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ABOUT COVER

Editorial Board Member of *World Journal of Clinical Oncology*, Che-Chun Su, MD, PhD, Associate Professor, Attending Doctor, Department of Internal Medicine, Changhua Christian Hospital, Changhua 500, Taiwan

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 Baishideng Publishing Group Inc
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Long-term stabilization of metastatic melanoma with sodium dichloroacetate

Akbar Khan, Doug Andrews, Jill Shainhouse, Anneke C Blackburn

Akbar Khan, Doug Andrews, Medicor Cancer Centres Inc, Toronto, ON M2N 6N4, Canada

Jill Shainhouse, Insight Naturopathic Clinic, Toronto, ON M4P 1N9, Canada

Anneke C Blackburn, the John Curtin School of Medical Research, the Australian National University, Canberra, ACT 2601, Australia

Author contributions: Khan A treated the patient and wrote most of the case report; Andrews D assisted in development of the natural medication protocol for reduction of DCA side effects, and wrote a portion of the case report; Shainhouse J treated the patient with natural therapy; Blackburn AC interpreted the case report in the context of the literature on *in vitro* and *in vivo* DCA research, wrote parts of the introduction and discussion, and reviewed the manuscript overall.

Informed consent statement: The patient described in this manuscript has given consent to publish his case anonymously.

Conflict-of-interest statement: One of the authors (Khan) administers dichloroacetate therapy for cancer patients through Medicor Cancer Centres at a cost, and without profit. The clinic is owned by a family member of this author. The other authors have nothing to disclose.

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Correspondence to: Akbar Khan, MD, Medical Director, Medicor Cancer Centres Inc, 4576 Yonge St., Suite 301, Toronto, ON M2N 6N4, Canada. akhan@medicorcancer.com
Telephone: +1-416-2270037
Fax: +1-416-2271915

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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 Criterial for 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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Core tip: Sodium dichloroacetate (DCA) has been studied as a metabolic cancer therapy since 2007. It has been shown that DCA therapy can result in a classic response which is measured by reduction or disappearance of

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.

Khan A, Andrews D, Shainhouse J, Blackburn AC. Long-term stabilization of metastatic melanoma with sodium dichloroacetate. *World J Clin Oncol* 2017; 8(4): 371-377 Available from: URL: <http://www.wjgnet.com/2218-4333/full/v8/i4/371.htm> DOI: <http://dx.doi.org/10.5306/wjco.v8.i4.371>

INTRODUCTION

Sodium dichloroacetate (DCA) caught the attention of the medical community in 2007, when Bonnet *et al*^[1] 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*^[2-4] had published several studies of DCA for the treatment of congenital lactic acidosis in mitochondrial diseases^[2-5]. 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^[4]. Most DCA side effects were modest, with the most serious one being reversible peripheral neuropathy^[6]. Reversible delirium has also been reported^[7]. Elevation of liver enzymes (asymptomatic and reversible) has been noted in a small percentage of patients^[3]. 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 usefulness of DCA in the cancer clinic^[8-11]. One limitation of these studies involving late stage patients is that they have only reported on treatment for short periods of time.

In Bonnet's 2007 publication^[1], DCA treatment was shown to reduce mitochondrial membrane potential which promoted apoptosis selectively in human cancer cells. Aerobic glycolysis inhibition (the Warburg effect) and mitochondrial potassium ion channel activation were identified as the mechanisms of action of DCA. Further investigations of DCA *in vitro* have confirmed the anti-cancer activity against a wide range of cancer types, which have been reviewed recently by Kankotia and Stacpoole^[12]. In addition, DCA is also able to enhance apoptosis when combined with other agents^[13-15]. Other anticancer actions of DCA have also been suggested, including angiogenesis inhibition^[16], alteration of HIF1- α expression^[17], alteration of cell pH

regulators V-ATPase and MCT1, and other cell survival regulators such as p53 and PUMA^[18]. However, many *in vitro* studies use unreasonably high concentrations of DCA that are not clinically achievable, in an effort to show cytotoxic activity^[12]. In other studies, more modest DCA concentrations were used, demonstrating that DCA could be cytostatic. The second report in 2010 of its *in vivo* anti-cancer activity found DCA alone to be cytostatic in a metastatic model of breast cancer^[19], inhibiting proliferation without triggering apoptosis. This suggests a role for DCA as a cancer stabilizer, similar to angiogenesis inhibitors.

In response to the 2007 report of the anti-cancer actions of DCA, Khan began using DCA for the treatment of cancer patients with short prognosis or who had stopped responding to conventional cancer therapies. A natural medication protocol was developed in collaboration with a naturopathic physician (Andrews) to address the dose-limiting neurologic toxicity of DCA. This consisted of 3 medicines: Acetyl L-carnitine^[20-22], R-alpha lipoic acid^[23-25] and benfotiamine^[26-28], for neuropathy and encephalopathy prevention. In over 300 advanced stage cancer patients, observational data revealed that DCA therapy benefitted 60%-70% 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 (clinic 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. In late 2011, another new cutaneous metastasis was identified on the left leg, within the scar from the original melanoma surgery. 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

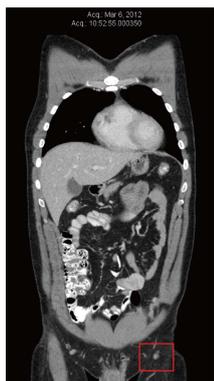


Figure 1 Computed tomography scan from March 2012 prior to natural therapies and prior to dichloroacetate therapy. Largest node measured 8 mm in diameter.

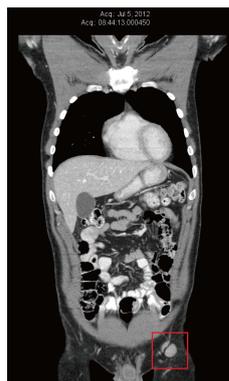


Figure 2 Computed tomography scan from July 2012 after 3 mo of natural therapy alone, just prior to the start of dichloroacetate therapy. Largest node measured 22 mm × 20 mm.

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)^[29], dandelion root^[30], curcumin^[31], and astragalus root^[32]. Parenteral therapy was also started, which consisted of intravenous vitamin C twice weekly^[33] and subcutaneous European mistletoe extract^[34]. 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 lipoic 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

Table 1 Blood panel prior to and during dichloroacetate therapy

Blood test	July 12 pre-DCA	October 12 3 mo DCA	June 16 4 yr DCA	Units	Normal range
Hemoglobin	154	150	157	g/L	135-175
White cell count	4.5	4.1	5	$\times 10^9/L$	4.0-11.0
Platelets	220	214	229	$\times 10^9/L$	150-400
Glucose	-	4.6	4.9	mmol/L	3.6-7.7
Urea	3.9	3.2	3.9	mmol/L	2.5-8.0
Creatinine	49 ¹	50 ¹	55 ¹	$\mu\text{mol/L}$	62-115
Calcium	2.47	2.41	2.47	mmol/L	2.15-2.60
Albumin	48	45	47	g/L	35-50
Bilirubin	8	10	13	$\mu\text{mol/L}$	< 22
Sodium	139	141	140	mmol/L	135-147
Potassium	4	4.3	3.9	mmol/L	3.5-5.5
Chloride	106	107	105	mmol/L	100-110
Alkaline Phosphatase	77	69	71	U/L	45-129
LDH	139	135	144	U/L	120-246
GGT	18	19	20	U/L	15-73
AST	18	25	21	U/L	7-37
ALT	18	28	19	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.

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 \times 25 mm \times 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_{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

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 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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The authors wish to thank Dr. Humaira Khan for her assistance, and also the patient for his support and consent to publish his case.

COMMENTS

Case characteristics

The 32-year-old male patient presented with a pigmented lesion on his leg.

Clinical diagnosis

The patient was diagnosed with a melanoma.

Laboratory diagnosis

Melanoma confirmed by excisional biopsy.

Imaging diagnosis

Enlarged inguinal node confirmed to be involved with melanoma (needle biopsy).

Pathological diagnosis

Melanoma, BRAF positive.

Treatment

Excision of primary lesion with skin graft, sentinel node dissection, multiple excisions of recurrent cutaneous metastases. Traditional therapy stopped and natural anti-cancer therapies started (AHCC, dandelion root, curcumin, astragalus root, *i.v.* vitamin C, *s.c.* European mistletoe). Progression after 3 mo, dichloroacetate (DCA) added. Regression and remission following addition of DCA lasting for over 4 years.

Related reports

Computed tomography scan reports demonstrate the course of the disease and response to therapies.

Term explanation

DCA: Dichloroacetate sodium; RECIST: Response Evaluation Criteria for Solid Tumours; ECOG: Eastern Cooperative Oncology Group.

Experiences and lessons

DCA can act as a pro-apoptotic and cytostatic drug, and can thus achieve regression as well as long-term stabilization of metastatic cancer without serious side effects, as illustrated by this melanoma case.

Peer-review

Dr. Khan described a 32-year-old man received DCA therapy, with other medications from natural therapists and maintained in a stabilization state (metastatic melanoma) for over 4 years. It is an interesting case.

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