

Use of Oral Dichloroacetate for Palliation of Leg Pain Arising from Metastatic Poorly Differentiated Carcinoma: A Case Report

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Abstract

Dichloroacetate sodium (DCA) is a nonproprietary drug currently used for treatment of inherited mitochondrial diseases. It was discovered in 2007 that DCA promotes human cancer cell death by a novel mechanism. Soon after this discovery, physicians began using DCA off-label for cancer treatment in a palliative setting. A case report is presented of a 71-year-old male with poorly differentiated carcinoma of unknown primary metastatic to the right leg and liver who achieved excellent palliation of leg pain by using oral DCA after failing conventional therapy.

Introduction

DICHLOROACETATE SODIUM (DCA) is a nonproprietary drug currently approved in Ontario, Canada for treatment of inherited mitochondrial diseases.¹ It was discovered in 2007 by Bonnet et al. that DCA promotes human cancer cell death by a novel mechanism of inhibition of aerobic glycolysis and apoptosis induction.² Soon after this discovery we began using DCA off-label in our cancer clinic³ for treatment of patients who had failed conventional therapies. We have observed that a significant number of such patients benefit from the use of this drug either by subjective criteria such as pain reduction or objective criteria such as tumor shrinkage.⁴ We report on a 71-year-old male with poorly differentiated carcinoma of unknown primary metastatic to the right leg and liver who achieved excellent palliation of leg pain by using oral DCA after failing conventional therapy.

Case Presentation

A 71-year-old male presented to our clinic in April 2010 requesting palliative treatment for a cancer of unknown primary with metastases to the liver and right calf after standard treatment options had been exhausted. Extensive notes were reviewed from the regional cancer hospital where he had been treated initially. They revealed a history of right calf pain dating back to 2006, but a calf mass was only discovered by magnetic resonance imaging (MRI) in April 2009. The diag-

nosis of cancer was made via biopsy in October 2009, which was reviewed by three pathologists. The final diagnosis was poorly differentiated carcinoma embedded within the fibromuscular tissue of the calf, although epithelioid sarcoma could not be excluded. Workup by several physicians failed to reveal the primary site.

The patient's case was reviewed by the tumor board at the regional cancer hospital, and the decision was made to treat him with palliative radiotherapy 66 Gy in 33 fractions. This began in November 2009 and was completed in January 2010. At the time, the patient had significant calf pain and swelling. His pain was treated by the palliative team at the regional cancer center with sustained release (SR) morphine 60 mg orally 2 times a day, gabapentin 900 mg orally 3 times a day, morphine 10 mg orally prn for breakthrough pain (patient was using 1–2 times daily), and oxycodone 5 mg orally prn.

By February 2010 (1 month post-radiotherapy), the gabapentin was discontinued and indomethacin 50 mg 3 times a day prn was added. The SR morphine was increased to 100 mg 2 times a day, and the morphine for breakthrough pain was adjusted to 25 mg hourly prn. (Immediate release morphine tablets are available in Canada in strengths of 5, 10, 20, 25, 30, 40, 50, and 60 mg.)

The patient was evaluated again in March 2010 (2 months post-radiotherapy) at which time he was re-staged with a leg MRI (Fig. 1). The right leg tumor can be clearly seen (*single arrow*). Edema of the subcutaneous tissue is also visible (*double*



FIG. 1. MRI showing right calf tumor (single arrow) and subcutaneous edema (double arrow).

arrow), and the right calf diameter is visibly larger than the left. The patient was using about 2 doses of 25-mg breakthrough morphine per day at the time. The treating oncologist presented an option for palliative chemotherapy. Due to unproven survival benefits and serious potential side effects, the patient declined chemotherapy.

The patient then elected to have a private, positron emission tomography (PET) scan to obtain additional information. The pertinent PET findings were a hypermetabolic lesion in the area of known tumor in the right calf with SUV_{max} of 4.0, and multiple new fluorodeoxyglucose (FDG)-avid liver metastases (largest lesion was 1.8 cm in maximal diameter with maximum standardized uptake value (SUV_{max}) of 3.5).

Treatment with Dichloroacetate (DCA)

The patient presented to our office in April 2010 (3 months post-radiotherapy) soon after receiving the PET scan report identifying disease progression to the liver. Review of symptoms at the time revealed low energy, constipation, restlessness, and right calf pain rated 4 to 5 out of 10 with no characteristic neuropathic component. He continued on the same pain regimen prescribed by the palliative team, except for taking indomethacin 50 mg once daily instead of 3 times daily. Breakthrough use was 1–2 morphine 25-mg tablets per day with good effect, resulting in a total morphine usage of 225–250 mg per day.

Examination revealed a generally healthy looking male with normal vital signs and a tense and edematous right calf.



FIG. 2. CT showing right calf tumor after 2 months of DCA therapy. Tumor is stable and calf edema has resolved.

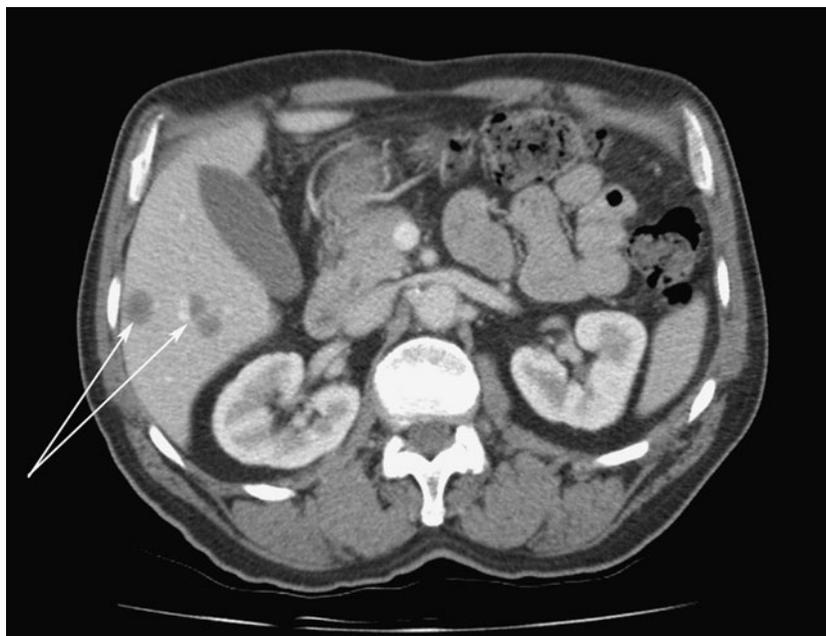


FIG. 3. CT showing multiple liver metastases.

There was mild calf tenderness and no erythema. The rest of the examination was noncontributory.

Various off-label nonchemotherapy cancer treatment options were discussed. Initial blood tests were normal except for mild anemia (hemoglobin (HB) = 131 g/L). The patient decided to try oral DCA therapy. He was started on 500 mg 3 times a day (21 mg/kg/day for a body weight of 71 kg) on a 2 week on/1 week off cycle. Three natural medicines with documented neuroprotective effects were added to help prevent DCA-induced neuropathy. These were: R+ alpha lipoic acid⁵ 150 mg orally 3 times a day, acetyl L-carnitine⁶ 500 mg orally 3 times a day, and benfotiamine⁷ (vitamin B1) 80 mg orally 2 times a day. Comprehensive weekly blood tests were ordered including complete cell counts, renal function, electrolytes, liver enzymes, and liver function.

The patient returned for follow-up after completion of 2 cycles (6 weeks) of DCA therapy. Other than new daytime sedation, he felt well. He noted the right leg was smaller, pain severity was now 0 to 1 out of 10 and only present in the morning. No breakthrough morphine doses were needed, so he had reduced the SR morphine on his own from 100 mg 2 times a day to 60 mg 2 times a day. Despite the reduction, he reported occasional myoclonus. He also reported weight loss of about 8 lb, which he found to be concerning. He started gardening and reported being more physically active. The right calf edema had decreased significantly and the calf was no longer tender to palpation.

Due to the pain reduction and symptoms of mild relative opiate overdose (sedation and myoclonus), the SR morphine was reduced to 60 mg morning and 45 mg evening. The patient was also given megestrol acetate 160 mg orally 3 times a day for appetite enhancement. He was given advice about further morphine reduction based on pain self-assessment and breakthrough usage.

By June 2010, the patient had stopped using indomethacin and breakthrough morphine. Pain was rated 0 out of 10 most

of the day, with only mild pain in the morning (present on waking and resolved after ambulating for a few minutes). He had reduced the SR morphine to 30 mg 2 times a day. His body weight had stabilized and appetite was good. The leg edema had completely resolved. Blood tests revealed a resolution of the mild anemia and no new abnormalities. A new, leg computed tomography (CT) scan showed a stable right calf tumor, reduced calf diameter, and resolution of subcutaneous edema (Fig. 2).

By July 2010 (3 months on DCA therapy), the patient's SR morphine dose was down to 30 mg total per day. Pain was rated 0 out of 10 for most of the day, and appetite was normal. Megestrol was stopped.

In August 2010, the SR morphine was brought down to 10 mg per day, and in September 2010 (5 months on DCA therapy) the patient completely stopped taking morphine. New CT scans showed mild growth of tumors in the liver (Fig. 3) and stable findings in the right leg (Fig. 4). Comprehensive blood tests remained normal.

As of November 2010, the patient had remained on DCA 500 mg orally 3 times a day, 2 weeks on/ 1week off for a total of 8 months, and had remained off opiates. He did not experience any side effects from the DCA treatment.

Summary and Conclusions

A 71-year-old male with poorly differentiated carcinoma metastatic to the right leg and liver (unknown primary) achieved an improvement in quality of life through pain reduction with DCA therapy.

Prior to DCA treatment, he was using 225–250mg/day of morphine plus indomethacin 50 mg/day. After starting DCA, the patient was able to gradually taper down his pain medications. By 5 months of DCA treatment, he was able to stop all pain medications. He experienced no adverse effects from DCA.



FIG. 4. CT after 5 months of DCA therapy showing stable right calf tumor and absence of calf edema.

Because DCA treatment was initiated 3 months after completion of radiotherapy (and the patient's leg pain was slowly increasing at that time), the reduction of pain can almost certainly be attributed to DCA. In retrospect, the 8-lb weight loss at the start of treatment was most likely related to reduction of edema fluid from the right leg, and megestrol had thus been prescribed unnecessarily.

In this case, it was demonstrated that dichloroacetate (DCA) led to a dramatic improvement in tumor pain over a period continuing beyond 8 months. The patient's leg metastasis was stable during this period, whereas there was mild growth of the liver metastases. There were no drug side effects, and no alteration in hematologic parameters.

We believe DCA should be formally studied as a palliative treatment in advanced-stage malignancies due to its favorable side effect profile⁸ and potential for quality-of-life improvements as demonstrated by this case. Even though it has now been established that DCA has activity against cancer in humans,⁹ ongoing DCA phase I/II trials have not been designed to evaluate quality-of-life parameters.¹⁰ Rather, they are focused on measurement of survival and tumor response rates by Response Evaluation Criteria for Solid Tumors (RECIST) guidelines. We believe these and future cancer trials of DCA should be expanded to include assessment of pain and other quality-of-life indicators.

Based on the judgment of the treating physician, DCA may be given consideration as an experimental alternative to palliative chemotherapy in cases where the benefits of chemotherapy are unknown, or when the advantages of chemotherapy are outweighed by the risks.

Acknowledgments

The author wishes to thank the patient, his son-in-law, and Dr. Humaira Khan for their assistance in preparation of this case report.

Author Disclosure Statement

The author prescribes cancer treatment medications (including dichloroacetate) that are provided through Medicor Cancer Centres for a cost. This clinic is owned by a family member of the author.

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