Healthcare Provider Resource

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Patterson Institute for

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General information

Proper Name
Dichloroacetate, Dichloroacetic acid

Common Name
DCA

Routes of Administration
Oral, Intravenous (IV)

Common Uses in Cancer Care
DCA has been prescribed to reduce tumour size, stabilize the disease, improve survival, and reduce cancer related symptoms. DCA is an experimental treatment.

Summary

Dichloroacetate (DCA) is an investigational drug for cancer. DCA acts primarily on cancer cell metabolism; it is thought to convert metabolism from fermentative glycolysis back to oxidative phosphorylation by inhibiting pyruvate dehydrogenase kinase. This process may induce cancer cell apoptosis through several mechanisms including increased oxidative stress and reduced lactate levels. DCA can be administered orally or intravenously. Typical doses range from 10-50mg/kg daily, with the most common oral dosing being 6.25-12.5mg/kg taken twice daily. One randomized controlled trial, five single-arm clinical trials, and several case reports have evaluated the effect of DCA in cancer. Outcomes in these studies have been mixed. Although most studies have found DCA to be safe and reasonably well tolerated, one study and a couple of case reports have raised some safety concerns. DCA should be administered under the guidance of a qualified healthcare professional with appropriate monitoring. The most common side effect is reversible peripheral neuropathy. There is some clinical trial evidence of disease stability with the use of DCA and a few encouraging case reports, but overall, there is insufficient evidence to clearly support thng o

diabetes, hypercholesterolemia, certain heart conditions, and cancer (6).

Pharmacokinetics

DCA is a small water soluble molecule of 150 Da, allowing it to achieve 100% bioavailability when given either orally or intravenously (6). When given orally, DCA is readily absorbed in the gastrointestinal tract and less than 1% of the total given dose is excreted in the urine (5, 8, 9). Metabolism of DCA occurs in the liver and follows a simple one compartment pharmacokinetic model (5, 6, 9, 10).

By relying heavily upon cytoplasmic aerobic glycolysis for energy, cancer cells are able to avoid the production of reactive oxygen species (ROS) via mitochondrial oxidative phosphorylation (20, 23, 24). DCA triggers the remodeling of mitochondrial metabolism, opening transition pores and increasing the levels of pro-apoptotic ROS through the activation of caspases (20, 21, 23). High levels of ROS (such as H_2O_2) can inhibit tumour growth and result in apoptosis (7).

Release of mitochondrial calcium

The lack of mitochondrial oxidative phosphorylation in cancer cells facilitates an increase in intracellular calcium (Ca++), resulting in an increase of proliferative transcription factors (25). Increased intracellular Ca++ is responsible for activating ornithine decarboxylase, the rate limiting enzyme in DNA synthesis, as well as the antiapoptotic nuclear factor of activated T lymphocytes (6, 25, 26). DCA causes a decrease in intracellular

dose-limiting toxicity (DLT) from oral DCA after 4 weeks of use. DCA was given orally at an initial dose of 8.0 mg/kg every 12 h which was modified according to tolerance or glutathione transferase zeta 1/maleylacetoacetate isomerase (GSTZ1/MAAI) genotype status (which has been found to affect DCA metabolism). The intention of the trial was to use a dose escalation protocol; however no patients did in fact escalate their dose. Eight patients completed 4-weeks of DCA. They remained clinically and radiologically stable and were on DCA for an average duration of 75.5 days (range 26–312). At the time of publication, three patients were alive, and five had died. No DLTs were identified, and adverse events were either grade 1 or 2 and included fatigue, gait abnormalities, hypersomnolence, and sensory peripheral neuropathy. The authors reported that DCA was safe, well tolerated, and feasible at the dose used.

One case report of a man with GBM treated with IV DCA and artesunate raised safety concerns following liver and bone marrow toxicity (40). After disease progression following surgery and radio-chemotherapy, the 52-year old man received IV DCA (unknown dose) and artesunate (2.5mg/kg). Hepatic and bone marrow toxicities occurred a few days after infusion. The patient received supportive treatment at hospital; however, his condition deteriorated, and he died ten days after receiving the combined treatment. The Roussel Uclaf Causality Assessment Method (RUCAM) scoring system revealed reasonable probability that the combination of DCA and ART induced liver injury.

Other cancer types

The only randomized, placebo-controlled, double-blind study of DCA was reviewed as a pre-print from personal communication, and is awaiting full publication (41). The study enrolled 50 patients with stages III - IVB head and neck cancer (HNC) who were scheduled for concurrent chemotherapy (cisplatin) and radiotherapy (CRT

DCA is metabolized in the liver; therefore caution is required when administering DCA in cases of compromised liver function or with hepatotoxic drugs. DCA has been shown to cause a reversible elevation in liver enzymes, and all patients undergoing DCA therapy drugs

References

1. Tataranni T, Piccoli C. Dichloroacetate (DCA) and Cancer: An Overview towards Clinical Applications. Oxid Med Cell Longev. 2019;2019:8201079.
2. Warburg O. On the origin of cancer cells. Science. 1956;123(3191):309-14.
3. Gatenby RA, Gillies RJ. Why do cancers have high aerobic glycolysis? Nature reviews Cancer. 2004;4(11):891-9.
4. Dhar S, Lippard SJ. Mitaplatin, a potent fusion of cisplatin and the orphan drug dichloroacetate. Proceedings of the National Academy of Sciences of the United States of America. 2009;106(52):22199-204.
5. Stacpoole PW, Henderson GN, Yan Z, James MO. Clinical pharmacology and toxicology of dichloroacetate. Environmental health perspectives. 1998;106 Suppl 4:989-94.
6. Michelakis ED, Webster L, Mackey JR. Dichloroacetate (DCA) as a potential metabolic-targeting therapy for cancer. British journal of cancer. 2008;99(7):989-94.
7. Bonnet S, Archer SL, Allalunis-Turner J, Haromy A, Beaulieu C, Thompson R, et al. A mitochondria-K+ channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. Cancer cell. 2007;11(1):37-51.
8. Curry SH, Lorenz A, Henderson GN, Mars DR, Stacpoole PW. Haemodialysis studies with dichloroacetate. European journal of clinical pharmacology. 1991;40(6):613-7.
9. Stacpoole PW, Henderson GN, Yan Z, Cornett R, James MO. Pharmacokinetics, metabolism and toxicology of dichloroacetate. Drug metabolism reviews. 1998;30(3):499-539.
10. Stacpoole PW. The pharmacology of dichloroacetate. Metabolism: clinical and experimental. 1989;38(11):1124-44.
11. Tian DD, Bennett SK, Coupland LA, Forwood K, Lwin Y, Pooryousef N, et al. GSTZ1 genotypes correlate

21. Semenza GL. HIF-1: upstream and downstream of cancer metabolism. Current opinion in genetics & development. 2010;20(1):51-6.
22. Cao W, Yacoub S, Shiverick KT, Namiki K, Sakai Y, Porvasnik S, et al. Dichloroacetate (DCA) sensitizes both wild-type and over expressing Bcl-2 prostate cancer cells in vitro to radiation. The Prostate. 2008;68(11):1223-31.
23. Ayyanathan K, Kesaraju S, Dawson-Scully K, Weissbach H. Combination of sulindac and dichloroacetate kills cancer cells via oxidative damage. PloS one. 2012;7(7):e39949.
24. Kluza J, Corazao-Rozas P, Touil Y, Jendoubi M, Maire C, Guerreschi P, et al. Inactivation of the HIF-1alpha/PDK3 signaling axis drives melanoma toward mitochondrial oxidative metabolism and potentiates the therapeutic activity of pro-oxidants. Cancer research. 2012;72(19):5035-47.
25. Flavin DF. Non-Hodgkin's Lymphoma Reversal with Dichloroacetate. Journal of oncology. 2010;2010.
26. Wong JY, Huggins GS, Debidda M, Munshi NC, De Vivo I. Dichloroacetate induces apoptosis in endometrial cancer cells. Gynecologic oncology. 2008;109(3):394-402.
27. Vella S, Conti M, Tasso R, Cancedda R, Pagano A. Dichloroacetate inhibits neuroblastoma growth by specifically acting against malignant undifferentiated cells. International journal of cancer Journal international du cancer. 2012;130(7):1484-93.
28. Madhok BM, Yeluri S, Perry SL, Hughes TA, Jayne DG. Dichloroacetate induces apoptosis and cell-cycle

Official journal of the European Photochemistry Association and the European Society for Photobiology. 2011;10(1):25-8.
65. Zwicker F, Kirsner A, Peschke P, Roeder F, Debus J, Huber PE, et al. Dichloroacetate induces tumor-specific radiosensitivity in vitro but attenuates radiation-induced tumor growth delay in vivo. Strahlenther Onkol. 2013;189(8):684-92.
66. Rajendran A, Bansal D, Marwaha RK, Singhi SC. Tumor lysis syndrome. Indian journal of pediatrics. 2013;80(1):50-4.