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Prolonged Survival After Dichloroacetate Treatment of Non-Small-Cell Lung Carcinoma-Related Leptomeningeal Carcinomatosis

Walter Lemmo[a, c], Gerard Tan[b]

Abstract

Here we present an observational case report of a 49-year-old female, non-smoker, having a poor performance status with non-small-cell lung cancer and leptomeningeal carcinomatosis (LMC), who upon introduction of oral dichloroacetate (DCA) survived approximately 64 weeks (454 days) following palliative whole brain radiation without the need for chemotherapy or further targeted therapy to specifically address the LMC. To our knowledge, this is the first case report incorporating the use of DCA in LMC. Our findings are discussed in the context of previously reported applications of DCA in malignancies of the central nervous system.

Keywords: Dichloroacetate; Dichloroacetic acid; Non-small-cell lung cancer; Leptomeningeal carcinomatosis

Introduction

Leptomeningeal carcinomatosis (LMC) can be a challenging comorbidity of various malignancies, in particular breast and lung cancer [1, 2]. Common treatment protocols favor chemotherapeutic approaches, including intrathecal (IT) applications [3, 4], targeted agents [5], palliative radiation [6, 7], and the use of a ventriculoperitoneal (VP) shunt to alleviate hydrocephalus complications [8-10]. There is a great need for research into new treatment modalities that are convenient, low risk, and efficacious, as the median survival continues to be only a few months for patients with advanced non-small-cell lung cancer (NSCLC).

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[a]LEMMO Integrated Cancer Care Inc., 327 Renfrew Street, Vancouver, BC V5K 5G5, Canada
[b]Gerard Tan & Associates Integrative Cancer Centre, Suite 105-2295 West Broadway, Vancouver, BC V6K 2E4, Canada
[c]Corresponding Author: Walter Lemmo, ND, FABNO, LEMMO Integrated Cancer Care Inc., 327 Renfrew Street, Vancouver, BC V5K 5G5, Canada.
Email: walter@lemmo.com

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Case Report

A 49-year-old non-smoker woman presented in May 2006 with inoperable NSCLC IIIb diffusely involving the right lung along with a right pleural effusion. Three cycles of gemcitabine and cisplatin beginning on July 26, 2006 were deemed ineffective. On September 18, 2006, she responded to talc pleurodesis. Subsequently, on October 5, second line paclitaxel was initiated but due to significant toxicity, it was replaced by nab-paclitaxel on October 26; the fourth and final doses were on January 2, 2007 due to progressive disease. She was then switched to erlotinib 100 mg/day on January 23, 2007, which continued until February 2009. Epidermal growth factor receptor (EGFR) mutational status was unknown as, at the time, this test was not subsidized by the Medical Service Plan of British Columbia, Canada. Despite stable appearing chest X-ray imaging between February 27, 2007 and December 29, 2007, and computerized tomography (CT) chest and abdomen imaging revealing no further abnormal findings as of April 28, 2008, carcinoembryonic antigen (CEA) continued to gradually rise beginning June 28, 2007 with a value of 28, to 170 on April 28, 2008. The CEA rise, in this case, appeared to correlate with underlying progressing disease.

In April 2008, the patient reported progressing symptoms of headache, neck tension, visual blurring, bilateral muscle weakness, and eventual seizure. A CT brain scan without contrast on May 6, 2008 reported unremarkable findings. Neurological consultation on July 3, 2008 revealed gross bilateral papilledema with hemorrhages and exudates and suspicions for LMC. Magnetic resonance imaging (MRI) utilization was conservative due to severe claustrophobia complaints by the patient. A brain CT with contrast on July 8, 2008 revealed a 5 mm enhancing mass projecting over the cortex of the right frontal lobe. A gadolinium (Gd)-enhanced MRI on July 9, 2008 confirmed a 5 mm enhancing mass in the right frontal lobe and evidence of LMC. By July 10, the patient continued with progressing neurological deterioration along with symptoms of vertigo, nausea and vomiting requiring an emergency room (ER) neurological evaluation and lumbar puncture where cerebrospinal fluid (CSF) cytology suggested LMC.

Palliative whole brain radiotherapy (WBR) was initiated from July 18 to July 24, 2008 with 2,000 cGy central dose given in 5 fractions by lateral opposed fields encompassing the whole brain, particularly the base of the brain and upper cervi-

cal first and second vertebrae. Unfortunately, this approach coincided with a degradation of right hearing and vision, which significantly compromised the patient's quality of life.

An emergency right VP shunt was placed on August 2, 2008 due to hydrocephalus complications and progressing symptoms. A Gd-enhanced brain MRI on August 21, 2008 revealed extensive thin rind enhancement surrounding most of the brain parenchyma supratentorially, which indicated extension of the LMC compared to MRI of July 9, 2008, along with the stable 5 mm small enhanced nodule in the right frontal lobe.

On October 1, 2008 the patient presented with declining performance status (PS), Karnofsky [11] score 20. The family reported a weight loss of approximate 13.5 kg since her last visit. No further oncological treatment was advised and end of life care was discussed.

Based on the public and media interest created by the work of Michelakis and co-workers [12], the corresponding author had begun to monitor and incorporate the off-label use of sodium dichloroacetate (DCA) in the oncological palliative care setting. DCA, in this case, was initiated as a last resort experimental treatment option, using a liquid suspension of 250 mg/mL, normally reserved for intravenous use, via the oral route. The DCA solution was prepared in a compounding pharmacy using sterile water, followed by sterile filtration. It was kept refrigerated between uses. DCA was administered in 250 mg doses twice daily, dissolved in juice or water. The dosing of DCA employed in this case factored in concerns for potential neurotoxicity, hence a more conservative dosing was selected compared to reports that utilized in previous non-oncological human data using upwards of 50 mg/kg/day [13]. Erlotinib was continued concurrently with DCA.

Within 3 - 4 days of initiating DCA, the patient's family observed significant improvement in cognition and muscle strength. Improvements continued quite dramatically, resulting in recovered appetite and weight gain of approximately 7 kg within a 4-week period. By November 4, 2008 the use of DCA was increased to 250 mg thrice daily (corresponding to approximately 14 mg/kg/day), based on the husband's own accord. Karnofsky performance was now 50.

It was observed that the use of DCA coincided with an aggravating knee pain of unknown etiology, which appeared to improve upon discontinuing DCA for 2 days. Moreover, the patient presented with unsteady gait, which was concerning, as it was uncertain if this may have been caused by the DCA therapy. As a consequence, it was decided that DCA be used in a cyclic pattern of 14 days, followed by a 14-day break. In addition, a B-vitamin complex (100 mg bid) was supplemented, as it has been reported that DCA may induce vitamin B1 (thiamine) deficiency [14, 15]. However, for practical reasons, it was decided to provide a more comprehensive B-vitamin spectrum. In addition, a very high dose vitamin B12 (methyl cobalamin, 25,000 µg) by intramuscular injection was incorporated. A follow-up brain CT scan with contrast on December 16, 2008 revealed no evidence of abnormal leptomeningeal enhancement compared to the August 1, 2008 CT scan. Moreover, it showed a reduced area of enhancement above the sylvan fissure on the right at the gray-white junction now measuring 3 mm (previously 5 mm). Diffuse white matter changes suggestive of leukoencephalopathy were also noted.

Unfortunately, the chest CT revealed interval progression in the right lung along with new nodules in the left lung. Erlotinib was discontinued in February 2009, and switched to carboplatin and pemetrexed to now address the lungs. A head CT without contrast on February 19, 2009 continued to reveal stable disease and no evidence of leptomeningeal enhancement. Following two cycles, carboplatin was stopped due to toxicity concerns and continued with single agent pemetrexed. The patient received, in total, 10 doses of pemetrexed, the last of which was eventually administered on November 6, 2009. Follow-up CT scan with contrast of the brain on April 9, 2009 revealed no new areas of abnormal enhancement. Moderate small vessel ischemic changes were seen again in the periventricular deep white matter region. The lungs continued to show subtle signs indicative of progressive disease; however, the CEA implied a trend for disease response to pemetrexed maintenance; values were 1,200 on March 23, 510 on June 15, 530 on October 7, and 490 on December 2, 2009. The patient reported continued cycled use of DCA 250 mg thrice daily in juice until April 6, 2009 with no apparent signs suggestive of neurological toxicity. A head CT scan without contrast on October 22, 2009 revealed no new intracranial masses and the ventricles appeared to have increased in size slightly since April 2009.

The follow-up with the patient at our clinic had ended at that point. We learned later that she had passed away on December 28, 2009 as a result of pneumonia complications related to the lung disease. The use of DCA was reported to have stopped several months following her last visit. In summary, the patient survived 454 days (64 weeks) following the introduction of DCA, and approximately 74 weeks after the diagnosis of LMC.

Discussion

DCA has recently been gaining further attention as a potential drug in oncology [16-21]. In the past, DCA was extensively studied for the treatment of mitochondrial diseases in both adults and children [13, 22-24]. Moreover, intravenous DCA has also been explored in patients with congestive heart failure [25-28] and pulmonary hypertension [29, 30]. Consequently, a foundation for safety data has been laid by this earlier work involving both oral and IV routes of administration. The main toxicity concern with DCA appears to be neurological in nature. Encephalopathy, peripheral neuropathy, and even a DCA-induced delirium have occasionally been observed, which appear to be reversible upon discontinuation, depending on the PS of the patient and expected survival. Peripheral, non-demyelinating neuropathy, which is dose-dependent, appears to be more common [31-39]. A mild, reversible elevation of liver enzymes is also occasionally associated with chronic DCA administration [40]. Furthermore, symptoms of fatigue, nausea, unsteady gait, and hypersomnolence have been reported [40, 41].

The interest in the application of DCA in oncology was originally introduced based on *in vitro* and animal data reported by Pan and Mak [42] and Bonnet et al [43] in 2007, which unlike more common chemotherapeutic agents, demonstrated how DCA metabolically targets the mitochondria, involving

inhibition of mitochondrial pyruvate dehydrogenase kinase, thus leading to selective cancer-cell apoptosis. As a consequence, the interest in the Warburg effect in oncology has been ignited once again [44-46]. The clinical use of DCA in oncology has slowly been gaining momentum, as demonstrated primarily by anecdotal case reports [47-50], and more recently, phase I and II trials [41, 40, 51].

To our knowledge, the first documented case report of DCA in neuro-oncology was published in 2010. It involved five glioblastoma patients, who demonstrated evidence of tumor regression in three of four patients initially treated with surgery, radiation, temozolomide and 15 months of DCA. In the three responsive patients, tissue samples before and after DCA administration, all demonstrated decreased cell proliferation, increased apoptosis, and increased pyruvate dehydrogenase activity [52].

In 2014, Dunbar and co-workers published the results of a prospective trial in 15 patients with recurrent malignant brain tumors, 13 with World Health Organization (WHO) grade III-IV gliomas and two with metastases from a primary cancer outside of the central nervous system (CNS). Eight evaluable patients had clinically and radiographically stable disease at the end of the fourth week of DCA treatment and remained on DCA for an average of 75.5 days (range 26 - 312) [40]. One of them was a lung adenocarcinoma patient [53].

In neuroblastoma, one *in vitro* study implied DCA hindered tumor cell growth in human neuroblastoma SH-SY5Y cells [54], while according to another paper, DCA increased proliferation in both neuro-2a and SkBr3 cells and in mice bearing neuro-2a xenografts [55].

In our case report, it appeared that the brain was particularly sensitive to DCA's suspected antineoplastic effects as compared to the lungs or "below the neck". DCA is a highly bioavailable drug that appears to have an affinity for the CNS. Brandsma et al published a case report accounting of a patient with metastatic melanoma who presented with encephalopathy and polyneuropathy following 4 weeks of oral DCA using 400 mg thrice daily (15 mg/kg/day) along with high dose vitamin A (150,000 IU qd). The CSF was positive for DCA following 2 days of discontinued use of both DCA and vitamin A and continued to be present on day 16, indicating an elimination half-life of 5 days from the CSF [32]. Dunbar et al reported responders within a 4-week period and recommended a dosage of 10 - 12.5 mg/kg/day [40].

Discussions are continuing involving the rapid clearance of DCA from the plasma, and thus the need for repeat dosing in order to sustain adequate plasma levels during 3 months of DCA treatment, which appears to be required to achieve a therapeutic effect [52]. However, limited data are available regarding specific tissue effects and better quantification in more compartmentalized areas, such as the CNS and CSF. This may help to explain why there was an unexpectedly rapid improvement in subjective symptoms in our patient in a matter of days.

It should be emphasized that the patient with metastatic melanoma described by Brandsma et al [32] survived for more than 3 years after the DCA incident requiring an 8-month period of physical therapy; yet the patient did not have any CNS involvement [56].

The significance of our patient's leukoencephalopathy is not fully understood, in particular whether this condition was actually caused by the DCA therapy, or whether it was simply related to the LMC and/or the previous oncologic interventions such as radiation and chemotherapy.

In our patient's case, it remains undetermined if DCA helped to overcome drug-resistance with erlotinib in the brain. It has been reported that erlotinib, used as a single agent, improved survival in responding LMC patients [57, 58]. To our knowledge, no published data exist evaluating the combination of DCA and erlotinib. However, it is also important to note that in our case erlotinib therapy was discontinued in February 2009, and follow-up brain imaging along with symptoms did not suggest disease growth in the CNS.

In terms of other targeted agents, DCA and vemurafenib reportedly induced a greater reduction in intracellular adenosine triphosphate (ATP) levels and cellular growth than either compound alone in BRAFV600E-mutant melanoma cells [59]. In addition, melanoma cells with *in vitro* acquired resistance to vemurafenib retained their sensitivity to DCA [60]. DCA has also demonstrated augmentative effects with platinum agents [51, 61, 62], 5-fluorouracil [63, 64], metformin [65], capecitabine [66], arsenic trioxide [67], estradiol analogue C9 [68], paclitaxel [69], tamoxifen [70], temozolomide [18, 71], sorafenib [72], sulindac [73], bevacizumab [74], bortezomib [75], doxorubicin [76], topotecan [77] as well as radiation [78-81], photodynamic therapy [82], and hyperthermotherapy [83]. However, further data are required as Zwicker et al demonstrated DCA tumor radiosensitivity *in vitro* but attenuated tumor growth in an *in vivo* human colorectal adenocarcinoma mouse xenograph model. DCA-induced *in vivo* tumor hypoxia was also noted and may have a link to this observation [78]. Moreover, Heshe et al reported hindered cytotoxicity with doxorubicin and cisplatin in pediatric cell lines [18]. DCA, to date, has not been associated with adverse interactions with other drugs.

It is interesting to note that in our patient's case the LMC response appeared to be long-lasting. It is uncertain whether the follow-up chemotherapy received for systemic effects also had an effect on maintaining the LMC. The patient received maintenance pemetrexed up to approximately 7 weeks prior to her passing. Pemetrexed has been shown to distribute into the CSF and may impact LMC to some degree [84].

Furthermore, it has been surmised that a potential delayed synergistic effect occurred between the WBR in July and the DCA introduction in October. However, this hypothesis seems rather unlikely since the MRI on August 21, recorded approximately 1 month following WBR, did in fact confirm signs of progressive LMC. Finally, one cannot completely rule out that VP shunting may have contributed to some degree to the long survival seen in this case.

Conclusion

Our case report demonstrates the general feasibility of concurrent administration of DCA with other treatment modalities for patients with LMC related to NSCLC.

Patients with NSCLC and possibly those who express EGFR mutation status and/or use tyrosine-kinase inhibitors

such as erlotinib may be a population group to consider with the concurrent use of DCA therapy.

DCA may also be considered in those patients who have appeared to fail WBR and it may as well be administered in combination. Moreover, the application of DCA to a broader base of CNS malignancies may have some merit as previously reported; however, this may hold some challenges in this population group due to concerns about the reported neurotoxic and other side-effects of DCA. As a consequence, a cyclic pattern of DCA dosing should be considered to help minimize toxicity, which apparently does not compromise the efficacy of the therapy.

We have successfully applied similar guidelines to other palliative care patients with CNS malignancies but utilize a "2 week on, 1 week off" cycle using 500 mg DCA twice daily dissolved in juice or water, irrespective of body weight. While impractical in an exclusively clinical setting, monitoring CSF levels for DCA would be of interest for fundamental medical research.

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Conflict of Interest

The corresponding author owns and operates Lemmo Integrated Cancer Care Inc. In this clinic, dichloroacetate is administered to cancer patients upon request for a fee.

Abbreviations

ATP: adenosine triphosphate; CEA: carcinoembryonic antigen; CNS: central nervous system; CSF: cerebrospinal fluid; CT: computerized tomography; DCA: dichloroacetate; EGFR: epidermal growth factor receptor; ER: emergency room; Gd: gadolinium; IT: intrathecal; LMC: leptomeningeal carcinomatosis; MRI: magnetic resonance imaging; NSCLC: non-small-cell lung cancer; PS: performance status; VP: ventriculoperitoneal; WBR: whole brain radiation; WHO: World Health Organization

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