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Dichloroacetate (DCA)

Proper Name
Dichloroacetate sodium, Dichloro Acetic acid

Common Name
DCA

Background Information
In the 1920s, a German physiologist and Nobel Prize laureate, Otto Heinrich Warburg, made an important discovery regarding the energy metabolism of cancer cells. Unlike normal cells that obtain 95% of their energy requirements via oxidative respiration, cancer cells rely heavily on glucose in a process known as anaerobic glycolysis (1). This phenomenon, identified as the "Warburg effect", led Warburg to propose that cancer may be a result of mitochondrial malfunction.

The process of glycolysis generates large amounts of lactic acid, which helps break down the extra-cellular matrix and further potentiates tumour growth and metastases by activating angiogenesis and increasing cell mobility (2). Inactivating the mitochondria also gives cancer cells the unique ability to avoid apoptosis and the various pathways that would customarily signal abnormal cells to undergo apoptosis (3). While unproven and controversial, dichloracetate (DCA) may be able to impact the metabolism of cancer cells, shifting them away from anaerobic glycolysis towards a more normalized process of aerobic oxidative energy production thereby purportedly leading to more selective cancer cell destruction via apoptosis.

Warburg's unique discovery surrounding cancer cells opened the door for further investigation into the use of drugs that act upon the metabolism of cells. Many medications that have been used for metabolic purposes are now being studied for their anticancer properties. DCA is a by-product of water chlorination that has been used as an investigational drug in medicine for over 30 years (4). DCA has been researched in adults, children, animals, and cells as a monotherapy as well as in combination with other therapies for the treatment of severe metabolic disorders including diabetes and hypercholesterolemia, lactic acidosis, certain heart conditions, and cancer (5).

Common Uses in Cancer Care
DCA has been prescribed to reduce tumour size and tumour markers, prevent angiogenesis, reduce cancer related symptoms, manage pain, and aid in palliation.

Routes of Administration
Oral, Intravenous (IV)

Pharmacokinetics

DCA is a small molecule of 150 Da, allowing it to achieve 100% bioavailability when given either orally or intravenously (5). 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 (4, 6, 7). Metabolism of DCA occurs in the liver and follows a simple one compartment model (4, 5, 7, 8).

It has been shown that DCA inhibits its own metabolism resulting in slower clearance from the body after multiple doses, which increases the potential for toxic effects (9, 10). Although the half-life with the initial dose is less than one hour, this half-life increases to several hours with successive doses. There appears to be a plateau of this effect and DCA serum levels do not continue to rise with ongoing use (11-13).

Mechanism of Action

While DCA has been studied extensively over the last 30 years for its medicinal use in metabolic disorders, the mechanism of action in cancer treatment has only recently begun to be understood. Additional research is still required to fully understand the cellular actions of DCA against cancer.

In normal cells, oxidative phosphorylation in the mitochondria generates 30 ATP molecules and results in the production of reactive oxygen species. Cancer cells favor cytoplasmic anaerobic glycolysis, a series of chemical reactions resulting in the conversion from glucose to lactate and the generation of 2 ATP molecules (14). DCA has direct and metabolic responses, targeting the unique metabolism of cancer cells.

Reversal of Cancer Cell Metabolism

DCA acts on the mitochondrial matrix of cancer cells, diverting metabolism from fermentative glycolysis back to oxidative phosphorylation (13, 14). DCA does this by activating the pyruvate dehydrogenase complex, inhibiting pyruvate dehydrogenase kinase. The shift from cytosolic metabolism of pyruvate to mitochondrial metabolism effectively reduces lactate levels by promoting the conversion of lactate into pyruvate (14, 15).

Decreased Mitochondrial Membrane Potential

DCA administration results in the reopening of voltage and redox sensitive mitochondrial transition pores (16). This allows for the pro-apoptotic mediators, *cytochrome c* and *apoptosis-inducing-factor,* to be released into the cytoplasm, resulting in an apoptotic cascade selective to cancer cells which were previously operating under anaerobic glycolysis (3).

ROS Production

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 (14, 17, 18). DCA triggers the remodeling of mitochondrial metabolism, opening transition pores and increasing the levels of pro-apoptotic ROS through the activation of caspases (14, 15, 17). High levels of ROS (such as H_2O_2) can inhibit tumour growth and result in apoptosis (13).

Release of Mitochondrial Calcium

The hibernation of mitochondrial metabolism in cancer cells facilitates an increase in intracellular calcium (Ca++), resulting in an increase of proliferative transcription factors (19). 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 (5, 19, 20). DCA causes a decrease in intracellular calcium, potentiating apoptosis in cancer cells and inhibiting proliferation (19, 20).

Mitochondrial K_+ Channel Axis

Cancer cells exhibit down regulation of the potassium (K+) channel Kv1.5 by decreasing the tonic efflux of K+ down its intracellular/extracellular gradient (13). K+ exerts a tonic inhibitory effect on caspases, and K+ channel inhibition suppresses apoptosis in cancer cells. DCA activates mitochondrial Kv channels in cancer cells, promoting apoptosis.

Clinical Evidence related to Effectiveness

In 2006, a Canadian researcher from the University of Alberta, Dr. Evangelos Michelakis, began using DCA to attempt a reverse in the way that cancer cells derive their energy from glucose under hypoxic conditions back to an oxidative pathway. In doing so, he hoped to restore the mitochondria to normal functioning within cancer cells, thereby resuming their ability to trigger apoptosis (5). Michelakis and his research team hoped that DCA would selectively target cancer cells without affecting healthy cells. In his initial research using rats, after just 3 weeks of receiving DCA, cancer progression was stopped and tumours shrank by 70% (13). Since this research was conducted, there have been a number of preclinical studies done including case studies and two small human trials. Although the work to date is mostly preclinical and does look promising, further human studies are needed.

Brain Cancer

DCA was initially studied in human glioblastoma cancer cell lines and shown to promote apoptosis and inhibit further cancer growth (13). Another study found that DCA was able to reverse mitochondrial hyperpolarization in 49 human glioblastoma cell lines without affecting the polarization of normal brain tissue (21). In one of the only published human studies, DCA was given to five patients with a primary diagnosis of glioblastoma. In this small uncontrolled clinical study, two of the patients were also treated with standard therapy and three were considered palliative. After 15 months of DCA therapy, three of the five patients demonstrated regression of their glioblastoma on MRI and a fourth was considered clinically stable (5, 13). At 18 months after starting treatment with DCA, four of the patients were still living and had no evidence of hematologic, hepatic, renal or cardiac toxicity from this therapy.

In a study looking at mice infected with human neuroblastoma tumours, treatment with DCA was shown to inhibit tumour growth in malignant, undifferentiated cells while having no effect on healthy cells (22).

Colon Cancer

Three preclinical studies assessing the use of DCA on colorectal cancer cells have been published with mixed results. In the first study, colorectal cancer cells and noncancerous cells were treated with DCA. The cancerous cells exhibited a dose-dependent inhibition of growth, with cell cycle arrest and apoptosis while the noncancerous cells were unaffected by the DCA (23). In a second study, colorectal cancer cells were treated with DCA alongside 5-Fluorouracil (5-FU), a first line chemotherapeutic agent used in colorectal cancer (24). The results demonstrated a synergistic, anti-proliferative effect on colorectal cells, resulting in apoptosis and cell cycle arrest. Based on these results, the authors suggested that this treatment combination may enhance the efficacy of current treatment options by potentiating the effects of certain anticancer drugs (24).

A third study examined the effects of hypoxia on apoptosis in human colorectal cancer cells (CRC) both in vivo and in vitro (25). Although DCA did cause significant apoptosis under normoxia in these cancerous cells, apoptosis was diminished under hypoxic conditions and there was increased growth of tumour xenografts in hypoxic regions of the tumours. Therefore, these results suggest that DCA may be cytoprotective for some CRC cells under hypoxic conditions, and further investigation is needed.

Breast Cancer

Breast cancer cell lines have been treated with DCA both in vitro and in vivo. The anti-proliferative and pro-apoptotic effects of DCA were observed with cancer cell growth inhibition in vitro and a 58% reduction of lung metastases in vivo (26). In a second study done on breast cancer cell lines, DCA was used in combination with arsenic trioxide, a drug typically used in the treatment of promyeloid leukemia (27). The results of this combination showed that the synergistic effect of the drugs had greater efficacy in inhibition of cell proliferation and apoptosis than either agent used alone.

Prostate Cancer

In the only study examining the use of DCA on human prostate cancer cell lines, DCA administration resulted in high rates of cytotoxicity, was associated with G1 cell cycle arrest, and produced increased rates of apoptosis (16). The researchers also studied the use of DCA with radiation, as localized prostate cancer is known to have high rates of recurrence after irradiation alone due to the low doses that have to be given in this sensitive area. This study was the first of its kind to investigate the use of DCA as a sensitizer to radiation in prostate cancer, and showed promising results warranting further investigation of DCA as a radiation sensitizer (16).

Gynecologic Cancers

Epithelial ovarian cancer cells are under increased oxidative stress, altering their metabolic activity and resulting in decreased rates of apoptosis (28). In one study, human epithelial ovarian cancer cells treated with DCA alone exhibited increased rates of apoptosis. Another study on endometrial cancer cell lines similarly demonstrated the ability of DCA to induce apoptosis without having any effect on non-cancerous cell lines (20). In a more recent study, it was found that a multifunctional hybrid platinum prodrug consisting of cisplatin, a common chemotherapy drug, combined with DCA

resulted in greater cytotoxicity in human ovarian cancer than when given alone (29). In a similar study looking at the use of DCA against cervical cancer HeLa cells, DCA was administered on its own and then in combination with cisplatin (30). The study showed that treatment with DCA alone resulted in cellular apoptosis and when given in tandem with cisplatin, there was synergism that inhibited cancer cell growth (30).

Lung Cancer

A recent study examined the efficacy of using DCA in combination with platinum based chemotherapeutic agents, as an apoptotic sensitizer for lung carcinoid cell lines (31). In vitro, the carcinoid cell lines were sensitive to the majority of chemotherapies, following treatment with DCA. In the most highly chemoresistant lung carcinoid cell lines, DCA was able to sensitize the cells to some of the platinum based agents (31).

Blood Based Cancers

The nature of blood based cancers makes them a more difficult target for treatment. A recent novel study formulated a DCA-hemoglobin conjugate to facilitate the entry of DCA into cancerous monocytic cells. The results demonstrated that the combination of these agents allowed for uptake into the cells where the DCA was able to activate the mitochondria, depolarizing the mitochondrial membrane potential and resulting in apoptosis, suggesting this as a possible treatment for monocytic leukemia (32). Recently, a case report was published regarding a patient with non-Hodgkin's lymphoma who relapsed after treatment with the popular chemotherapy regimen of rituximab-CHOP(33). This patient then underwent a rigorous treatment cycle with DCA, alpha lipoic acid, and B vitamins and achieved complete remission of his cancer as evidenced by PET scans, CT scans, and laboratory testing (33). Four years later, the patient remained cancer free.

Renal

In one study investigating the use of DCA for the treatment of renal cell carcinoma, two human kidney cell lines were treated with DCA (34). DCA was shown to reverse the mitochondrial remodeling of the RCC cells, decreasing proliferation and angiogenesis and increasing apoptosis (34). A case report was also recently published outlining the complete long-term remission of a patient with metastatic renal squamous cell carcinoma (35). After completing palliative radiation, this patient began a cyclical regimen of oral DCA for three months' time. Follow up imaging revealed no evidence of the disease and the patient remains cancer free five years after initially achieving remission following treatment with DCA (35).

Thyroid Cancer

In one case report, a 51 year old male with a diagnosis of medullary thyroid carcinoma that metastasized to the lungs achieved partial remission for seven years following treatment with numerous chemotherapies (36). However, his cancer eventually returned and resulted in the generation of numerous tumors throughout his central body. The patient was then started on DCA therapy, and had a positive reaction as evidenced by a reduction in his tumor marker, calcitonin, and a dramatic reduction in all tumors on his PET scan. At the time of publishing, the patient remained in remission and was continuing with DCA treatment (36).

Pain Management

In another case report, a 71 year old male with poorly differentiated metastatic carcinoma began using DCA in a palliative setting (37). After 5 months of treatment with DCA, the patient had improved quality of life through reduction of his leg pain and was able to stop using all pain medication (37). In one study, 18 pancreatic and biliary tract cancer patients were treated with a combination of DCA and Omeprazole and exhibited markedly reduced pain or had prevention of pain within one week (38). This combination also reduced massive ascites in 50% of the patients without adjuvant chemotherapy.

Multiple Cell Lines

In one study, noncancerous cells and six cancer cell lines from various cancer types were exposed to DCA at increasing concentrations (39). High levels of cell death were observed in five of the cancerous cell lines initially; however, three of the lines had subsequent delayed cell death at later stages. One cell line, HCT116, was completely unaffected by DCA at the lower concentration. Two of the noncancerous cell lines also died when treated with DCA, and at the highest concentrations, all cell lines showed high rates of death (39). This study was the first of its kind to find that noncancerous cells are not entirely resistant to DCA.

Adverse Events and Side Effects

In the majority of patients, DCA is well tolerated. Side effects are mild but can include fatigue, confusion, memory loss, sedation, tremors, hallucination, agitation, depression, heartburn (oral), and nausea (oral). Known adverse effects from therapeutic use include minor liver enzyme elevation, transient central neuropathy, peripheral neuropathy and hypocalcemia, all of which are reversible upon discontinuation of treatment (9, 42).

In studies of adults with MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes), ongoing administration of oral DCA at 25 mg/kg/day for 6 months resulted in a reversible peripheral neuropathy (42, 43). However, administration of the same dose to children with congenital lactic acidosis produced no evidence of neuropathy after prolonged treatment (38).

Interactions with other Therapies

POSITIVE INTERACTIONS

Multiple preclinical studies have been published using DCA in combination with other standard therapies including chemotherapeutics, radiotherapy, and phototherapy (44). Combining cisplatin with DCA creates a multifunctional pro-drug, mitaplatin; this combination results in greater cytotoxicity on cell lines from human testicular cancer, human cervical cancer, human osteosarcoma, human lung carcinoma, human breast adenocarcinoma, and human ovarian cancer (3, 29). Elesclomol, a pro-oxidative drug currently in development for the treatment of melanomas, was combined with DCA leading to a better result than from either single agent alone (18). DCA also has a synergistic antitumour effect with 5-fluorouracil on colorectal cancer cells in vitro (24).

DCA has also been shown to sensitize chemoresistant lung cancer cell lines to carboplatin and oxoplatin (31). DCA markedly sensitised sorafenib-resistant liver cancer cells to sorafenib-induced apoptosis and resulted in superior tumour regression than sorafenib alone (45) .Targeting gene-virotherapy in combination with DCA has also been studied as an efficient strategy in cancer treatment (29). Finally, it has also been shown that DCA is able to sensitize cancer cells to improve the efficacy of phototherapy and radiation (16,46).

NEGATIVE INTERACTIONS

There has been limited research published on the interactions between DCA and other therapies. In one study evaluating the use of DCA alongside three standard anticancer drugs, pediatric tumour lines were tested with the various combinations. The results of this study showed that DCA reduced the cytotoxicity of both cisplatin and doxorubicin but did not affect the cytotoxicity of temozolomide (47). In another study, researchers found that DCA increased the cytotoxicity of carboplatin, satraplatin, JM118, and oxoplatin in vitro, but not cisplatin, picoplatin, and oxaliplatin (48). Due to the limited research available on combination treatment with DCA, each case requires individual evaluation to determine the overall risks and benefits of proceeding with combination treatment.

<u>Cautions and Contraindications</u>

DCA has been used therapeutically in both children and adults over many years and is shown to be safe even in doses much higher than those used in cancer treatment (8,43). No studies have been conducted on the use of DCA during pregnancy or in lactation; therefore pregnant and lactating women are advised to avoid therapy with DCA due to the unknown effects. Reliable birth control should be used while undergoing therapy with DCA.

DCA is metabolized in the liver; therefore caution is required when administering DCA in cases of compromised liver function. DCA has been shown to cause a reversible elevation in liver enzymes, and all patients undergoing DCA therapy will require close monitoring of these values prior to initiating treatment and at frequent intervals during treatment (7). DCA has been shown to cause liver cancer in mice given drinking water mixed with DCA (49). The dose at which this occurred was 100x that used for cancer treatment and there has been no research duplicated in humans.

Generally, DCA is well tolerated and there are limited side effects reported in most patients. The main dose-dependent side effect noted in patients is a reversible peripheral neuropathy. This is especially common in patients with MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) given oral doses daily for a prolonged period of time (42). The incidence of neuropathy is best avoided with intravenous treatment alongside alpha lipoic acid (ALA) or in oral doses given in a cyclical manner, also alongside ALA (42, 43). DCA induced delirium has been observed, and is also reversible upon discontinuation of the drug (41). It is recommended that DCA be avoided in patients also undergoing treatment with cannabinoids, benzodiazepines, or any other medications with potential neurological effects.

In a phase I trial of oral DCA for adults with recurrent brain tumors, it was found that carriers of the wildtype (EGT) allele have a more rapid plasma clearance of DCA than those who are not EGT carriers (50). In this trial, one patient whose genotype was EGM had markedly higher plasma levels of DCA than other patients and subsequently experienced worsening peripheral neuropathy resulting in his removal from the trial. These findings suggest the importance of knowledge of genotypes prior to assigning oral dose regimens for DCA therapy.

Because of the possible accentuation of chemotherapies when administered in tandem with DCA, there may be an increased risk of tumour lysis syndrome (TLS). TLS is most common in individuals being treated for leukemia and lymphoma or in cases of rapid tumour cell death as is commonly seen with bulky tumours (51). Close monitoring is required to monitor for symptoms of TLS such as chills, sweating, fever, bleeding at the site of tumours, sodium imbalances, heart arrhythmias, and renal damage.

Dosing, frequency and length of treatment

Patients are typically started at a lower dose and slowly increased until benefit is observed or adverse effects become apparent. Doses are based upon weight, and optimal therapeutic dosing is typically achieved at a range of 50 mg/kg to 80 mg/kg. In order to avoid adverse effects such as peripheral neuropathy, intravenous DCA is administered twice weekly and oral DCA is given in a cyclical nature with two weeks of administration being followed by a week-long break from treatment.

Patients at the OICC are typically started at a dose of 20mg/kg intravenously and slowly titrated up to a therapeutic dose of between 50 mg/kg and 80 mg/kg. Intravenous DCA is given up to two times a week and doses are increased at each administration. All intravenous doses of DCA are immediately followed by intravenous alpha lipoic acid as well as intravenous B complex administration.

At the OICC, oral DCA is started at 15 mg/kg daily, taken in divided doses for fourteen days. This is followed by a seven day break from DCA. Oral alpha lipoic acid and a B-vitamin complex containing bentofiamine (vitamin B1) should also be taken alongside the oral DCA. Doses of oral DCA are increased after each three week “cycle” as long as no adverse effects are observed.

All patients undergoing treatment with DCA require close monitoring of blood lab values as well as completion of a self-reported scale to monitor for adverse side effects such as peripheral neuropathy. As DCA is an off-label prescription drug, patients are required to be seen by the OICC physician for consideration of this therapy and to sign a consent form prior to the initiation of DCA therapy.

Disclaimer

The OICC has prepared this monograph, as part of a series of monographs being developed to share results of a review of the research evidence related to common therapies and products used within cancer patient care. The monograph is designed to summarize evidence-based research and does

not advocate for or against the use of a particular therapy. Every effort is made to ensure the information included in this monograph is accurate at the time it is published. Please note that this monograph does not include an exhaustive list of all potential adverse events; individuals may experience unique side effects. The information in this monograph should not be interpreted as medical advice nor should it replace the advice of a licensed health care provider. Prior to using a new therapy or product, always consult a licensed health care provider.

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