Dichloroacetate- Phase 1 Trial in Adults with Malignant Brain Tumors

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Abstract
Dichloroacetate (DCA) has been used for many years as an investigational drug to treat children born with mitochondrial disorders. Through its inhibition of Pyruvate Dehydrogenase Kinase (PDK), a key component of the pyruvate dehydrogenase complex, DCA has shown promise in facilitating oxidative phosphorylation in cell mitochondria. Recently, DCA has received more attention as a possible treatment for numerous forms of cancer. In this research highlight, we will discuss a paper from Dunbar *et al.* in which a Phase 1 trial for DCA was run in adults with recurrent malignant brain tumors (RMBTs). These tumors often carry a poor prognosis. As DCA has the ability to pass through the blood-brain barrier, it is being investigated as a possible treatment for RMBTs. The goal of the trial was to establish dose ranges that are safe to administer to patients with recurrent malignant gliomas.

Keywords: dichloroacetate, malignant glioma, pyruvate dehydrogenase complex, pyruvate dehydrogenase kinase, phase 1 trial, Warburg effect

Introduction

In a recent issue of *Investigational New Drugs,* Dunbar *et al.* utilize the fact that recurrent malignant brain tumors (RMBTs) share a common biochemical pathobiology. Anaerobic glycolysis becomes the primary metabolic process in RMBT cells through what is known as the Warburg effect. A mitochondrial enzyme, pyruvate dehydrogenase kinase (PDK), is responsible for inhibiting the catalytic activity of the pyruvate dehydrogenase complex (PDC). When aerobic glycolysis increases, it induces stable upregulation of hypoxia inducible factor-1alpha (HIF-1α). This results in an increase in PDK.

By inhibiting PDK, DCA allows PDC to remain in its active form, thus facilitating mitochondrial oxidation via the tricarboxylic (TCA) acid cycle (Figure 1). As a result of this, DCA activates the PDC which reverses the Warburg effect, initiating changes in the tumor cell metabolism.

This change in metabolism has been proven to lead to decreased angiogenesis and increased apoptotic cell death. Dosing was decided upon using previous DCA standards obtained from studies on its effect on infant mitochondrial disease. These studies indicated that an enzyme known as Glutathione Transferase Z1 (GSTZ1) was responsible for the metabolism of DCA. Thus, DCA dosage was determined by analyzing the GSTZ1 enzyme in each patient and then administering the appropriate dosage according to the variations in the enzyme that each patient presented with.

Authors' Results

The researchers set out to complete a phase 1 trial in adults with RMBT. The primary goal of this trial was to determine drug safety and tolerability in relation to the GSTZ1 genotype. The researchers attempted to find if DCA had a dose-limiting toxicity (DLT) in patients. The secondary goal was to determine how effective DCA was in combating recurrent malignant brain tumors. The trial was conducted as an open-label, non-randomized trial and patients selected included those with malignant RMBTs that had failed first-line therapy as well as those with stage IV metastases. The initial dose was 8.0 mg/kg/12 h. This dose was either increased to

12.50 mg/kg/12 h or decreased to 5.00 mg/kg/12 h according to dose tolerance. It was found that individuals who have at least one wild type haplotype for GSTZ1 metabolize DCA more quickly than those who do not have this haplotype. The wild type haplotype of GSTZ1 is known as GSTZ1c.

In order to quantify DCA metabolism, a Pyruvate Breath Test (PVT) was used. This new method involved the injection of radiolabeled pyruvate into the body.

This pyruvate is used during normal cellular respiration, and CO_2 derived from it was then measured. This radiolabeled $^{13}CO_2$ that was released during respiration was measured in order to estimate PDC activity in vivo.

In total, fifteen patients were enrolled in the study, with one remaining in the study at the time the paper was submitted. Two of the patients had metastatic disease and 13 had progressive malignant gliomas. All of the patients had previously undergone various types of treatment including: surgery, radiation and chemotherapy. Three patients dropped out of the study for non-study related reasons. Eight patients had radiographically stable disease after the fourth week on DCA. This shows promise that DCA is a possible cancer treating agent. Furthermore, no patient was withdrawn from the study due to toxicity related to DCA. While sensory and motor peripheral neuropathy was reported as a side effect attributed to DCA, this was completely reversible after discontinuation of treatment.

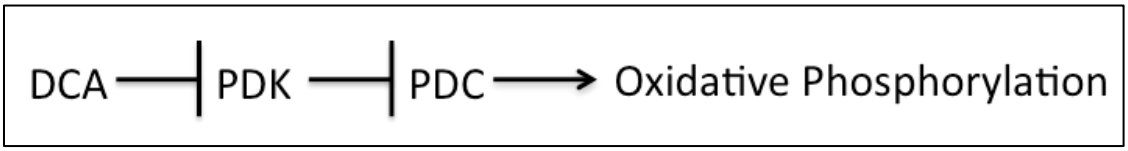

Figure 1. Scheme of DCA's effect on oxidative phosphorylation

Conclusions

According to this study, DCA was proven to be safe and well tolerated in adults with RMBTs. Furthermore, while the phase I trial cannot provide definitive answers on its effectiveness, DCA therapy was able to stabilize the disease in 8 patients over a 4-week period. It is clear that DCA shows great promise as a possible cancer-fighting agent, and hopefully more studies will confirm those findings.

References

1. Dunbar EM, Coats BS, Shroads AL, Langaee T, Lew A, Forder JR, Shuster JJ, Wagner DA, Stacpoole PW, et al. (2014) Phase 1 trial of dichloroacetate (DCA) in adults with recurrent malignant brain tumors. Invest New Drugs 32(3): 452-64.

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