell line OVCAR3 was incubated with canfosfamide alone or in combination with doxorubicin, carboplatin or paclitaxel. Marked enhancement of cytotoxicity was observed when canfosfamide was combined with any of these agents compared with incubation of the cells with the single agents. Similarly, the combination of canfosfamide and docetaxel or gemcitabine was more effective in inhibiting the proliferation of MCF7 cells than any drug alone. In the A549 lung cancer cell line, the combination of canfosfamide with either cisplatin or paclitaxel was also highly effective in inhibiting cell proliferation. Synergy or marked enhancement of cytotoxicity was observed when the human colon cancer cell lines HT-29 and DLD-1 were incubated with canfosfamide and oxaliplatin (23-25).

Pharmacokinetics and Metabolism

The pharmacokinetic and metabolic profiles of canfosfamide have been evaluated in several species. In samples of fresh whole blood drawn from rats, dogs and humans and incubated with canfosfamide, the drug demonstrated low binding to red blood cells and low protein binding. In rats and dogs administered single i.v. doses of 300 and 50 mg/kg, respectively, the blood concentrations of canfosfamide declined rapidly after the end of the infusion, with an elimination half-life of 36 min in rats and 7 min in dogs. Urinary excretion in both species was low. In studies with human hepatic microsomes, assays specific for P-450 isozymes demonstrated that concentrations of canfosfamide necessary to inhibit the isozymes were significantly higher than those achieved in patients given the recommended dose of canfosfamide. These results suggested that drug-drug interactions mediated via protein binding or P-450 isozymes were unlikely (26).

Clinical Studies

In a dose-escalating phase I study, patients with advanced, refractory solid malignancies were treated with canfosfamide once every 3 weeks to determine the dose-limiting toxicities (DLTs), maximum tolerated dose (MTD) and pharmacokinetics of canfosfamide. In this first study in humans, 35 adult patients were treated with 109 cycles of canfosfamide at 9 dose levels ranging from 60 to 1280 mg/m^2 as a 30-min i.v. infusion. The most common types of malignancies were colorectal and breast cancer, NSCLC and sarcoma. All patients had metastases and had received multiple prior chemotherapeutic regimens. The median number of cycles administered per patient was 2 (range = 1-9). The MTD of canfosfamide for this regimen was established at 1280 mg/m^2, with 3 of 5

patients at this dose level reporting DLTs of pancreatitis or bladder symptoms. No grade 3 or 4 hematological toxicities were observed, and the most frequently reported nonhematological toxicities were nausea, vomiting, fatigue, hematuria and hypokalemia. Pharmacokinetic assessments were performed in cycle 1 in all patients and revealed dose-proportional increases in peak blood levels (C_{max}) and area under the blood concentration-time curve (AUC) for all doses up to 960 mg/m^2. Canfosfamide was rapidly eliminated from the blood, with a mean half-life of 18 min. In terms of antitumor effects, 31 patients received a minimum of 2 cycles of treatment, underwent tumor assessment on day 43 and were considered evaluable. Four patients experienced tumor regressions and 9 had stable disease. Canfosfamide was well tolerated in this study, without clinically significant myelosuppression, and the safety and pharmacokinetic data supported a dose of 960 mg/m^2 given once every 3 weeks in further disease-specific studies (27-29).

The favorable safety profile observed in the first human study led to the further evaluation of canfosfamide administered weekly in escalating doses from 60 to 960 mg/m^2. In this study, 37 patients with advanced solid tumors received a total of 111 cycles of canfosfamide at 8 dose levels. A treatment cycle was defined as 3 weekly treatments. The most frequently represented tumor type was colorectal cancer (12 patients), and all patients had metastatic disease, the majority having received multiple prior chemotherapeutic regimens. A total of 12 patients received canfosfamide at the highest dose of 960 mg/m^2 without any DLT. One patient at the highest dose had grade 3 hematological toxicity. Nonhematological toxicities were comparable to those observed in the initial phase I study. Nine of 31 patients evaluable for tumor response had a best response of stable disease or minor tumor regressions, demonstrating antitumor activity for canfosfamide monotherapy. Further pharmacokinetic assessment showed little interindividual variability in the plasma concentration-*versus*-time curve for canfosfamide, indicating predictable pharmacokinetics for the typical individual. Comparison of the safety profile of the regimens indicated that canfosfamide was also well tolerated when administered at the higher dose intensity weekly schedule (29-32).

In a multicenter phase II study in 36 patients with platinum- and paclitaxel-refractory or -resistant ovarian cancer, canfosfamide was administered at a dose of 1000 mg/m^2 once every 3 weeks. Approximately 50% of the patients had also failed between 1 and 3 additional salvage therapies, including liposomal doxorubicin, topotecan, gemcitabine and docetaxel. At least 117 cycles of canfosfamide treatment were administered at 99% of the specified dose intensity. Durable objective responses by RECIST criteria were observed, with a complete response in 1 patient, partial responses in 4 patients and stable disease in 12 patients. These responses were associated with clinical symptom improvement. Median survival and progression-free survival of responders were 19.5 and 7.1 months, respectively, greater than expected historically in this heavily pretreated population. Only 6% of patients experienced grade 3 toxicities, and no cumulative toxicity or clinically significant hematological toxicity was observed (33-35).

Canfosfamide was also administered as a weekly regimen to patients with platinum- and paclitaxel-refractory or -resistant advanced ovarian cancer. A total of 23 patients received canfosfamide 960 mg/m^2 weekly in this phase II study. Of 11 patients evaluable at interim analysis, objective responses were obtained in 2 patients. Canfosfamide was well tolerated when administered weekly, with infrequent grade 3 toxicities and no dose reductions required (36).

In a dose-ranging phase I/II study, canfosfamide was administered in combination with liposomal doxorubicin to patients with platinum-refractory or -resistant ovarian cancer. Canfosfamide was administered at doses of 500, 750 or 960 mg/m^2 with liposomal doxorubicin at 40 or 50 mg/m^2 every 4 weeks. At interim analysis, 16 patients had received 59 cycles of therapy. The maximum dose of 960/50 mg/m^2 canfosfamide/liposomal doxorubicin was administered to 7 patients, and was well tolerated, without DLT. At these doses, a partial response was obtained in 2 patients and 2 other patients had stable disease, indicating early evidence of enhanced activity (37, 38). Preliminary results of another phase I/II study in platinum-resistant or -refractory ovarian cancer patients have also shown early efficacy of canfosfamide (500 mg/m^2) administered with carboplatin (AUC6) every 3 weeks (39).

In a multicenter phase II study, 73 patients with refractory colorectal cancer who had failed previous therapy with 5-fluorouracil, leucovorin and irinotecan received canfosfamide at a dose of 1000 mg/m^2 every 3 weeks. Of 36 patients evaluable for response at interim analysis, 5 had stable disease as best response, with a median decrease of 42% in the CEA (carcinoembryonic antigen) tumor marker. The estimated median survival was 172 days. Canfosfamide was well tolerated. The lack of an objective response in this population indicated that investigation of a more intensive dose schedule, or use of canfosfamide in combination with other agents, may be warranted (40).

Patients with stage 3B or 4 NSCLC who had failed prior platinum-based chemotherapy were enrolled in a multicenter phase II study. Fifty-two patients received a total of 152 treatments of canfosfamide at a dose of 1000 mg/m^2 every 3 weeks. Over half the patients had failed third-line salvage therapy including gemcitabine and epidermal growth factor receptor (EGFR) inhibitors. Of 41 patients evaluable for response at interim analysis, 21 (51%) achieved disease stabilization. Median survival exceeded 10 months and had not been reached at time of reporting (41). In another phase II study in a similar population, weekly doses of canfosfamide of 960 mg/m^2 were administered to 22 patients. Of 12 patients evaluable for response at interim analysis, the disease stabilization rate was 58%, including 1 patient with a robust partial response by RECIST criteria (42). Canfosfamide was well tolerated in both studies, with infrequent grade 3

adverse events and no cumulative toxicity. Nausea and vomiting were well controlled with antiemetics.

In a dose-ranging phase I/II study, patients with platinum-resistant NSCLC received canfosfamide 500, 750 or 960 mg/m^2 with docetaxel 75 mg/m^2 every 3 weeks. Thirty patients were available for interim analysis. Of 24 patients evaluable for response at the highest dose of canfosfamide, 6 had a partial response and 11 had stable disease. The combination was well tolerated in this setting, with adverse events consistent with those expected for docetaxel regimens (43).

Canfosfamide was administered as third-line therapy at a dose of 960 mg/m^2 weekly in a phase II study in patients with advanced metastatic breast cancer. All patients had failed prior chemotherapeutic regimens and the majority had also failed anthracyclines and taxanes. At interim analysis, 21 of 35 patients were evaluable for response. The disease stabilization rate was 48%, including 1 patient with a robust partial response. This patient had tumor reduction of > 90% and was progression-free beyond 8 months. Adverse events were comparable to those observed in other phase II studies (44).

Phase III trials with canfosfamide have been initiated. In 2003, the multinational ASSIST-1 (ASsessment of Survival in Solid Tumors-1) study was initiated in patients with ovarian cancer who had failed previous platinum-based chemotherapy and 1 second-line treatment. The trial will evaluate the efficacy of canfosfamide in improving survival compared with a control group receiving liposomal doxorubicin or topotecan. In the first quarter of 2004, ASSIST-2 was initiated. The trial is expected to enroll up to 520 patients with locally advanced or metastatic NSCLC. Patients are randomized to receive either canfosfamide or gefitinib, the current third-line treatment for the disease. Both indications have received FDA fast track designation (45-47).

Source

Telik, Inc. (US).

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