Long-term stabilization of metastatic melanoma with sodium dichloroacetate

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Abstract

Sodium dichloroacetate (DCA) has been studied as a metabolic cancer therapy since 2007, based on a publication from Bonnet et al demonstrating that DCA can induce apoptosis (programmed cell death) in human breast, lung and brain cancer cells. Classically, the response of cancer to a medical therapy in human research is measured by Response Evaluation Criteria in Solid Tumours definitions, which define "response" by the degree of tumour reduction, or tumour disappearance on imaging, however disease stabilization is also a beneficial clinical outcome. It has been shown that DCA can function as a cytostatic agent in vitro and in vivo, without causing apoptosis. A case of a 32-year-old male is presented in which DCA therapy, with no concurrent conventional therapy, resulted in regression and stabilization of recurrent metastatic melanoma for over 4 years' duration, with trivial side effects. This case demonstrates that DCA can be used to reduce disease volume and maintain long-term stability in patients with advanced melanoma.

Key words: Dichloroacetate; Cancer; BRAF; Melanoma; Cytostatic

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tumours on imaging. However, DCA can also halt cancer cell growth without causing apoptosis (cytostatic effect). This can result in long-term stabilization of metastatic cancer. We present a case of oral DCA therapy resulting in reduction and stabilization of metastatic melanoma in a 32-year-old male for over 4 years, with only minor side effects.

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INTRODUCTION

Sodium dichloroacetate (DCA) caught the attention of the medical community in 2007, when Bonnet et al. published the first in vitro and in vivo study illustrating the value of DCA as a metabolic cancer therapy, through its inhibitory action on the mitochondrial enzyme pyruvate dehydrogenase kinase. Previously, Stacpoole et al. had published several studies of DCA for the treatment of congenital lactic acidosis in mitochondrial diseases. These studies demonstrated that oral DCA is a safe drug for human use. DCA was noted to have an absence of renal, pulmonary, bone marrow and cardiac toxicity. Most DCA side effects were modest, with the most serious one being reversible peripheral neuropathy. Reversible delirium has also been reported. Elevation of liver enzymes (asymptomatic and reversible) has been noted in a small percentage of patients. The prior human research in mitochondrial disorders has enabled the rapid translation of DCA into human use as an off-label cancer therapy. Several reports of clinical trials using DCA as cancer therapy have now been published, confirming its safety profile, and indicating an increasing recognition of the potential of cases. The neuropathy risk when natural neuroprotective medicines were combined with DCA was approximately 20% using 20-25 mg/kg per day dosing on a 2 wk on/1 wk off cycle (clinical observational data published online at www.medicorcancer.com). Here, a patient case report illustrating both the apoptotic and anti-proliferative effects of chronic DCA treatment over a period of over four years is presented.

CASE REPORT

A 32 years old previously healthy fair-skinned male originally noted that a mole on his left calf began to change in 2006. He consulted a doctor and the mole was excised. A pathologic diagnosis of melanoma was made. A sentinel node dissection was carried out, and was negative for metastatic disease. In 2007, the patient noted enlargement of left inguinal lymph nodes, and small melanocytic lesions on the skin of his left leg. He was treated with interferon alpha under a clinical trial at a regional cancer hospital, with reduction of the nodes and resolution of the skin metastases. Interferon was stopped after 9 mo due to side effects.

The patient remained well until 2010, when a new left leg skin metastasis appeared. This was surgically excised. A recurrence within the left leg skin graft. This was biopsied and a diagnosis of recurrent melanoma was confirmed. He was then treated with wide excision and skin graft.

In March 2012, the patient was diagnosed with a recurrence within the left leg skin graft. This was excised and a new skin graft procedure was performed. Pathology revealed positive margins of the excised
metastasis, so a re-excision was performed, again with positive margins. At the same time, needle biopsy of a left inguinal lymph node confirmed the presence of BRAF-positive metastatic melanoma. A Computed tomography (CT) scan performed in Mar 2012 revealed no evidence of distant metastases. The largest left inguinal node was 8mm in diameter, which was reported as “insignificant by size criteria” (Figure 1).

In April 2012, the patient consulted a naturopathic doctor (Shainhouse) and began therapy with the following oral natural anti-cancer agents: Active hexose correlated compound or AHCC (mushroom extract)

, dandelion root

dand, curcumin
curcuma

, and astragalus root


. Parenteral therapy was also started, which consisted of intravenous vitamin C twice weekly

and subcutaneous European mistletoe extract

. The patient also changed to a vegan diet.

In May 2012, the patient attended the author’s clinic (Khan) looking to pursue additional non-traditional therapies. DCA therapy was discussed, but the patient decided to give the natural anti-cancer therapies (prescribed by Shainhouse) an adequate trial first. CT scan was performed again in May 2012 (after only 1 mo of natural therapy) and indicated mild growth of multiple inguinal and external iliac nodes, with sizes ranging from 10 mm × 11 mm to 14 mm × 15 mm.

In July 2012, CT scan was repeated to assess the patient’s natural anti-cancer therapies. At that time, the left inguinal and external iliac nodes had enlarged again, and ranged in size from 13 mm × 16 mm to 22 mm × 20 mm (Figure 2). PET scan was also performed in preparation for entering a clinical trial in Boston, MA (United States), and confirmed increased glucose uptake in the left inguinal nodes. There was new low intensity (2/10) aching pain in the left inguinal region. Examination revealed a 20 mm non-tender left inguinal lymph node, and two small skin metastases within the left calf skin graft.

The patient was thus diagnosed with disease progression. At that point he decided to initiate DCA therapy. He began oral DCA 500 mg 3 times per day, which was equivalent to 17 mg/kg per day (manufacturer: Tokyo Chemical Industry, United States) in addition to maintaining the other natural therapies. The DCA treatment cycle was 2 wk on and 1 wk off. To minimize the occurrence of DCA side effects, 3 additional natural medications were prescribed: Oral acetyl L-carnitine 500 mg 3 times a day, oral benfotiamine 80 mg twice a day and oral R-alpha lipoid acid 150 mg 3 times a day. These supplements were taken daily (no cycle). Routine baseline blood tests were performed (Table 1). These were all normal, except for low creatinine which was felt to be insignificant.

In November 2012, 4 mo after the addition of DCA to his original natural anti-cancer therapies, the patient was re-assessed. He felt generally well. Two new symptoms were reported to have begun only after initiation of DCA therapy: Slightly reduced sensation of the finger tips and toes, and slightly reduced ability to concentrate during the 2 wk periods in which he was taking DCA. The mild sensory loss was not worsening and was felt to be mild DCA-related neuropathy. Both the numbness and reduced concentration were reported to resolve during the weeks when the patient was off DCA. Blood panel from October 2012 showed no significant changes (Table 1). August 2012 and November 2012 CT scans revealed significant regression of all previously enlarged lymph nodes. The largest node was 10 mm, and there was no evidence of intra-thoracic or intra-abdominal disease, and no bone metastases (Figure 3).

The patient continued to feel well on DCA therapy, and did not notice any new skin metastases or new enlargement of inguinal nodes. He continued to have frequent clinical monitoring with his naturopathic doctor (Shainhouse), and annual follow-up with his medical doctor (Khan). The listed natural anti-cancer therapies (prescribed by Shainhouse) and DCA therapy were maintained into 2016. Blood panel results in June 2016 continued to be normal (Table 1). CT scan was repeated in August 2016, showing no evidence of metastatic melanoma, after a full 4 years of ongoing DCA therapy, combined with natural anti-cancer therapy (Figure 4). By December 2016, the patient reported an increase in work-related stress and a reduction in compliance.
with his medications. At the time, he noted a new left inguinal mass. Ultrasound imaging was obtained, which revealed a new conglomerate of enlarged lymph nodes measuring 40 mm × 25 mm × 23 mm, with colour Doppler showing blood flow within the mass. This was interpreted as re-growth of melanoma, after approximately four and a half years of continuous DCA therapy. Further workup was performed including a PET/CT scan, which confirmed disease recurrence in 3 left inguinal nodes (SUV \(_{\text{max}}\) ranging from 13 to 17.8).

In summary, the patient received conventional therapy for recurrent stage 3 melanoma over a period of 6 years, consisting of primary surgical excision with lymph node dissection, interferon alpha and surgical excisions for recurrent cutaneous metastases on 5 occasions. The patient then received natural anti-cancer therapy alone (prescribed by Shainhouse) for 3 mo with no response, evidenced by steady disease progression on serial CT scans. Finally the patient added oral DCA therapy to the natural anti-cancer therapy, with 3 concurrent neuroprotective medicines (lipoic acid, acetyl L-carnitine and benfotiamine) and no concurrent conventional cancer therapies. The result was a complete radiological remission lasting for over 4 years, followed by recurrence. During the course of DCA therapy, the patient experienced trivial side effects consisting of slight neuropathy and slight reduction of concentration. The patient maintained ECOG level 0 function, and he was able to work full time.

DISCUSSION

The use of oral DCA in the metastatic melanoma patient described herein demonstrates tumour shrinkage and long-term disease stability according to clinical status and CT imaging. Disease stability was maintained for over 4 years while taking DCA in the absence of any concurrent conventional therapy, with a survival time since the initial diagnosis of 10 years. According to the National Cancer Institute’s SEER cancer statistics, the survival of this patient who showed no evidence of distant metastases is

| Blood test | July 12 pre-DCA | October 12 3 mo DCA | June 16 4 yr DCA | Units | Normal range |
|------------|----------------|-------------------|----------------|-------|-------------|
| Hemoglobin | 154 g/L        | 150 g/L           | 157 g/L        | g/L   | 135-175     |
| White cell count | 4.5 × 10⁹/L | 4.1 × 10⁹/L | 5 × 10⁹/L | × 10⁹/L | 4.0-11.0 |
| Platelets | 220 × 10⁹/L | 214 × 10⁹/L | 229 × 10⁹/L | × 10⁹/L | 150-400 |
| Glucose | - | 4.6 mmol/L | 4.9 mmol/L | mmol/L | 3.6-7.7 |
| Urea | 3.9 mmol/L | 3.2 mmol/L | 3.9 mmol/L | mmol/L | 2.5-8.0 |
| Creatinine | 49 µmol/L | 50¹ µmol/L | 55³ µmol/L | µmol/L | 62-115 |
| Calcium | 2.47 mmol/L | 2.41 mmol/L | 2.47 mmol/L | mmol/L | 2.15-2.60 |
| Albumin | 48 g/L | 45 g/L | 47 g/L | g/L | 35-50 |
| Bilirubin | 8 µmol/L | 10 µmol/L | 13 µmol/L | µmol/L | < 22 |
| Sodium | 139 mmol/L | 141 mmol/L | 140 mmol/L | mmol/L | 135-147 |
| Potassium | 4.3 mmol/L | 3.9 mmol/L | 3.9 mmol/L | mmol/L | 3.5-5.5 |
| Chloride | 106 mmol/L | 107 mmol/L | 105 mmol/L | mmol/L | 100-110 |
| Alkaline Phosphatase | 77 U/L | 69 U/L | 71 U/L | U/L | 45-129 |
| LDH | 139 U/L | 135 U/L | 144 U/L | U/L | 120-246 |
| GGT | 18 U/L | 19 U/L | 20 U/L | U/L | 15-73 |
| AST | 18 U/L | 25 U/L | 21 U/L | U/L | 7-37 |
| ALT | 18 U/L | 28 U/L | 19 U/L | U/L | 12-49 |

¹Indicates abnormal value. DCA: Dichloroacetate; LDH: Lactate dehydrogenase; GGT: Gamma-glutamyltransferase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

Figure 3 Computed tomography scan from November 2012 after 4 mo of dichloroacetate therapy. Largest node measured 10 mm.

Figure 4 Computed tomography scan after 4 years of dichloroacetate therapy without any concurrent conventional cancer therapies. Scan demonstrates absence of cancer re-growth. All nodes measure less than 10 mm.
not remarkable (62.9% 5-year survival rate for melanoma with spread to regional lymph nodes, [https://seer.cancer.gov/statfacts/html/melan.html]). What is remarkable is that in a situation where involved lymph nodes were clearly enlarging, the addition of oral DCA therapy was efficacious in shrinking the enlarging nodes (Figures 2 and 3), and in achieving a remission lasting over 4 years. It is possible that the natural anti-cancer therapies the patient received synergized with DCA, but it is also clear that these natural therapies alone cannot account for the disease regression. DCA has been reported to have both apoptotic and cytostatic effects[14,17,19,35,36], which is consistent with this patient’s clinical course of regression (apoptotic) and prolonged remission (cytostatic). The recurrence after 4 years coincided with reduced compliance, suggesting that this method of cancer management with DCA requires the metabolic pressure to be maintained continuously. Despite recurrence, the patient remained clinically well and planned to start new immunotherapy medications. It remains to be seen if a change in therapy can once again achieve disease regression or stability.

In addition to the maintenance of remission for over 4 years, this case illustrates that DCA can be well-tolerated in a cancer patient for a prolonged time period, as compared to all published DCA cancer clinical trials. Notably, this patient was able to tolerate 17 mg/kg per day in a regime of 2 wk on/1 wk off for 4 years with minimal side effects. This is similar to our previous case report of chronic DCA usage in colon cancer[37], where the patient was able to tolerate 16 mg/kg per day (but not 25 mg/kg per day) in the same regime, but contrasts with the clinical trials for DCA, which recommend a lower dose of 10-12.5 mg/kg per day given continuously[9,11]. The 1 wk break or the neuroprotective supplements may both contribute to the ability of the patients in the case reports to tolerate the higher dose. Genetic polymorphisms in GSTZ1, the liver enzyme that metabolises DCA, may also contribute to the dose of DCA that can be tolerated[9,38]. Variable drug levels have been reported in the trials, but not all of them have considered this pharmacogenetic aspect of DCA therapy[9,11], and further studies are needed to clarify if this is a significant contributor to DCA tolerance. As of this writing, a DCA multiple myeloma human trial[39,40], and further studies are needed to clarify if this is a significant contributor to DCA tolerability.

As of this writing, a DCA multiple myeloma human trial is ongoing, which is examining both GSTZ1 genotypes and drug levels to contribute to our understanding of these issues (Australia New Zealand Clinical Trials Register #ACTRN12615000226505, [http://www.anzctr.org.au]).

This case report shows that chronic DCA therapy can be used without reducing quality of life, as compared to conventional melanoma therapies such as interferon. To determine the optimal protocol for maximum tolerable acute or chronic treatment with DCA, human trials are needed. But more importantly, it still remains to be clarified what dose is required for on-target effects that will be efficacious against cancer. This information is necessary before investing in larger, long term studies on patient outcomes. DCA deserves further investigation in clinical trials as a non-toxic cancer therapy due to its modest cost and low toxicity, and deserves consideration as an off-label cancer therapy.

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