

## Combination of Metabolic Treatment of Aggressive Primary Brain Tumour and Multiple Metastases of the Brain

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### Abstract

**Background:** The combination of hydroxycitrate and lipoic acid has been demonstrated by several laboratories to be effective in reducing murine cancer growth. In previous article in 2014, we reported the fate of 11 patients treated for metastatic cancer unresponsive to chemotherapy. As of today, 32 months after inclusion, five of these patients (45%) are still alive.

**Patients and Methods:** We report the cases of 12 patients with advanced brain tumor. They were all treated with conventional treatment and a combination of sodium R lipoate (800 mg *bid*), hydroxycitrate at 500 mg *tid* and low-dose naltrexone at 5 mg at bedtime. Eight patients had primary brain tumour (n=8 including five glioblastomas) four patients had multiple brain metastases.

**Results and Discussion:** The combination of conventional and metabolic treatment was well tolerated. Four out of five patients with glioblastoma are still alive and well. The longest follow-up is 7 years. The four patients with disease widely metastatic to the brain have experienced long-term survival. A randomized clinical trial of metabolic treatment associated with conventional treatment is warranted.

**Keywords:** Hydroxycitrate; Alpha-lipoic acid; Low-dose naltrexone; Glioblastoma; Cancer metastatic to the brain.

In the previous article[1], we reported the fate of the first patients treated with a combination of low-dose naltrexone, lipoic acid  $\alpha$ -(LA) and hydroxycitrate (HCA). In this report, we focus more precisely on the fate of patients with either very aggressive primary brain cancer or disease

widely metastatic to the brain. The prognosis of these malignancies is widely known to be dismal. Our results reported here appear to be encouraging enough to warrant rigorous clinical trials of such a combination.

The alteration of glucose metabolism in cancer was first described by Warburg almost 90 years ago [2]. In cancer cells, there are altered mitochondria and a dysfunctional Krebs's cycle [3-5]. In order to sustain ATP synthesis, there is increased glucose uptake resulting in increased anaerobic glycolysis. Because of alteration of the mitochondria, the metabolic fluxes are diverted toward the synthesis of lactate and the pentose phosphate shunt. The pentose phosphate shunt is necessary for the synthesis of DNA and RNA [3-5].

In order to increase mitochondrial efficiency, our laboratory had screened a large number of compounds, most of which were clearly targeted at the altered metabolic pathways frequently present in cancer cells due to the Warburg effect [6-8]. We demonstrated that the combination of  $\alpha$ -LA and HCA reduces both anaerobic glycolysis and cancer growth in murine models, whatever the primary tumour site [6-8].

The first human toxicity trials were conducted using increasing dosage of oral lipoic acid ( $\alpha$ -LA) and HCA in addition to standard anticancer cytotoxic chemotherapy. The minimum and maximum doses of  $\alpha$ -LA administered were 0.4 g/day and 1.8 g/day and for HCA 1.2 g/day and dose 3 g/day, respectively. The recorded side-effects were related to the respective chemotherapies administered, except for gastrointestinal disorders of mild intensity. Three patients out of five treated with higher doses of  $\alpha$ -LA and HCA, 1.8 g/day and 3 g/day, respectively, had a number of grade 1 to 3 side-effects, including stomach pain, diarrhoea and nausea, and two patients reported weight loss. Most of the patients receiving treatment for more than 6 months displayed partial tumour regression or stabilization [9-11].

More recently, we published the results of the results of 11 other patients [1]. At the time, in early 2014, the results were encouraging enough to warrant publication. Six patients with advanced heavily pre-treated metastatic cancer were still alive 16 months after the start of metabolic treatment. As of today, 32 months after the start of metabolic treatment five out of the first 11 (45%) are still alive. One has progressive disease (metastatic adenocarcinoma of the oesophagus) but the other four (metastatic adenocarcinoma of the parotid, metastatic sarcoma of the uterus, metastatic adenocarcinoma of unknown origin and hormone-resistant metastatic adenocarcinoma of the prostate) have returned to an almost normal life.

In the meantime, Berkson et al. treated four patients with pancreatic cancer with a combination of  $\alpha$ -LA and naltrexone. The results were strikingly positive, and the first

patient treated was alive and well 78 months following the initiation of treatment [12,13].

In this article, we report the cases of several patients with brain tumours of poor prognosis.

## Patients and Methods

In order to speed research and patient care, a patient support group was set up in 2013 named "Cancer and Metabolism" and registered under French law as a non-profit organization. Desperate patients were given advice and followed-up by interviews or phone call and/or mail. Medical records were analysed by Board-certified oncologists (Paris, France). Unless specified the metabolic treatment was: i) 800 mg lipoic acid *bid* (Solgar, Leonia, NJ, USA) 500 mg HCA *tid* (Solgar); and 5 mg naltrexone (Revia; Bristol-Myers Squibb, Rueil-Malmaison, France) at bed time.

We report the cases of 12 patients with advanced brain tumours. These patients were self-referred. Their cases were reviewed by two board-certified oncologists. They were treated with standard care and metabolic treatment.

## First Group – Primary Brain Tumour

**Case 1:** A 38-year-old Italian female was diagnosed with glioblastoma multiforme in October 2008. After partial resection of the lesion, she started a 2-year combination of temozolomide and  $\alpha$ -LA and HCA. She experienced relapse in June 2011 and started the same treatment. As of August 2015, there was evidence of tumour progression on imaging but her Karnofsky performance status (KPS) was 90, 7 years after diagnosis. She was still alive in January 2016.

**Case 2:** A 63-year-old French male presented in January 2013 with an unresectable grade III astrocytoma. He was treated with high dose (59.4 Gy) radiation therapy and postoperative temozolomide combined with  $\alpha$ -LA, HCA and low-dose naltrexone. The metabolic treatment was continued after completion of chemotherapy. Thirty months later, there was no evidence of active disease and the KPS was 100. He was still fine in January 2016.

**Case 3:** A 41-year-old French female with a biopsy-proven glioblastoma (December 2013) was treated with a combination of radiation therapy (45 Gy) followed by temozolomide combined with  $\alpha$ -LA, HCA and low-dose naltrexone. There was no evidence of active disease 18 months later and the KPS was 90. She was still clinically fine in January 2016.

**Case 4:** A 57-year-old French female was diagnosed with glioblastoma in February 2014. She was treated with radiation therapy and temozolomide. In October 2014, she was started on a combination of  $\alpha$ -LA, HCA and a ketogenic diet. The tumour, which was stable in size between February and October 2014, shrank by 60% in the subsequent three months. Aphasia disappeared. The radiological examination on magnetic resonance imaging (MRI) was unchanged in January 2016 and KPS was 70.

**Case 5:** A 59-year-old man diagnosed with glioblastoma was treated by radiation therapy and temozolomide in December 2014. He started a ketogenic diet and  $\alpha$ -LA with HCA in July 2015. Repeat MRI showed stable disease and the KPS was 80. He died of tumour recurrence in November 2015.

**Case 6:** A 38-year-old Italian female was diagnosed in 2000 with a grade II astrocytoma. She experienced relapse in 2008. Tumour was grade III. She was treated with radiation therapy and chemotherapy (procarbazine, lomustine and vincristine followed by temozolomide). Because of tumour progression she was discharged in July 2013. She was treated with  $\alpha$ -LA (600mg), 500 mg HCA *i.v. tid* and low-dose naltrexone. She experienced several episodes of seizures (treatment-related?). The tumour grew slowly and she died one year later in June 2014.

**Case 7:** A 31-year-old male was diagnosed with aggressive brainstem glioma. The tumour recurred after a combination of temozolomide and radiation therapy (September 2013). A combination of natulan and lomustine failed to provide benefit. Metabolic treatment was started in June 2014 and an MRI in July 2015 showed stable disease. He was alive in January 2016 but experiencing slowly progressing disease.

**Case 8:** A 56-year-old male was diagnosed with glioblastoma in January 2014 and was treated by radiation therapy followed by temozolomide. In May 2014, metabolic treatment was started and his disease has remained stable since. In June 2015, he stopped both the HCA and  $\alpha$ -LA diet and started a glucose diet. As of January 2016, he was living a normal life.

## Second Group: Cancer Metastatic to the Brain

**Case 9:** This 73-year-old female was diagnosed with a sarcoma of the uterus in 2007. She was treated with surgery, postoperative radiation therapy and chemotherapy. The patient developed severe radiation enteritis resulting both in

weight loss and in multiple surgeries. In January 2013, the tumour relapsed with 14 different brain metastases; one of 30 mm in the life expectancy was of a few months. In early March 2013, this started 2g sodium R lipoate per day, as well as 500 mg HCA, 3 times per day. The last MRI in June 2015 showed almost complete disappearance of the brain lesions. The patient has been free of symptoms but had two episodes of seizure in late September 2013. As of January 2016, she was living a normal life. CT scan failed to demonstrate any residual lesion.

**Case 10:** This 65-year-old Italian male underwent nephrectomy for an adenocarcinoma in 2001. He suffered from hemianopsia in early 2012. Staging revealed brain, lung and lymph nodal metastases. Life expectancy was less than three months. The patient refused chemotherapy and radiation therapy. Metabolic treatment was started in April 2012. He died of Parkinson's disease in July 2015.

**Case 11:** This 50 year old female patient was diagnosed with metastatic non-small cell lung cancer in 2013. Computed tomographic (CT) scan revealed more than 20 brain metastases (September 2013). She was treated with Alimta alone. There was partial regression of the metastases up to February 2014. Because of tumour regrowth, therapy was switched to Tarceva and  $\alpha$ -LA with HCA. The primary lung lesion regressed and the brain metastases were stable. Radiation therapy was started (37 Gy) in June 2014. During the course of radiation therapy, the patient experienced one episode of seizure and acute psychosis. The husband was informed of his wife's imminent death. In September 2014, oedema was increased on CT scan. In June 2015, the oedema had disappeared, and the lesion had shrunk by 75%. The patient returned to work in December 2015.

**Case 12:** This 48-year-old female was diagnosed as having T1N0M0 breast cancer in 1999. She suffered local and distant relapse in 2004. In mid 2014, she presented with metastatic spread to the meninges. Intrathecal methotrexate was started combined with  $\alpha$ -LA and HCA. At the last CT (18 months later), the brain metastases were under control but there was progression of the bone metastases.

## Results and Discussion

Current drug development in oncology is non-selective as it typically focuses on pathways essential for the survival of all dividing cells. The unique metabolic profile of cancer cells, which is characterized by increased glycolysis and suppressed mitochondrial glucose oxidation, provides cancer cells with a proliferative advantage [2,4,5].

At this stage, there is ample evidence that targeting cancer metabolism may offer selectivity in cancer treatment. Pyruvate dehydrogenase kinase (PDK) is a mitochondrial enzyme that is activated in a variety of cancer types and results in the selective inhibition of pyruvate dehydrogenase, a complex of enzymes that converts cytosolic pyruvate to mitochondrial acetyl-CoA, the substrate for the Krebs' cycle. Inhibition of PDK with either  $\alpha$ -LA, small interfering RNAs or dichloroacetate (DCA) shifts the metabolism of cancer cells from glycolysis to glucose oxidation [6, 13].

Such metabolic rewiring is effective in reducing cancer cell growth in mice [7-9, 14]. The efficacy of cytotoxic chemotherapy is enhanced by the combination of  $\alpha$ -LA and HCA (7). Similarly, DCA enhances the efficacy of cytotoxic chemotherapy or radiation therapy [15-17].

There are scant case reports in the literature suggesting that metabolic rewiring may have an impact on survival of patients with brain cancer. In a small but mechanistic clinical trial on patients with glioblastoma, a highly aggressive and vascular form of brain cancer, DCA reduced tumour growth, suggesting that metabolic-targeting therapies can be translated directly to patients [13,14].

The median survival for patients with glioblastoma multiforme is 9 months; 5-year survival is less than 4% [18]. Similarly, patients with multiple brain metastases have a dismal prognosis [19].

Our data are from a diverse group of patients [there are patients with primary brain tumours (n=8) and patients with multiple brain metastases (n=4)]. It is therefore difficult to draw a definitive conclusion from this series of patients. Nevertheless, it appears probable that metabolic treatment slows down cancer growth (cases 1 and 9) and potentiates the efficacy of conventional treatment (mainly radiation therapy).

Radiation therapy is a key part of treatment of both glioblastoma and metastatic brain cancer. The role of radiation therapy in modulating tumour metabolism is a key area of basic research. Part of the efficacy of radiation is mediated by change in cancer cell metabolism [20-25]. Radiation therapy alleviates the Warburg effect [21]. Pyruvate is directed toward the mitochondria and not towards production of lactic acid. Tumours with high glycolytic rates confer a dismal prognosis [5]. The decrease of anaerobic glycolysis increases the efficacy of radiation

therapy. *In vivo*, the combinatorial treatment of DCA and radiotherapy improved the survival of glioblastoma-bearing mice [24].

Our data suggest that modulating the anaerobic pathway may increase the efficacy of radiation therapy. It is also probable that metabolic treatment may increase the side-effects of radiation therapy. One patient (case 10) experienced an acute psychotic event during radiation therapy and diffuse brain oedema. This side-effect of treatment is highly uncommon.

## Conclusion

To our knowledge, this is the first attempt to treat cancer using a combination of molecules targeting abnormal cancer metabolism.

None of these patients experienced major side-effects of metabolic treatment.

At this stage of development, not a single case proves the efficacy of treatment. But at the time of writing, most patients were alive and well several months after having been sent home to await their death. Several months of life without symptoms strongly suggests that targeting cancer metabolism may be a reasonable option in therapy of advanced brain cancer.

The role of metabolic treatment and its association with existing therapy remains to be explored in well-conducted trials.

## Conflicts of Interest

Laurent Schwartz patented the combination of lipoic acid and hydroxycitrate. The other Authors have no competing interests.

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