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DARINAPARSIN

Rec INN; USAN

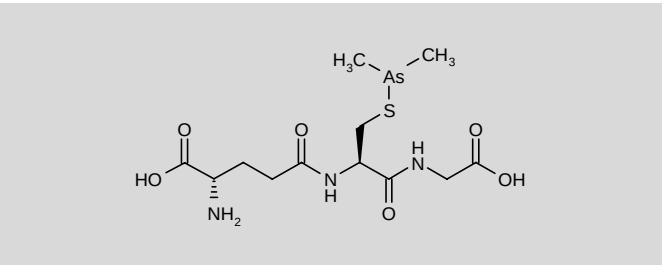
Organic Arsenical
Apoptosis Inducer
Oncolytic

DMS(III)G
SGLU1
ZIO-101
Zinapar™

L-γ-Glutamyl-*S*-(dimethylarsino)-L-cysteinyl-glycine

S-(Dimethylarsino)glutathione

InChI=1/C12H22AsN3O6S/c1-13(2)23-6-8(11(20)15-5-10(18)19)16-9(17)4-3-7(14)12(21)22/h7-8H,3-6,14H2,1-2H3,(H,15,20)(H,16,17)(H,18,19)-(H,21,22)/t7-,8-/m0/s1



$C_{12}H_{22}AsN_3O_6S$
Mol wt: 411.306
CAS: 69819-86-9
EN: 354374

ABSTRACT

Darinaparsin is a novel organic arsenic molecule synthesized by conjugating dimethylarsenic to glutathione. Its mechanism of action involves targeted disruption of mitochondrial function, modified signal transduction and inhibition of angiogenesis, leading to cell cycle arrest and apoptosis. Darinaparsin is active against several hematological and solid cancers both in vitro and in vivo. Data suggest that this organic arsenical induces apoptosis by mechanisms different than arsenic trioxide and can kill arsenic trioxide-resistant cells. Darinaparsin is less toxic than arsenic trioxide in human cells, and animal studies showed that darinaparsin can be given at doses 5- to 10-fold higher than the inorganic compound without damaging the heart. Other dose-limiting toxicities of inorganic arsenicals such as damage to the liver, bone marrow and skin are less prominent with darinaparsin. Clinical studies in cancer patients have demonstrated that darinaparsin is safe at doses with anticancer activity. This drug is currently in phase II clinical trials in patients with advanced multiple myeloma, hematological malignancies and solid tumors, and preliminary data from these studies have shown promising results.

SYNTHESIS

Darinaparsin can be obtained by reaction of glutathione (I) under nitrogen atmosphere with either dimethylchloroarsine (II) in the presence of pyridine in dimethoxyethane (1, 2) or water/ethanol (3), or with dimethylarsinic acid (III) in water (4). Scheme 1.

BACKGROUND

Arsenicals are potent anticancer agents limited in use due to their severe toxicity at high doses. Inorganic arsenicals such as arsenic trioxide (As_2O_3) are active in several leukemias and As_2O_3 is a proven effective salvage treatment for patients with acute promyelocytic leukemia (5). Arsenic trioxide deregulates numerous proteins through binding to sulfhydryl groups, inhibits mitochondrial respiratory function, induces the production of reactive oxygen species (ROS) and triggers apoptosis in several cancer cell lines. However, it has not been possible to extend the use of As_2O_3 to other cancers due to its reduced anticancer effects at clinically achievable doses (5, 6). Organic arsenicals, in contrast, are substantially less toxic (6). Recent interest has focused on arsenic biotransformation products, specifically on methylated intermediates, some of which have proven to be more potent growth inhibitors and apoptosis inducers than inorganic arsenicals. As_2O_3 is methylated in the liver to mono- and dimethylated metabolites, which are potent cytotoxins, genotoxins and enzyme inhibitors and may contribute to the in vivo therapeutic effect of inorganic arsenicals (7).

Darinaparsin is a novel organic arsenical synthesized by conjugating dimethylarsenic to glutathione (8). Phase I clinical studies have shown darinaparsin to be safe when administered at doses associated with anticancer activity. The compound is in phase II clinical trials for the treatment of advanced multiple myeloma, hematological malignancies and solid tumors.

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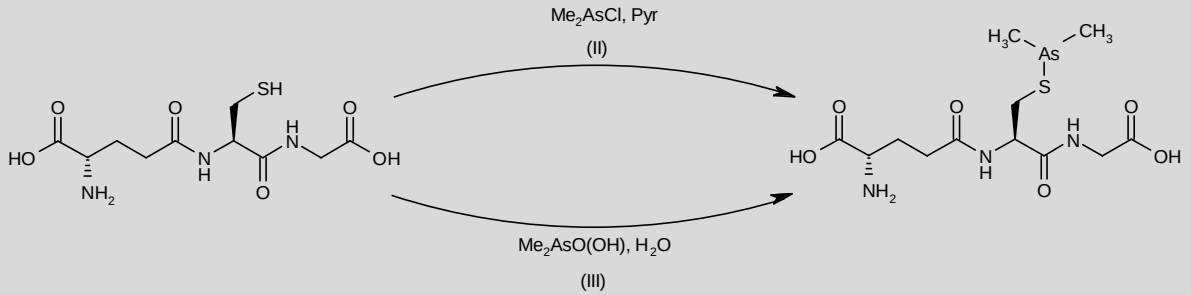
Scheme 1. Synthesis of Darinaparsin



PRECLINICAL PHARMACOLOGY

Darinaparsin is active against various cancers in experimental models while showing an LD_{50} about 50-fold higher than As_2O_3. Darinaparsin is 5- to 10-fold more efficient in entering cancer cells than As_2O_3 and more specifically affects the proapoptotic signaling pathway than does As_2O_3. These features result in greater damage to mitochondria and greater cell killing with darinaparsin than with As_2O_3 (8).

Darinaparsin induced apoptosis in multiple myeloma cell lines with different sensitivities to As_2O_3 (RPMI 8226, U266, KMS11 and MM.1s). Sensitivity to the two compounds was different, since the cells most resistant to arsenic trioxide (RPMI 8226) were highly sensitive to darinaparsin (9). Several in vitro investigations based on ROS formation and genetic pattern expression demonstrated that darinaparsin did not induce protective pathways in these myeloma cell lines in culture, nor did it initiate the apoptotic cascade by inducing oxidative stress, while arsenic trioxide did. These differences in the mechanism of action suggest that darinaparsin could be active in cancer cells resistant to arsenic trioxide (10, 11). In vitro studies in leukemia (NB4) and lymphoma (U-937) cell lines also showed that darinaparsin and As_2O_3 induced apoptosis by different mechanisms, further supporting the notion that darinaparsin may be active in cancer cells resistant to arsenic trioxide (12).

The in vivo activity of darinaparsin in multiple myeloma was first demonstrated in two SCID-hu mouse models of human myeloma. SCID mice were implanted with fragments of either human melphalan- or bortezomib-resistant tumors. These models were used to explore different doses and schedules of darinaparsin, demonstrating the activity of the drug in multiple myeloma at doses of 100-200 mg/kg i.v. once or twice daily 1, 3 or 5 days/week (13).

Darinaparsin is highly active in vitro against certain leukemia cells that are resistant to As_2O_3. Its superior antitumor activity was found to be due to more potent induction of oxidative stress and apoptosis. Activity also correlated with substantially greater accumulation of arsenic in darinaparsin-treated leukemia cells than those treated with inorganic arsenic, possibly because inorganic arsenic is more efficiently exported by drug resistance proteins. The study also demonstrated that darinaparsin triggers apoptosis by inducing signaling pathways that do not completely overlap with As_2O_3. Whereas both darinaparsin and As_2O_3 act via the Jun kinase (JNK) pathway, darinaparsin did not act via mechanisms normally associated with As_2O_3's therapeutic activity, including the degradation of the promyelocytic leukemia/retinoic acid receptor (PML-RAR) oncoprotein and rearrangement of PML nuclear bodies (14).

Angiogenesis plays a critical role in tumor growth and metastasis. The antiangiogenic effects of darinaparsin have been demonstrated both in vitro and in vivo. Darinaparsin inhibited the growth and proliferation of human umbilical vein endothelial cells (HUVEC) in culture (IC_{50} = 0.1-0.3 μM), as well as the formation of capillary-like microtubule structures by these cells in vitro. In vivo, the drug markedly reduced new blood vessel formation in the mouse matrigel plug model commonly used to measure neovascularization (15).

PHARMACOKINETICS AND METABOLISM

Arsenic is an element with particular affinity for sulfur, and the organic forms of the element interfere with cellular metabolism by chemical reaction with sulfhydryl groups of enzymes and other proteins (4). Arsenic is metabolized by living systems using oxidation–reduction and methylation reactions. Dimethylarsinic acid and its derivatives are easily reduced by thiols such as glutathione to give the organosulfur derivatives of arsenic (4, 16). In humans and animal models arsenic is enzymatically methylated in the liver, and it is believed that the methylation of inorganic arsenicals results in a reduction in general toxicity, facilitating their conjugation with glutathione, which is required for biliary excretion of arsenic (17). However, several studies suggest that methylation of inorganic arsenic activates it to more reactive and toxic forms (18-20).

Pharmacokinetic studies with oral darinaparsin in animal models showed that the molecule is orally bioavailable (15), but phase I and II clinical studies in cancer patients have used i.v. darinaparsin.

Combined data from three phase I studies in patients with advanced cancer using i.v. darinaparsin at 214 mg/m^2/day showed a t_{max} of 1 h, a C_{max} of 685 μg/mL, a $t_{1/2}$ of 13.9 h and an $AUC_{0-\infty}$ of 14.9 μg.h/mL (21-24). In multiple myeloma patients darinaparsin at 420 mg/m^2/day showed a t_{max} of 1 h, a C_{max} of 1.06 μg/mL, a $t_{1/2}$ of 17.8 h and an $AUC_{0-\infty}$ of 25.9 μg.h/mL (25). Studies using lower doses showed corresponding parameters (26).

SAFETY

Darinaparsin is toxic to rat liver cells in culture due to its conversion to dimethylarsenic and glutathione. However, this toxicity may not be seen in humans, since the presence of glutathione or physiological concentrations of human serum, human albumin and human red blood cells in the culture reduced both the cytotoxicity and cellular arsenic uptake induced by exposure to darinaparsin (27).

Darinaparsin proved to be well tolerated and safe at doses resulting in blood levels associated with substantial anticancer activity. Adverse effects seen with darinaparsin include hyperglycemia, decreases in albumin, calcium, potassium or phosphate, febrile neutropenia and rash (21-24, 26, 28-30). No significant renal, liver, bone marrow or cardiac toxicity was observed (26).

The estimated maximum tolerated dose (MTD) in phase I studies was 420-500 mg/m^2/day and the dose-limiting toxicities were transient and reversible confusion and ataxia (23). The starting dose for these studies was 78 mg/m^2/day i.v. for 5 days every month, with 20-40% dose increases. Therapy at the MTD was safe and fatigue was the only major toxicity, occurring in 25% of patients. Darinaparsin did not induce Q-T_c prolongation or other limiting toxicities seen with inorganic arsenic (23, 29).

Preliminary results from a phase II clinical study in patients with advanced hematological malignancies where darinaparsin was administered i.v. for 5 consecutive days every 28 days showed that the drug was well tolerated, although grade 3 toxicities were seen in some patients. Major toxicities were infection, respiratory failure, pain, fever and chills, anemia, decrease in oxygen saturation, elevated ferritin, blood transfusion reaction and falls. No significant hepatic or cardiac toxicities were reported (31). Similar results were reported from an ongoing phase II study in heavily pretreated patients with advanced lymphoma (32).

CLINICAL STUDIES

Results from phase I studies in patients with advanced solid tumors showed clinical benefit in approximately 30% of the patients treated with darinaparsin, including patients with acute myelogenous leukemia, multiple myeloma and solid tumors such as colorectal, kidney, head and neck, and pancreatic cancer (23, 25, 26, 28). In these studies, some patients failing As_2O_3 responded to darinaparsin (26, 28).

Preliminary data from phase II studies in patients with leukemias and lymphomas have shown promising results. In one study in 18 patients treated with darinaparsin i.v. for 5 days every 28 days, 1 unconfirmed complete response and 2 cases of stable disease were reported (31). In another study in 13 heavily pretreated evaluable patients treated with 300 mg/m^2 i.v. for 5 days every 28 days, 1 had a complete response, 3 had partial responses and 2 had stable disease (32).

Darinaparsin is currently in phase I/II clinical trials for the treatment of hematological cancers, solid tumors, lymphoma and multiple myeloma (33-39).

SOURCE

Ziopharm Oncology (US).

REFERENCES

1. Zingaro, R.A., Freireich, E.L., Sotelo-Lerma, M., Kantarjian, H., Verstovsek, S., Dukale, H. (University of Texas System; Texas A&M University). *S-Dimethylarsino-thiosuccinic acid S-dimethylarsino-2-thiobenzoic acid S-(dimethylarsino)glutathione as treatments for cancer.* CA 2472633, EP 1474128, JP 2005527487, US 2004034095, US 6911471, WO 2003057012.
2. Zingaro, R.A., Duzkale, H., Freireich, E.J., Kantarjian, H., Sotelo-Lerma, M., Verstovsek, S., Gao, M. (Texas A&M University; University of Texas System). *Compounds and methods for treatment of cancer.* EP 1771459, JP 2008506710, WO 2006020048.
3. Gutsch, P., Renzelmann, B. (Ziopharm Oncology, Inc.). *Compounds and methods for the treatment of cancer*. CA 2617049, EP 1919564, JP 2009502971, US 2007183972, WO 2007027344.
4. Cullen, W.R., McBride, B.C., Reglinski, J. *The reaction of methylarsenicals with thiols: Some biological implications*. J Inorg Biochem 1984, 21(3): 179-94.
5. Douer, D., Tallman, M.S. *Arsenic trioxide: New clinical experience with an old medication in hematologic malignancies*. J Clin Oncol 2005, 23(10): 2396-410.
6. Verstovsek, S., Giles, F., Quintás-Cardama, A. et al. *Arsenic derivatives in hematologic malignancies: A role beyond acute promyelocytic leukemia?* Hematol Oncol 2006, 24(4): 181-8.
7. Chen, G.Q., Zhou, L., Styblo, M. et al. *Methylated metabolites of arsenic trioxide are more potent than arsenic trioxide as apoptotic but not differentiation inducers in leukemia and lymphoma cells.* Cancer Res 2003, 63(8): 1853-9.
8. Camacho, L.H., Verstovsek, S., Gutierrez, C. et al. *A novel organic arsenic molecule: ZIO-101 (S-dimethylarsino-glutathione): Molecular biology and results of a phase-1 study in solid cancers*. 17th AACR-NCI-EORTC Int Conf Mol Targets Cancer Ther (Nov 14-18, Philadelphia) 2005, Abst C90.
9. Boise, L.H., Morales, A.A., Gutman, D., Lee, K.P. *In vitro activity of a novel organic arsenical (S-dimethylarsino-glutathione, ZIO-101) against multiple myeloma*. Blood [47th Annu Meet Am Soc Hematol (Dec 10-13, Atlanta) 2005] 2005, 106(11): Abst 5163.
10. Boise, L.H., Morales, A.A., Croutch, C.R., Gutman, D., Gale, R.P., Lee, K.P. *S-Dimethylarsinoglutathione (SGLU/ZIO101) is a novel active organic arsenical that displays a unique gene expression profile in myeloma cells.* Blood [48th Annu Meet Am Soc Hematol (Dec 9-12, Orlando) 2006] 2006, 108(11): Abst 5043.
11. Boise, L.H., Morales, A.A., Croutch, C.R., Gutman, D., Gale, R.P., Lee, K.P. *S-Dimethylarsinogluthathine (ZIO-101): A novel organic arsenic with a unique gene expression profile in myeloma* Proc Am Assoc Cancer Res (AACR) 2007, 48: Abst 4827.
12. Manshouri, T., Freireich, E., Zingaro, R., Gale, R., Andreff, M., Kantarjian, H., Verstovesk, S. *Organic and inorganic arsenics operate by different biochemical pathways to induce apoptosis in cancer cells.* Eur J Cancer Suppl [18th EORTC-NCI-AACR Symp Mol Targets Cancer Ther (Nov 7-10, Prague) 2006] 2006, 4(12): Abst 438.
13. Campbell, R.A., Sanchez, E., Chen, H. et al. *ZIO-101, a novel organic arsenic, inhibits human myeloma cell growth in a SCID-hu model.* Blood [48th Annu Meet Am Soc Hematol (Dec 9-12, Orlando) 2006] 2006, 108(11): Abst 3462.
14. Diaz, Z., Mann, K.K., Marcoux, S., Kourelis, M., Colombo, M., Komarnitsky, P.B., Miller, W.H. Jr. *A novel arsenical has antitumor activity toward As2O3-resistant and MRP1/ABCC1-overexpressing cell lines*. Leukemia 2008, 22(10): 1853-63.

15. Komarnitsky, P.B., Qu, Z., Schwartz, B., Wallner, B. *ZIO-101 an oral multi-targeted anti-cancer drug with anti-angiogenic activity*. Proc Am Assoc Cancer Res (AACR) 2007, 48: Abst 4000.

16. Scott, N., Hatlelid, K.M., MacKenzie, N.E., Carter, D.E. *Reactions of arsenic(III) and arsenic(V) species with glutathione.* Chem Res Toxicol 1993, 6(1): 102-6.

17. Kala, S.V., Neely, M.W., Kala, G. et al. *The MRP2/cMOAT transporter and arsenic-glutathione complex formation are required for biliary excretion of arsenic*. J Biol Chem 2000, 275(43): 33404-8.

18. Styblo, M., Serves, S.V., Cullen, W.R., Thomas, D.J. *Comparative inhibition of yeast glutathione reductase by arsenicals and arsenothiols.* Chem Res Toxicol 1997, 10(1): 27-33.

19. Lin, S., Cullen, W.R., Thomas, D.J. *Methylarsenicals and arsinothiols are potent inhibitors of mouse liver thioredoxin reductase*. Chem Res Toxicol 1999, 12(10): 924-30.

20. Vega, L., Styblo, M., Patterson, R., Cullen, W., Wang, C., Germolec, D. *Differential effects of trivalent and pentavalent arsenicals on cell proliferation and cytokine secretion in normal human epidermal keratinocytes*. Toxicol Appl Pharmacol 2001, 172(3): 225-32.

21. Camacho, L.H., Hong, D.S., Verstovsek, S. et al. *Phase-1 trial of ZIO-101, a novel organic arsenic in advanced cancer.* Ann Oncol [31st Eur Soc Med Oncol (ESMO) Congr (Sept 29-Oct 3, Istanbul) 2006] 2006, 17(Suppl. 9): Abst 413P.

22. Camacho, L.H., Hong, D.S., Gutierrez, C. et al. *Phase-1 trial of ZIO-101, a novel organic arsenic in patients with advanced cancers.* J Clin Oncol [42nd Annu Meet Am Soc Clin Oncol (ASCO) (June 3-6, Atlanta) 2006] 2006, 24(18, Suppl.): Abst 13041.

23. Camacho, L., Kornblau, S., Berenson, J., Kurzrock, R., Gale, R. *ZIO-101: A new organic arsenic in advanced cancers*. Eur J Cancer Suppl [18th EORTC-NCI-AACR Symp Mol Targets Cancer Ther (Nov 7-10, Prague) 2006] 2006, 4(12): Abst 479.

24. Camacho, L.H., Hong, D.S., Gutierrez, C. et al. *Organic arsenic in patients (pts) with advanced solid tumors: Phase 1 results of ZIO-101 (s-dimethylarsino-glutathione).* J Clin Oncol [43rd Annu Meet Am Soc Clin Oncol (ASCO) (June 1-5, Chicago) 2007] 2007, 25(18, Suppl.): Abst 3554.

25. Hussein, M.A., Belch, A., Boccia, R.V. et al. *Use of a novel organic arsenic (ZIO-101) after autotransplants for multiple myeloma*. Annu Meet Am Soc Blood Marrow Transplant (ASBMT) (Feb 8-12, Keystone) 2007, Abst 146.

26. Kornblau, S.M., Jackson, C.E., Worthing, J.A. et al. *A phase 1 trial of a novel organic arsenic S-dimethylarsino-glutathione (ZIO-101) in hematological malignancies*. J Clin Oncol [42nd Annu Meet Am Soc Clin Oncol (ASCO) (June 3-6, Atlanta) 2006] 2006, 24(18, Suppl.): Abst 16503.

27. Sakurai, T., Kojima, C., Kobayashi, Y., Hirano, S., Sakurai, M.H., Waalkes, M.P., Himeno, S. *Toxicity of a trivalent organic arsenic compound, dimethylarsinous glutathione in a rat liver cell line (TRL 1215)*. Br J Pharmacol 2006, 149(7): 888-97.

28. Berenson, J.R., Boccia, R.V.V., Hussein, M.A. et al. *Phase-1 study of ZIO-101: A new organic arsenic active in acute myelogenous leukemia (AML) and multiple myeloma (MM).* Blood [48th Annu Meet Am Soc Hematol (Dec 9-12, Orlando) 2006] 2006, 108(11): Abst 1966.

29. Berenson, J.R., Jaganath, S., Reece, D. et al. *ZIO-101 (S-dimethylarsino-glutathione): Phase I/II trials in advanced/progressive multiple myeloma.* J Clin Oncol [43rd Annu Meet Am Soc Clin Oncol (ASCO) (June 1-5, Chicago) 2007] 2007, 25(18, Suppl.): Abst 8109.

30. Boccia, R., Kornblau, S., Schwartz, B. et al. *A novel organic arsenic S-dimethylarsino-glutathione (ZIO-101) experience in hematological malignancies*. Eur J Cancer Suppl [14th Eur Cancer Conf (ECCO) (Sept 23-27, Barcelona) 2007] 2007, 5(4): Abst 6016.

31. Craig, M., Tallman, M., Boccia, R. et al. *Phase II trial of darinaparsin (ZIO-101) in leukemias and lymphomas.* Proc Am Assoc Cancer Res (AACR) 2008, 49: Abst 5527.

32. Craig, M., Shah, S., Tallman, M. et al. *A phase II trial of darinaparsin in advanced lymphomas: Report on safety and activity.* Blood [50th Annu Meet Am Soc Hematol (Dec 6-9, San Francisco) 2008] 2008, 112(11): Abst 1562.

33. *Phase II study of ZIO-101 in advanced blood and bone marrow cancers (SGL2003) (NCT00421213)*. ClinicalTrials.gov Web site, February 6, 2009.

34. *A phase II trial of ZIO-101 in advanced multiple myeloma: Protocol SGL2001b (SGL2001b) (NCT00423644)*. ClinicalTrials.gov Web site, February 6, 2009.

35. *A phase I trial of ZIO-101 in hematological cancers (NCT00592046)*. ClinicalTrials.gov Web site, February 6, 2009.

36. *Phase I study of oral ZIO-101-C in advanced solid tumors and lymphomas (NCT00592163)*. ClinicalTrials.gov Web site, February 6, 2009.

37. *A phase I trial of ZIO-101 in solid tumors (NCT00591396)*. ClinicalTrials.gov Web site, February 6, 2009.

38. *Phase I study of oral ZIO-101 in advanced solid tumors (NCT00591422)*. ClinicalTrials.gov Web site, February 6, 2009.

39. *Study of ZIO-101 in multiple myeloma (NCT00303199)*. ClinicalTrials.gov Web site, February 6, 2009.