

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

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## 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).

## 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-

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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 ring 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 sylvian 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

## References

1. Riess JW, Nagpal S, Iv M, Zeineh M, Gubens MA, Ramchandran K, Neal JW, et al. Prolonged survival of patients with non-small-cell lung cancer with leptomeningeal carcinomatosis in the modern treatment era. *Clin Lung Cancer*. 2014;15(3):202-206.
2. Salgia S, Fleming GF, Lukas RV. Leptomeningeal carcinomatosis from breast cancer treated with intrathecal topotecan with concomitant intravenous eribulin. *J Clin Neurosci*. 2014;21(7):1250-1251.
3. Oliveira M, Braga S, Passos-Coelho JL, Fonseca R, Oliveira J. Complete response in HER2+ leptomeningeal carcinomatosis from breast cancer with intrathecal trastuzumab. *Breast Cancer Res Treat*. 2011;127(3):841-844.
4. Park MJ. Prolonged response of meningeal carcinomatosis from non-small cell lung cancer to salvage intrathecal etoposide subsequent to failure of first-line methotrexate: a case report and literature review. *Am J Case Rep*. 2015;16:224-227.
5. Riess JW, Nagpal S, Neal JW, Wakelee HA. A patient with anaplastic lymphoma kinase-positive non-small cell lung cancer with development of leptomeningeal carcinomatosis while on targeted treatment with crizotinib. *J Natl Compr Canc Netw*. 2013;11(4):389-394.
6. Souchon R, Feyer P, Thomssen C, Fehm T, Diel I, Nitz U, Janni W, et al. Clinical Recommendations of DEGRO and AGO on Preferred Standard Palliative Radiotherapy of Bone and Cerebral Metastases, Metastatic Spinal Cord Compression, and Leptomeningeal Carcinomatosis in Breast Cancer. *Breast Care (Basel)*. 2010;5(6):401-407.
7. Pentheroudakis G, Pavlidis N. Management of leptomeningeal malignancy. *Expert Opin Pharmacother*. 2005;6(7):1115-1125.
8. Lee SH, Kong DS, Seol HJ, Nam DH, Lee JI. Ventriculoperitoneal shunt for hydrocephalus caused by central nervous system metastasis. *J Neurooncol*. 2011;104(2):545-551.
9. Lin N, Dunn IF, Glantz M, Allison DL, Jensen R, Johnson MD, Friedlander RM, et al. Benefit of ventriculoperitoneal cerebrospinal fluid shunting and intrathecal chemotherapy in neoplastic meningitis: a retrospective, case-controlled study. *J Neurosurg*. 2011;115(4):730-736.
10. Gonda DD, Kim TE, Warnke PC, Kasper EM, Carter BS, Chen CC. Ventriculoperitoneal shunting versus endoscopic third ventriculostomy in the treatment of patients with hydrocephalus related to metastasis. *Surg Neurol Int*. 2012;3:97.
11. Peus D, Newcomb N, Hofer S. Appraisal of the Karnofsky Performance Status and proposal of a simple algorithmic system for its evaluation. *BMC Med Inform Decis Mak*. 2013;13:72.
12. Michelakis ED, Webster L, Mackey JR. Dichloroacetate (DCA) as a potential metabolic-targeting therapy for cancer. *Br J Cancer*. 2008;99(7):989-994.
13. Barshop BA, Naviaux RK, McGowan KA, Levine F, Nyhan WL, Loupis-Geller A, Haas RH. Chronic treatment of mitochondrial disease patients with dichloroacetate. *Mol Genet Metab*. 2004;83(1-2):138-149.
14. Hanberry BS, Berger R, Zastre JA. High-dose vitamin B1 reduces proliferation in cancer cell lines analogous to dichloroacetate. *Cancer Chemother Pharmacol*.

- 2014;73(3):585-594.
15. Stacpoole PW, Harwood HJ, Jr., Cameron DF, Curry SH, Samuelson DA, Cornwell PE, Sauberlich HE. Chronic toxicity of dichloroacetate: possible relation to thiamine deficiency in rats. *Fundam Appl Toxicol.* 1990;14(2):327-337.
  16. Fulda S, Galluzzi L, Kroemer G. Targeting mitochondria for cancer therapy. *Nat Rev Drug Discov.* 2010;9(6):447-464.
  17. Kankotia S, Stacpoole PW. Dichloroacetate and cancer: new home for an orphan drug? *Biochim Biophys Acta.* 2014;1846(2):617-629.
  18. Heshe D, Hoogestraat S, Brauckmann C, Karst U, Boos J, Lanvers-Kaminsky C. Dichloroacetate metabolically targeted therapy defeats cytotoxicity of standard anticancer drugs. *Cancer Chemother Pharmacol.* 2011;67(3):647-655.
  19. Hur H, Xuan Y, Kim YB, Lee G, Shim W, Yun J, Ham IH, et al. Expression of pyruvate dehydrogenase kinase-1 in gastric cancer as a potential therapeutic target. *Int J Oncol.* 2013;42(1):44-54.
  20. Lin G, Hill DK, Andrejeva G, Boulton JK, Troy H, Fong AC, Orton MR, et al. Dichloroacetate induces autophagy in colorectal cancer cells and tumours. *Br J Cancer.* 2014;111(2):375-385.
  21. Shahrzad S, Lacombe K, Adamcic U, Minhas K, Coomber BL. Sodium dichloroacetate (DCA) reduces apoptosis in colorectal tumor hypoxia. *Cancer Lett.* 2010;297(1):75-83.
  22. Nicolson GL. Mitochondrial dysfunction and chronic disease: treatment with natural supplements. *Altern Ther Health Med.* 2014;20(Suppl 1):18-25.
  23. Spruijt L, Naviaux RK, McGowan KA, Nyhan WL, Sheehan G, Haas RH, Barshop BA. Nerve conduction changes in patients with mitochondrial diseases treated with dichloroacetate. *Muscle Nerve.* 2001;24(7):916-924.
  24. Stacpoole PW, Kurtz TL, Han Z, Langae T. Role of dichloroacetate in the treatment of genetic mitochondrial diseases. *Adv Drug Deliv Rev.* 2008;60(13-14):1478-1487.
  25. Koshkarian GM. Congestive heart failure and sodium dichloroacetate. *J Am Coll Cardiol.* 1995;25(3):804-805.
  26. Lewis JF, DaCosta M, Wargowich T, Stacpoole P. Effects of dichloroacetate in patients with congestive heart failure. *Clin Cardiol.* 1998;21(12):888-892.
  27. Wilson JR, Mancini DM, Ferraro N, Egler J. Effect of dichloroacetate on the exercise performance of patients with heart failure. *J Am Coll Cardiol.* 1988;12(6):1464-1469.
  28. Bersin RM, Wolfe C, Kwasman M, Lau D, Klinski C, Tanaka K, Khorrami P, et al. Improved hemodynamic function and mechanical efficiency in congestive heart failure with sodium dichloroacetate. *J Am Coll Cardiol.* 1994;23(7):1617-1624.
  29. McMurtry MS, Bonnet S, Wu X, Dyck JR, Haromy A, Hashimoto K, Michelakis ED. Dichloroacetate prevents and reverses pulmonary hypertension by inducing pulmonary artery smooth muscle cell apoptosis. *Circ Res.* 2004;95(8):830-840.
  30. Michelakis ED, McMurtry MS, Wu XC, Dyck JR, Moudgil R, Hopkins TA, Lopaschuk GD, et al. Dichloroacetate, a metabolic modulator, prevents and reverses chronic hypoxic pulmonary hypertension in rats: role of increased expression and activity of voltage-gated potassium channels. *Circulation.* 2002;105(2):244-250.
  31. Anselm IA, Darras BT. Dichloroacetate causes toxic neuropathy in MELAS: a randomized, controlled clinical trial. *Neurology.* 2006;67(7):1313; author reply 1313.
  32. Brandsma D, Dorlo TP, Haanen JH, Beijnen JH, Boogerd W. Severe encephalopathy and polyneuropathy induced by dichloroacetate. *J Neurol.* 2010;257(12):2099-2100.
  33. Calcutt NA, Lopez VL, Bautista AD, Mizisin LM, Torres BR, Shroads AL, Mizisin AP, et al. Peripheral neuropathy in rats exposed to dichloroacetate. *J Neuropathol Exp Neurol.* 2009;68(9):985-993.
  34. Felitsyn N, Stacpoole PW, Notterpek L. Dichloroacetate causes reversible demyelination in vitro: potential mechanism for its neuropathic effect. *J Neurochem.* 2007;100(2):429-436.
  35. Kurlemann G, Paetzke I, Moller H, Masur H, Schuierer G, Weglage J, Koch HG. Therapy of complex I deficiency: peripheral neuropathy during dichloroacetate therapy. *Eur J Pediatr.* 1995;154(11):928-932.
  36. Saijo T, Naito E, Ito M, Takeda E, Hashimoto T, Kuroda Y. Therapeutic effect of sodium dichloroacetate on visual and auditory hallucinations in a patient with MELAS. *Neuropediatrics.* 1991;22(3):166-167.
  37. Stacpoole PW, Shroads AL, Felitsyn NM, Notterpek L, Calcutt NA. Mechanism and age dependence of dichloroacetate-induced peripheral neuropathy. *Mitochondrion.* 2006;6(5):17-18.
  38. Stacpoole PW. The dichloroacetate dilemma: environmental hazard versus therapeutic goldmine - both or neither? *Environ Health Perspect.* 2011;119(2):155-158.
  39. Debray FG, Lambert M, Vanasse M, Decarie JC, Cameron J, Levandovskiy V, Robinson BH, et al. Intermittent peripheral weakness as the presenting feature of pyruvate dehydrogenase deficiency. *Eur J Pediatr.* 2006;165(7):462-466.
  40. Dunbar EM, Coats BS, Shroads AL, Langae T, Lew A, Forder JR, Shuster JJ, et al. Phase I trial of dichloroacetate (DCA) in adults with recurrent malignant brain tumors. *Invest New Drugs.* 2014;32(3):452-464.
  41. Chu QS, Sangha R, Spratlin J, Vos LJ, Mackey JR, McEwan AJ, Venner P, et al. A phase I open-labeled, single-arm, dose-escalation, study of dichloroacetate (DCA) in patients with advanced solid tumors. *Invest New Drugs.* 2015;33(3):603-610.
  42. Pan JG, Mak TW. Metabolic targeting as an anticancer strategy: dawn of a new era? *Sci STKE.* 2007;2007(381):pe14.
  43. Bonnet S, Archer SL, Allalunis-Turner J, Haromy A, Beaulieu C, Thompson R, Lee CT, et al. A mitochondrial K<sup>+</sup> channel axis is suppressed in cancer and its normalization promotes apoptosis and inhibits cancer growth. *Cancer Cell.* 2007;11(1):37-51.
  44. Strum SB, Adalsteinsson O, Black RR, Segal D, Peress

- NL, Waldenfels J. Case report: Sodium dichloroacetate (DCA) inhibition of the "Warburg Effect" in a human cancer patient: complete response in non-Hodgkin's lymphoma after disease progression with rituximab-CHOP. *J Bioenerg Biomembr*. 2013;45(3):307-315.
45. Strum S, Adalsteinsson O, Black R, Segal D, Peress N, Waldenfels J. Erratum to: Case Report: Sodium dichloroacetate (DCA) inhibition of the 'Warburg Effect' in a human cancer patient: complete response in non-Hodgkin's lymphoma after disease progression with rituximab-CHOP. *J Bioenerg Biomembr*. 2013;45(3):317.
  46. Ohashi T, Akazawa T, Aoki M, Kuze B, Mizuta K, Ito Y, Inoue N. Dichloroacetate improves immune dysfunction caused by tumor-secreted lactic acid and increases antitumor immunoreactivity. *Int J Cancer*. 2013;133(5):1107-1118.
  47. Flavin DF. Non-Hodgkin's Lymphoma Reversal with Dichloroacetate. *J Oncol*. 2010;2010
  48. Khan A, Marier D, Marsden E, Andrews D, Eliaz I. A novel form of dichloroacetate therapy for patients with advanced cancer: a report of 3 cases. *Altern Ther Health Med*. 2014;20(Suppl 2):21-28.
  49. Flavin D. Medullary thyroid carcinoma relapse reversed with dichloroacetate: A case report. *Oncol Lett*. 2010;1(5):889-891.
  50. Khan A. Use of oral dichloroacetate for palliation of leg pain arising from metastatic poorly differentiated carcinoma: a case report. *J Palliat Med*. 2011;14(8):973-977.
  51. Garon EB, Christofk HR, Hosmer W, Britten CD, Bahng A, Crabtree MJ, Hong CS, et al. Dichloroacetate should be considered with platinum-based chemotherapy in hypoxic tumors rather than as a single agent in advanced non-small cell lung cancer. *J Cancer Res Clin Oncol*. 2014;140(3):443-452.
  52. Michelakis ED, Sutendra G, Dromparis P, Webster L, Haromy A, Niven E, Maguire C, et al. Metabolic modulation of glioblastoma with dichloroacetate. *Sci Transl Med*. 2010;2(31):31ra34.
  53. Stacpoole PW. Personal communication. 2015.
  54. Pajuelo-Reguera D, Alan L, Olejar T, Jezek P. Dichloroacetate stimulates changes in the mitochondrial network morphology via partial mitophagy in human SH-SY5Y neuroblastoma cells. *Int J Oncol*. 2015;46(6):2409-2418.
  55. Feuerecker B, Seidl C, Pirsig S, Bruchelt G, Senekowitsch-Schmidtke R. DCA promotes progression of neuroblastoma tumors in nude mice. *Am J Cancer Res*. 2015;5(2):812-820.
  56. Brandsma D. Personal communication. 2011.
  57. Katono K, Kasajima M, Ishihara M, Hayashi N, Nagashima Y, Igawa S, Masuda N. [A case of lung adenocarcinoma with coexisting G719X and T790M EGFR mutations in which erlotinib was effective for the treatment of leptomeningeal carcinomatosis]. *Gan To Kagaku Ryoho*. 2013;40(3):375-377.
  58. Yi HG, Kim HJ, Kim YJ, Han SW, Oh DY, Lee SH, Kim DW, et al. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are effective for leptomeningeal metastasis from non-small cell lung cancer patients with sensitive EGFR mutation or other predictive factors of good response for EGFR TKI. *Lung Cancer*. 2009;65(1):80-84.
  59. Abildgaard C, Dahl C, Basse AL, Ma T, Guldborg P. Bioenergetic modulation with dichloroacetate reduces the growth of melanoma cells and potentiates their response to BRAFV600E inhibition. *J Transl Med*. 2014;12:247.
  60. Kluza J, Corazao-Rozas P, Touil Y, Jendoubi M, Maire C, Guerreschi P, Jonneaux A, et al. Inactivation of the HIF-1alpha/PDK3 signaling axis drives melanoma toward mitochondrial oxidative metabolism and potentiates the therapeutic activity of pro-oxidants. *Cancer Res*. 2012;72(19):5035-5047.
  61. Kumar A, Kant S, Singh SM. Antitumor and chemosensitizing action of dichloroacetate implicates modulation of tumor microenvironment: a role of reorganized glucose metabolism, cell survival regulation and macrophage differentiation. *Toxicol Appl Pharmacol*. 2013;273(1):196-208.
  62. Xie J, Wang BS, Yu DH, Lu Q, Ma J, Qi H, Fang C, et al. Dichloroacetate shifts the metabolism from glycolysis to glucose oxidation and exhibits synergistic growth inhibition with cisplatin in HeLa cells. *Int J Oncol*. 2011;38(2):409-417.
  63. Tong J, Xie G, He J, Li J, Pan F, Liang H. Synergistic antitumor effect of dichloroacetate in combination with 5-fluorouracil in colorectal cancer. *J Biomed Biotechnol*. 2011;2011:740564.
  64. Xuan Y, Hur H, Ham IH, Yun J, Lee JY, Shim W, Kim YB, et al. Dichloroacetate attenuates hypoxia-induced resistance to 5-fluorouracil in gastric cancer through the regulation of glucose metabolism. *Exp Cell Res*. 2014;321(2):219-230.
  65. Choi YW, Lim IK. Sensitization of metformin-cytotoxicity by dichloroacetate via reprogramming glucose metabolism in cancer cells. *Cancer Lett*. 2014;346(2):300-308.
  66. Zheng MF, Shen SY, Huang WD. DCA increases the antitumor effects of capecitabine in a mouse B16 melanoma allograft and a human non-small cell lung cancer A549 xenograft. *Cancer Chemother Pharmacol*. 2013;72(5):1031-1041.
  67. Emadi A, Sadowska M, Carter-Cooper B, Bhatnagar V, van der Merwe I, Levis MJ, Sausville EA, et al. Perturbation of cellular oxidative state induced by dichloroacetate and arsenic trioxide for treatment of acute myeloid leukemia. *Leuk Res*. 2015;39(7):719-729.
  68. Stander XX, Stander BA, Joubert AM. Synergistic anticancer potential of dichloroacetate and estradiol analogue exerting their effect via ROS-JNK-Bcl-2-mediated signaling pathways. *Cell Physiol Biochem*. 2015;35(4):1499-1526.
  69. Zhou X, Chen R, Yu Z, Li R, Li J, Zhao X, Song S, et al. Dichloroacetate restores drug sensitivity in paclitaxel-resistant cells by inducing citric acid accumulation. *Mol Cancer*. 2015;14:63.
  70. Ishiguro T, Ishiguro R, Ishiguro M, Iwai S. Co-treatment of dichloroacetate, omeprazole and tamoxifen exhibited synergistically antiproliferative effect on malignant tumors: in vivo experiments and a case report. *Hepatogastroenterology*. 2012;59(116):994-996.

71. Wicks RT, Azadi J, Mangraviti A, Zhang I, Hwang L, Joshi A, Bow H, et al. Local delivery of cancer-cell glycolytic inhibitors in high-grade glioma. *Neuro Oncol.* 2015;17(1):70-80.
72. Shen YC, Ou DL, Hsu C, Lin KL, Chang CY, Lin CY, Liu SH, et al. Activating oxidative phosphorylation by a pyruvate dehydrogenase kinase inhibitor overcomes sorafenib resistance of hepatocellular carcinoma. *Br J Cancer.* 2013;108(1):72-81.
73. Ayyanathan K, Kesaraju S, Dawson-Scully K, Weissbach H. Combination of sulindac and dichloroacetate kills cancer cells via oxidative damage. *PLoS One.* 2012;7(7):e39949.
74. Kumar K, Wigfield S, Gee HE, Devlin CM, Singleton D, Li JL, Buffa F, et al. Dichloroacetate reverses the hypoxic adaptation to bevacizumab and enhances its antitumor effects in mouse xenografts. *J Mol Med (Berl).* 2013;91(6):749-758.
75. Sanchez WY, McGee SL, Connor T, Mottram B, Wilkinson A, Whitehead JP, Vuckovic S, et al. Dichloroacetate inhibits aerobic glycolysis in multiple myeloma cells and increases sensitivity to bortezomib. *Br J Cancer.* 2013;108(8):1624-1633.
76. Dai Y, Xiong X, Huang G, Liu J, Sheng S, Wang H, Qin W. Dichloroacetate enhances adriamycin-induced hepatoma cell toxicity in vitro and in vivo by increasing reactive oxygen species levels. *PLoS One.* 2014;9(4):e92962.
77. Stockwin LH, Yu SX, Borgel S, Hancock C, Wolfe TL, Phillips LR, Hollingshead MG, et al. Sodium dichloroacetate selectively targets cells with defects in the mitochondrial ETC. *Int J Cancer.* 2010;127(11):2510-2519.
78. Zwicker F, Kirsner A, Peschke P, Roeder F, Debus J, Huber PE, Weber KJ. Dichloroacetate induces tumor-specific radiosensitivity in vitro but attenuates radiation-induced tumor growth delay in vivo. *Strahlenther Onkol.* 2013;189(8):684-692.
79. Shavit R, Ilouze M, Feinberg T, Lawrence YR, Tzur Y, Peled N. Mitochondrial induction as a potential radiosensitizer in lung cancer cells - a short report. *Cell Oncol (Dordr).* 2015;38(3):247-252.
80. Shen H, Hau E, Joshi S, Dilda PJ, McDonald KL. Sensitization of Glioblastoma Cells to Irradiation by Modulating the Glucose Metabolism. *Mol Cancer Ther.* 2015;14(8):1794-1804.
81. Cao W, Yacoub S, Shiverick KT, Namiki K, Sakai Y, Porvasnik S, Urbanek C, et al. Dichloroacetate (DCA) sensitizes both wild-type and over expressing Bcl-2 prostate cancer cells in vitro to radiation. *Prostate.* 2008;68(11):1223-1231.
82. Kwitniewski M, Moan J, Juzeniene A. Metabolic-targeted therapy with dichloroacetate (DCA): a novel treatment strategy to improve the outcome of photodynamic therapy. *Photochem Photobiol Sci.* 2011;10(1):25-28.
83. Saito M, Yano K, Kamigaki T, Goto S. A patient with scirrhus stomach cancer treated with combination of hyperthermotherapy and 5-aminolevulinic acid (ALA). *Anticancer Res.* 2013;33(7):2957-2963.
84. Kumthekar P, Grimm SA, Avram MJ, Kaklamani V, Helenowski I, Rademaker A, Cianfrocca M, et al. Pharmacokinetics and efficacy of pemetrexed in patients with brain or leptomeningeal metastases. *J Neurooncol.* 2013;112(2):247-255.