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Enclosures

## Metabolic Treatment of Cancer: Intermediate Results of a Prospective Case Series

LAURENT SCHWARTZ<sup>1,2</sup>, LUDIVINE BUHLER<sup>3</sup>, PHILIPPE ICARD<sup>4</sup>,  
HUBERT LINCET and JEAN-MARC STEYAERT<sup>1</sup>

<sup>1</sup>Ecole Polytechnique, Palaiseau, France;

<sup>2</sup>Assistance Publique des hôpitaux de Paris (AH-HP)

<sup>3</sup>Faculté de médecine, C.H.U. Lille, France;

<sup>4</sup>Chirurgie thoracique, C.H.U Caen, Côte de Nacre, France

**Abstract.** *Background:* The combination of hydroxycitrate and lipoic acid has been demonstrated by several laboratories to be effective in reducing murine cancer growth. *Patients and Methods:* All patients had failed standard chemotherapy and were offered only palliative care by their referring oncologist. Karnofsky status was between 50 and 80. Life expectancy was estimated to be between 2 and 6 months. Ten consecutive patients with chemoresistant advanced metastatic cancer were offered compassionate metabolic treatment. They were treated with a combination of lipoic acid at 600 mg i.v. (Thioctacid), hydroxycitrate at 500 mg t.i.d. (Solgar) and low-dose naltrexone at 5 mg (Revia) at bedtime. Primary sites were lung carcinoma (n=2), colonic carcinoma (n=2), ovarian carcinoma (n=1), esophageal carcinoma (n=1), uterine sarcoma (n=1), cholangiocarcinoma (n=1), parotid carcinoma (n=1) and unknown primary (n=1). The patients had been heavily pretreated. One patient had received four lines of chemotherapy, four patients three lines, four patients two lines and one patient had received radiation therapy and chemotherapy. An eleventh patient with advanced prostate cancer resistant to hormonotherapy treated with hydroxycitrate, lipoic acid and anti-androgen is also reported. *Results:* One patient was unable to receive i.v. lipoic acid and was switched to oral lipoic acid (Tiobec). Toxicity was limited to transient nausea and vomiting. Two patients died of progressive disease within two months. Two other patients had to be switched to conventional chemotherapy combined with metabolic treatment, one of

when had a subsequent dramatic tumor response. Disease in the other patients was either stable or very slowly progressive. The patient with hormone-resistant prostate cancer had a dramatic fall in Prostate-Specific Antigen (90%), which is still decreasing. *Conclusion:* These very primary results suggest the lack of toxicity and the probable efficacy of metabolic treatment in chemoresistant advanced carcinoma. It is also probable that metabolic treatment enhances the efficacy of cytotoxic chemotherapy. These results are in line with published animal data. A randomized clinical trial is warranted.

The alteration of glucose metabolism in cancer was first described by Warburg almost 90 years ago (1). In cancer cells, there is an increased uptake of glucose which cannot be degraded via the Krebs cycle. Metabolic fluxes are then diverted toward the synthesis of lactate and the pentose phosphate shunt. Pentose phosphate is necessary for the synthesis of DNA and RNA (2-5). In cancer cells, the Krebs cycle is also abnormal, with citrate flowing outside the mitochondria to contribute to lipid synthesis.

Our laboratory has screened large numbers of compounds, most of which have been clearly targeted at the altered metabolic pathways frequently present in cancer cells due to the Warburg effect (6-8).

Given this, it is logical to target the altered metabolic pathways in order to inhibit cancer growth. As a consequence, it is not surprising that a rather large number of potential inhibitors of glycolysis have been evaluated both *in vitro* and *in vivo* as potential anticancer drugs (for reviews see 8, 9).

Our first study (1) utilized a library of 27 compounds known to affect glucose metabolism drawn from a detailed literature analysis. *In vitro* tests were conducted on four cell lines at concentrations consistent with human dosage levels in order to assess antiproliferative activity. From the effective compounds, further *in vitro* testing was conducted on binary

*Correspondence to:* L. Schwartz, Ecole Polytechnique Laboratoire LIX, 91128 Palaiseau, France. E-mail: laurent.schwartz@polytechnique.edu

**Key Words:** Hydroxycitrate, alpha lipoic acid, low-dose naltrexone, metabolism, advanced cancer.

Table I. Summary of the medical characteristics of the patients reported in the study

Patient	Site of primary	Number of chemotherapy lines	Evolution
1	Lung	3	9 Months' stabilization
2	Lung	2	Death
3	Colon	3	Stable disease
4	Colon	2	Death
5	Ovarian	3	Slow progression
6	Esophagus	2	Partial regression with chemotherapy
7	Uterine sarcoma	1	Stabilization
8	Liver	2	Partial stabilization
9	Unknown	2	Partial stabilization and then progression
10	Parotid	2	Stable disease
11	Prostate	2	Regression

combinations and the seven combinations that showed significant activity in the *in vitro* tests were then evaluated *in vivo* against mice bearing a syngeneic MBT-2 bladder tumor. The most effective treatment was a combination of hydroxycitrate (HCA) and alpha-lipoic acid ( $\alpha$ -LA), which we have designated as METABLOC™. The efficacy of this combination was confirmed in mice with B16-F10 melanoma and LL/2 Lewis lung carcinoma. The HCA/ $\alpha$ -LA combination slowed tumor growth and increased survival, with an efficacy similar to that of conventional chemotherapy. These encouraging results have since been repeated in a second laboratory (2).

The first human toxicity trials were conducted using increasing dosage of oral  $\alpha$ -LA and HCA in addition to standard anticancer cytotoxic chemotherapy. Between 2009 and 2011, 11 patients with histologically proven malignant disease were treated according to the standard protocol in use for their cancer type and stage (11). In addition to their normal chemotherapeutic regimen, a combination of  $\alpha$ -LA and HCA was administered. Informed consent was obtained and efficacy results and side-effects were registered. The minimum oral dose of  $\alpha$ -LA administered was 0.4 g/day, and the maximum dose was 1.8 g/day. The minimum dose of HCA was 1.2 g/day and the maximum dose was 3 g/day.

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, diarrhea and nausea, and two patients reported weight loss.

These side-effects disappeared on using proton pump inhibitors or by reducing the dose. Seven patients tolerated the  $\alpha$ -LA plus HCA treatment without side-effects. Two of these patients were administered proton pump inhibitors as part of their treatment, but the other five had no accompanying treatment. The minimum duration of

treatment was two months, while the maximum duration was 44 months.

Most of the patients receiving treatment for more than six months displayed partial regression or stabilization. Of the eleven patients, disease in five was characterized by partial regression, three by stable disease, and three by progression.

One patient affected by a pancreatic adenocarcinoma with liver metastases displayed tumor regression during a few months. After she decided to stop her treatment, she died. She had survived 18 months after starting this treatment (10). A patient with parotid gland carcinoma also responded to this therapy, with regression of primary tumor and metastases. However, the cancer finally recurred. Another patient is alive and well at four years after the diagnosis of widely metastatic bulky peritoneal metastasis of a colonic carcinoma (11).

In the meantime, Berkson *et al.* (12, 13) 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.

An other group synthesized, CPI-613, an  $\alpha$ -LA analog, and reported activity in one patient with metastatic pancreatic adenocarcinoma (14).

We decided to test if metabolic treatment alone (a combination of  $\alpha$ -LA, HCA and low dose-naltrexone) was safe and effective in refractory end stage cancer.

## Patients

In this series, all patients had failed standard chemotherapy and were offered only palliative care by their oncologists. Karnofsky status was between 50 and 80. Life expectancy was estimated to be between two and six months.

Ten patients with chemoresistant advanced metastatic cancer were treated with a combination of 600 mg *i.v.*  $\alpha$ -LA (Thioctacid; Meda Pharma GmbH & Co. KG, Bad Homburg, Germany), 500 mg hydroxycitrate *t.i.d.* (Solgar, Leonia, NJ 07605, USA) and low-dose

naltrexone (5 mg; Revia, Bristol-Myers Squibb, Rueil-Malmaison cdx, France) at bedtime. Primary sites were lung carcinoma (n=2), colonic carcinoma (n=2), ovarian carcinoma (n=1), esophageal carcinoma (n=1), uterine sarcoma (n=1) and cholangiocarcinoma (n=1) and parotid carcinoma (n=1) and unknown primary (n=1).

The patients had been heavily pretreated. One patient had received four lines of chemotherapy, four patients: three lines, four patients: two lines respectively, one patient radiation therapy and chemotherapy.

An eleventh patient with hormone refractory prostate cancer treated himself, without medical advice, with HCA,  $\alpha$ -LA and anti-androgen. His case is reported below.

## Results

**Case 1.** A 58-year-old lady had a right inferior lobectomy (07/2011) for a pT3N0 stage IIB papillary adenocarcinoma. Despite adjuvant chemotherapy (cisplatin, gemzar), she developed tumor recurrence and multiple lung metastases (02/2012). Alimta was first ineffective and followed by an ineffective experimental association of drugs (phase Ib trial of an oral inhibitor Phosphoinositide 3-kinase (PI3K) and Mitogen-activated protein kinase kinase (MEK)). After failure in the trial, the patient was left with no therapeutic option but best supportive care. She was told by her referring oncologist in 12/2012, that she had less than three months to live. Because of extensive lung metastases, she was receiving oxygen (3 L/min).

Since mid-January 2013 (for chest Computed Tomography see Figure 1), she has been treated with *i.v.*  $\alpha$ -LA at 600 mg/day, HCA at 500 mg three times a day, naltrexone at 4.5 mg/day, bicarbonate at 7g/d, medrol (methylprednisolone) at 16 mg/day and inxium (esomeprazole) at 40 mg/day. No side-effects have been reported. Radiological evaluation (Positron Emission Tomography (PET) scan 05/2013, Computed Tomography (CT) scan 06/2013) showed stabilization of the disease. Late in 09/2013, she developed acute pulmonary distress, no CT scan was performed, and she was transferred to palliative care. She was then switched to chemotherapy and is alive in 12/13.

**Case 2.** A 64-year-old former smoker had been diagnosed in 04/2012 with a stage IV lung adenocarcinoma, with brain and bone metastases. Between 04/2012 and 01/2013 he was treated with carboplatin and bevacizumab. In 01/2013, bevacizumab was switched to pemetrexed because of tumor progression. The brain metastases were treated by radiation therapy in 02/2013. He started *i.v.*  $\alpha$ -LA doses and HCA in late 04/2013. He died of tumor progression seven weeks later.

**Case 3.** The third patient had a colonic carcinoma with multiple liver metastases. She failed three lines of chemotherapy with cetuximab, vectibix and one experimental treatment. She was left with no therapeutic options. She

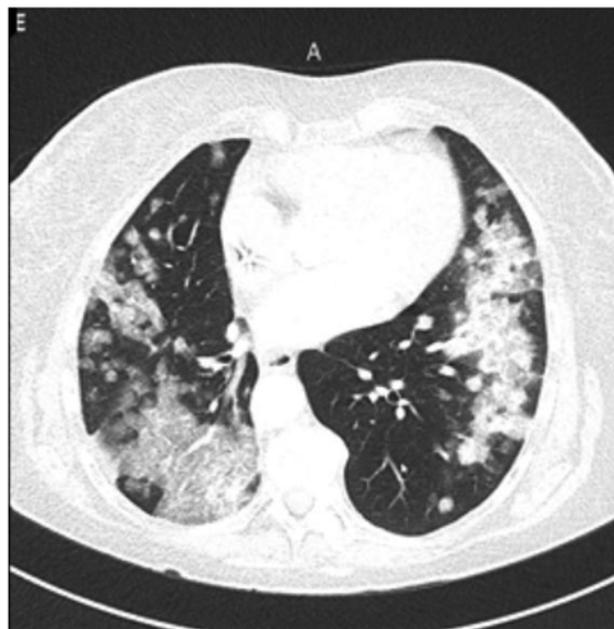


Figure 1. Chest CT of the first patient. Repeated CT demonstrated stable disease.

started metabolic treatment at 03/2013. The first CT scan 05/2013 demonstrated tumor progression but the next one, one month later showed stable disease. She had to be treated by radiation therapy because of extrinsic compression of bile ducts. She is alive in 12/13.

**Case 4.** The fourth patient was diagnosed with colonic adenocarcinoma T4N1 M1 with multiple liver metastases in 11/2011. Chemotherapy with 5-fluorouracil (5 FU) and oxaliplatin was ineffective. Oxaliplatin was switched to paclitaxel in 01/2013 and was also ineffective. He started metabolic treatment in 04/2013 and died two months later because of tumor progression.

**Case 5.** This 53-year-old lady was diagnosed in 09/2008 with metastatic ovarian carcinoma. She was first treated with paclitaxel, carboplatin and bevacizumab, then bevacizumab, caelix and cyclophosphamide, followed by immunotherapy. In 03/2013, she started metabolic treatment. In 05/2013, a pleural effusion was responsible for dyspnea. She started paclitaxel-based chemotherapy with oral metabolic therapy. The ovarian tumor has grown slowly since. A pleurodesis was performed late 09/2013. She died in 12/13 of tumor progression.

**Case 6.** The sixth patient is a 58-year-old man who had been diagnosed in 10/2011 with an adenocarcinoma of the

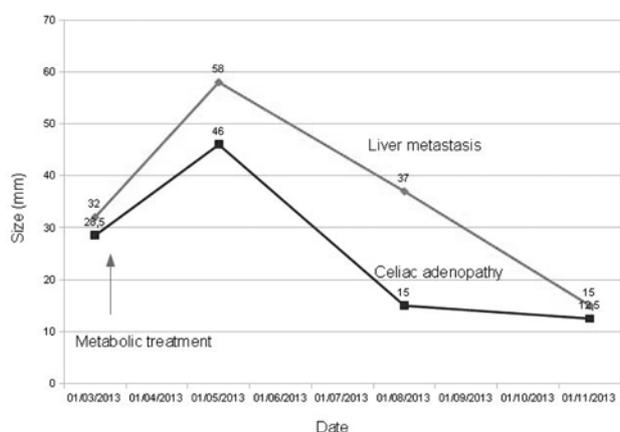


Figure 2. Response of the liver metastases of an adenocarcinoma of the esophagus to combined metabolic therapy and chemotherapy.

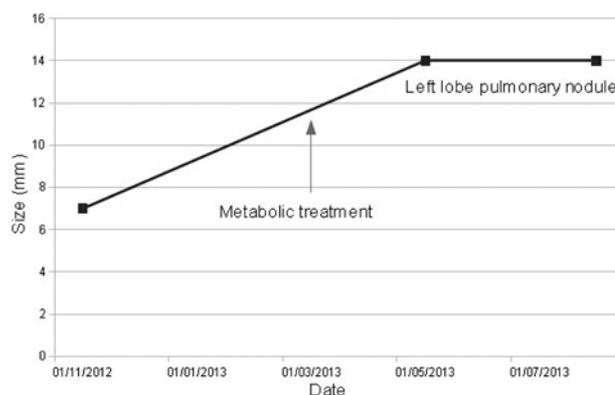


Figure 3. Response to metabolic treatment of a metastatic cholangiocarcinoma to the lung.

esophagus with multiples metastases to the liver and lymph nodes. FOLFOX (a combination of folinic Acid, 5 FU an oxaliplatin) was stopped in 04/2012 due to a complete response. Because of local and metastatic relapse, metabolic treatment was started in 03/2013 but failed to prevent massive tumor growth. In 05/2013, treatment was switched to chemotherapy with fluorouracil and irinotecan in combination with oral  $\alpha$ -LA, HCA and naltrexone. It resulted in massive tumor shrinkage. The last CT scan of late 11/2013 demonstrated partial regression of the liver metastases. Gastroscopy was negative. Karnofsky status was 90. Figure 2 shows the dramatic reduction of the tumor mass after a combination of chemotherapy and metabolic treatment.

*Case 7.* This 69-year-old lady was diagnosed with a sarcoma of the uterus in 2007. She was treated with surgery, postoperative radiation therapy and chemotherapy. She developed severe radiation enteritis resulting both in weight loss and in multiple surgeries. In 01/2013, the tumor relapsed with 14 different brain metastases, one of 30 mm in the frontal lobe. She was treated with palliative radiation therapy (30 Gy in 10 fractions). Living in a remote area, she could not undergo daily *i.v.* infusion. Because of low weight (45 kg), the doses were reduced. In early March 2013, she started oral R  $\alpha$ -LA at 650 mg/per day, HCA at 250 mg *t.i.d.* and naltrexone at 5 mg. The last Magnetic Resonance Imaging (MRI) dated 18th June showed almost complete disappearance of brain lesions. She is free of symptoms but had two episodes of seizure in late 09/2013. As of late 2013, she is living a normal life.

*Case 8.* This 53-year-old lady had a partial hepatectomy in 02/2012 for a T1N1M0 cholangiocarcinoma. Despite

FOLFOX, she developed multiple lung metastases in 6/12. Sutent was ineffective. She started metabolic treatment in 03/2013 with *i.v.*  $\alpha$ -LA at 600 mg, HCA at 500 mg *t.i.d.* and 5 mg naltrexone associated with sutent until 05/2013. CT scan showed no progression of the disease. The last PET scan of late August 2013 showed stabilization of the lung metastases but the appearance of small abdominal lymph node metastases (Figure 3). In 11/2013 there was a limited tumor progression and xeloda was added.

*Case 9.* The ninth patient is a 63-year-old man who was diagnosed in 08/2010 with metastatic adenocarcinoma to the bone and liver. No primary lesion was found. His tumor responded well to local radiation therapy and FOLFOX. In 01/2012, a PET scan was negative but demonstrated relapse in 06/2012. Palliative radiation therapy was effective and chemotherapy (gemcitabine) was started in 01/2013. Because of grade III toxicity, the patient stopped chemotherapy and switched to metabolic treatment in 04/2013. A PET scan in July 2013 showed the appearance of a new liver metastasis and regression of known metastatic lesions. In 10/2013, a PET scan showed increased tumor uptake in the liver; the patient was clinically well. He started a 40 days fast and was doing well in 12/2013.

*Case 10.* This 35-year-old lady presented with a parotid tumor which was first thought to be a pleomorphic adenoma in 01/2010. The tumor relapsed in the tumor bed in 11/2011. The draining lymph nodes were involved. Further surgery demonstrated parotid carcinoma. Multiple lung metastases were diagnosed in 10/2012. Chemotherapy with carboplatin and paclitaxel was ineffective. The addition of bevacizumab had no positive effect. In 06/2013, she started metabolic

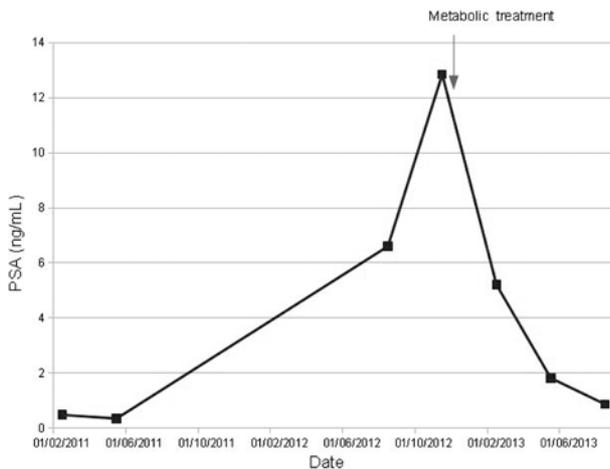


Figure 4. Dramatic decrease of PSA following metabolic treatment.

treatment. She experienced nausea and vomiting and had to switch two months later to a better tolerated oral form. In 09/2013, a CT scan demonstrated stabilization of disease.

**Case 11.** A 73-year-old patient had been diagnosed in 2005 with a high-grade prostate adenocarcinoma T3N0M0. Despite surgery and postoperative radiation therapy, the PSA level remained elevated. Treatment with decapeptyl was effective up to 01/2013. Because of marked increase in PSA, casodex was added. The patient was informed of the dismal prognosis of the disease. He decided by himself to add 600 mg  $\alpha$ -LA combined with HCA at 500 mg/day associated with casodex and decapeptyl. The level of PSA is shown in Figure 4.

## Discussion

Cancer is not only a disease of the genome but also a disease of the metabolism. Since the work of the Nobel Prize winner Otto Warburg, we know that the metabolism of cancerous cells clearly differs from that of normal cells (3, 15, 16). This is the actual basis for PET imagery, in which the *i.v.* injection of a radioactive substance similar to glucose is used to visualize the cancer and its metastases (17). This fact, which had long been forgotten, is starting to re-surface. A considerable amount of recent work shows that this metabolic disorder could be the source of cancer development (3, 18).

Interest in the Warburg effect waned considerably for a long period of time. Part of the reason was the fact that Warburg was convinced that the altered glucose metabolism in cancer cells was itself actually the cause of cancer and that the most likely explanation for his observation was damage

to the mitochondria (11). Since then, modern molecular biology has demonstrated that cancer cannot originate without a change to a cell's genome and that, at least in most cases; damage to the mitochondria is not the explanation for why many cancer cells adopt aerobic glycolysis as the principal pathway for glucose metabolism. However, during the past 15 years, there has been a considerable increase in interest regarding the Warburg effect and its role in cancer (7, 19-21).

There is considerable logic in targeting metabolic changes as an approach to the development of pharmaceutical agents to treat cancer. It has been hypothesized that this widespread prevalence is because aerobic glycolysis provides a competitive advantage to cancer cells, allowing the synthesis of compounds required for proliferation (3, 16).

A number of specific inhibitors of key enzymes involved in the aerobic glycolytic pathway have been evaluated as potential anticancer drugs (3, 22). However, few compounds have been used clinically, with a relative lack of success (22). This suggests that a single inhibitor of cancer cell metabolism might be insufficient to significantly inhibit cancer proliferation. Given the extreme plasticity of malignant tissue, it seemed logical to attempt to use at least two different compounds, each one targeted to interact with enzymes catalyzing different steps.

$\alpha$ -LA and HCA are products that in combination have strong antiproliferative effects against cancer cells, both *in vitro* and *in vivo*, by targeting the cell metabolism.

The biological rationale for the use of this combination comes from the fact that  $\alpha$ -LA and HCA target two major enzymes of the metabolism of glucose, namely pyruvate dehydrogenase (PDH) kinase (PDK) for  $\alpha$ -LA and ATP citrate lyase (ACL) for HCA. As described before, the Warburg effect results in the conversion of glucose into pyruvate and then into lactate, even in the presence of oxygen. By inhibiting PDK,  $\alpha$ -LA will increase the activity of PDH, resulting in the intra-mitochondrial use of pyruvate into the Krebs cycle over cytoplasmic conversion of pyruvate into lactate. HCA inhibits ATP ACL, limiting the conversion of cytoplasmic citrate into acetyl-CoA available for lipid synthesis. Effects of  $\alpha$ -LA and HCA would allow metabolic reprogramming of cancer cells into metabolism based on oxidative phosphorylation. This metabolic reprogramming would ultimately limit the availability of compounds required for proliferation (3, 16).

$\alpha$ -LA is a drug approved in several countries (including Austria and Germany) for the treatment of diabetic polyneuropathy. It is also sold over the counter as an antioxidant. The treatment protocol for diabetic polyneuropathy is 600 mg per day *i.v.* for two to four weeks followed by 600 mg per day of the oral form, with no indication of the duration of the maintenance treatment. Higher doses have been used in clinical trials for diabetic

polyneuropathy. McIluff and Rutkove reviewed five randomized clinical trials up to April 2011 for this indication (23). Two studies used the *i.v.* route alone and one study used both *i.v.* and oral routes. Based on these results, 600 mg per day *i.v.* for three weeks appears to be safe, with no more side-effects than with placebo, while 600 mg twice per day *i.v.* for three weeks was responsible for more side-effects than the placebo, but all were minor and reversible.

Another study on diabetic patients, this time to improve vascular endothelial function, used 600 mg *i.v.* per day for three weeks and authors reported “no adverse events or side-effects were detected in our study” (24). Other groups have reported daily *i.v.* administration of 600 mg of  $\alpha$ -LA for two to three weeks in pre-diabetic or diabetic patients, with no mention of serious adverse events (25-28), except for one patient who experienced chest distress, which resolved after lowering the velocity of administration (26).

In patients with cancer, two groups reported the use of *i.v.*  $\alpha$ -LA with no serious adverse effects. In Austria, Gedlicka used *i.v.*  $\alpha$ -LA to treat polyneuropathy in 14 patients who experienced symptoms due to treatment with docetaxel and cisplatin (28). Symptoms of polyneuropathy improved rapidly with 600 mg *i.v.* once a week for 3-5 weeks followed by 1800 mg orally twice daily until full recovery or for a maximum of six months. Apart from moderate gastric pain in two patients and WHO grade 1 and 2 nausea in one patient each, *i.v.*  $\alpha$ -LA did not cause any other adverse reactions.

Hydroxycitrate is sold over the counter for weight loss, although its efficacy for this purpose was not demonstrated in a well-conducted clinical trial (29). In that trial, 1500 mg of HCA were administered daily for 12 weeks. No patient was removed from the trial due to side-effects and no difference was observed in the type and frequency of side-effects between the HCA and the placebo groups.

According to Soni *et al.*, a total of 15 clinical studies involving approximately 914 subjects examining the effects of HCA have appeared in the literature (30). Except for two studies, the dosages of HCA ranged from 900 to 2800 mg/day. In 14 placebo-controlled, double blind trials and one single arm, open trial, employing up to 2800 mg/day HCA, no treatment-related adverse effects were reported.

Naltrexone is a drug approved for the treatment of opioid intoxication, and opioid and alcohol dependence. The interest of using low-dose naltrexone together with  $\alpha$ -LA and HCA to treat patients with cancer comes from several observations.

In the early 1980s, Zagon and McLaughlin reported an antiproliferative effect of naltrexone at low dose but not at standard dose (31). This was later confirmed by several groups and in several models (32-44). The exact mechanism of actions of this antiproliferative effect has not yet been elucidated. A role for the inhibition of the opioid growth factor receptor was suggested by Zagon and McLaughlin (31). The literature also suggests that naltrexone may be an

antagonist of toll-like receptor 4 (28). There is also evidence that naltrexone has an effect on the insulin growth factor pathway, which could also explain its antiproliferative effect. Naltrexone has been shown to be able to reverse insulin resistance and to reduce insulin-like growth factor I levels in patients (38-40). The insulin growth factor system is well known to play a role in tumor initiation and progression (41) and is the object of great interest in cancer research (42). Interest is even stronger for two of its downstream pathways, Phosphoinositide 3-kinase/Protein kinase B/Mammalian Target of Rapamycin (PI3K/Akt/mTOR) signaling and Mitogen Activated Protein/Extracellular signal-regulated kinase (MAP/ERK) pathway (41-43). Therefore, it is hypothesized that naltrexone could have an effect on the insulin growth factor system and downstream pathways, contributing to the metabolic reprogramming of cancer cells.

Low-dose naltrexone has been used in adults at the dose of 0.5 mg to 4.5 mg in several clinical trials for multiple sclerosis, fibromyalgia, Crohn's disease, irritable bowel syndrome, systemic sclerosis and complex regional pain syndrome (45-50). All side-effects reported were minor and the most frequent ones were vivid dreams (not usually reported as unpleasant), headaches and transient insomnia during a few days after initiation of the treatment. Other less frequent side-effects were stomatitis, atopic dermatitis, nausea, epigastric pain, mood alteration and joint pain. No grade III or IV side-effects and no serious adverse events were related to the study medication.

There is preliminary data reporting concomitant use of  $\alpha$ -LA and low-dose naltrexone (4.5 mg per day at bedtime) in patients with advanced cancer appears to be safe and has shown signs of efficacy in patients with advanced diseases reported by Berkson *et al.* (12, 13). Berkson *et al.* described five case reports indicating possible efficacy in several cancer types. They reported using  $\alpha$ -LA together with low-dose naltrexone in many patients with cancer. This series of patients is under evaluation by the best-case series methodology implemented by the US National Cancer Institute (NCI).

Our preliminary work strongly suggests the lack of major toxicity of metabolic treatment. The dose-limiting toxicity appears to be nausea and vomiting. Three patients tried to increase the dose of  $\alpha$ -LA to 1.2 g but complained of severe nausea. No attempt to increase the dose of HCA was reported.

## 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 most patients are alive and well several months after having sent home to die. Several months of life without symptoms strongly suggests that targeting cancer metabolism may be a reasonable option in advanced disease.

These results are in line with the previously published animal data (51).

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

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## References

- Schwartz L, Abolhassani M, Guais A, Sanders E, Steyaert JM, Campion F and Israel M: A combination of alpha-lipoic acid and calcium hydroxycitrate is efficient against mouse cancer models: Preliminary results. *Oncol Rep* 23: 1407-1416, 2010.
- Abolhassani M, Guais A, Sanders E, Campion F, Fichtner I, Bonte Jacques, Baronzio G, Fiorentini G, Israel M and Schwartz L: Screening of well-established drugs targeting cancer metabolism: Reproducibility of the efficacy of a highly effective drug combination in mice. *Invest New Drugs* 4: 1331-1342, 2012.
- Israel M and Schwartz L: The metabolic advantage of tumor cells. *Mol Cancer* 10: 70-85, 2011.
- Warburg O: On the origin of cancer cells. *Science* 123: 309-314, 1956.
- Gatenby RA and Gillies RJ: Why do cancers have high aerobic glycolysis? *Nat Rev Cancer* 11: 891-899, 2004.
- Bui T, Thompson CB. Cancer's sweet tooth. *Cancer Cell* 9: 419-420, 2006.
- Gatenby RA, Gawlinski ET, Gmitro AF, Kaylor B and Gillies RJ: Acid-mediated tumor invasion: a multidisciplinary study. *Cancer Res* 66: 5216-5223, 2006.
- Pelicano H, Martin DS, Xu R-H and Huang P: Glycolysis inhibition for anticancer treatment. *Oncogene* 25(34): 4633-4646, 2006
- Moreno-Sanchez R, Rodríguez-Enríquez S, Marín-Hernández A and Saavedra E: Energy metabolism in tumor cells. *FEBS* 274(6): 1393-1418, 2007.
- Guais A, Baronzio G, Sanders E, Campion F, Mainini C, Fiorentini G *et al*: Adding a combination of hydroxycitrate and lipoic acid (METABLOCTM) to chemotherapy improves effectiveness against tumor development: experimental results and case report. *Invest New Drugs* 30(1): 200-211, 2012.
- Baronzio G, Schwartz L, Crespi E, Guais A, Sanders E, Delépine N and Fiorentini G: Early clinical and toxicological results of a combination of natural glycolysis inhibitors (METABLOC™) on cancer patients. *BIOMEDICAL RESEARCH-INDIA* (no pubmed indexation) 23: 219-223, 2012.
- Berkson BM, Rubin DM and Berkson AJ: The long-term survival of a patient with pancreatic cancer with metastases to the liver after treatment with the intravenous alpha-lipoic acid/low-dose naltrexone protocol. *Integr Cancer Ther* 5: 83-89, 2006.
- Berkson BM, Rubin DM and Rubin AJ: Revisiting the alpha-LA/N (alpha-lipoic acid/low dose naltrexone) protocol for people with metastatic and nonmetastatic pancreatic cancer: a report of three new cases. *Integr Cancer Ther* 8: 416-422, 2009.
- Lee K, Khaira D, Rodriguez R, Mauro C, O'Donnell K and Shorr R: Case study: long-term stable disease of stage IV pancreatic neuroendocrine tumors and without significant adverse effect by CPI-613, an investigational novel anticancer agent. *Case Study Case Report 1*: 137-145, 2011.
- Warburg O. On the origin of cancer cells. *Science* 123: 309-314, 1956.
- Vander Heiden MG, Cantley LC and Thompson CB: Understanding the Warburg effect: the metabolic requirements of cell proliferation. *Science* (New York, NY) 324: 1029-1033, 2009.
- Gambhir SS: Molecular imaging of cancer with positron emission tomography. *Nat Rev Cancer* 2: 683-693, 2002.
- Levine AJ and Puzio-Kuter AM: The control of the metabolic switch in cancers by oncogenes and tumor suppressor genes. *Science* 330: 1340-1344, 2010.
- Cairns RA, Harris IS and Mak TW: Regulation of cancer cell metabolism. *Nat Rev Cancer* 11: 85-95, 2011
- Pan JG and Mak TW: Metabolic targeting as an anticancer strategy: dawn of a new era? *Sci STKE* 2007: e14, 2007.
- Tomita M and Kami K: Cancer. Systems biology, metabolomics, and cancer metabolism. *Science* 336: 990-991, 2012.
- Porporato PE, Dhup S, Dadhich RK, Copetti T and Sonveaux P: Anticancer targets in the glycolytic metabolism of tumors: a comprehensive review. *Front Pharmacol* 2: 49, 2011
- McIllduff CE and Rutkove SB: Critical appraisal of the use of alpha lipoic acid (thioctic acid) in the treatment of symptomatic diabetic polyneuropathy. *Therapeutics and Clinical Risk Management* (no pubmed indexation) 7: 377-385, 2011.
- Heinisch BB, Francesconi M, Mittermayer F, Schaller G, Gouya G, Wolzt M *et al*: Alpha-lipoic acid improves vascular endothelial function in patients with type 2 diabetes: a placebo-controlled randomized trial. *European Journal of Clinical Investigation* (no pubmed indexation) 40: 148-154, 2010.
- Ametov AS, Novosadova M V, Barinov AN, Samigullin R, Trischler H-J: Long-term effect of 3-week intravenous alpha-lipoic acid administration in symptomatic diabetic polyneuropathy with clinical manifestations. *Terapevticheski Arkhiv* 82: 61-64, 2010.
- Mittermayer F, Pleiner J, Francesconi M and Wolzt M: Treatment with alpha-lipoic acid reduces asymmetric dimethylarginine in patients with type 2 diabetes mellitus. *Translational Research: the Journal of Laboratory and Clinical Medicine* 155: 6-9, 2010.
- Liu F, Zhang Y, Yang M, Liu B, Shen Y, Jia W-P and Xiang K: Curative effect of alpha-lipoic acid on peripheral neuropathy in type 2 diabetes: a clinical study. *Zhonghua Yi Xue Za Zhi* 87: 2706-2709, 2007.
- Gedlicka C: Amelioration of docetaxel/cisplatin induced polyneuropathy by alpha-lipoic acid. *Annals of Oncology* 14: 339-340, 2003.
- Heysmsfield S and Allison D: Garcinia cambogia (hydroxycitric acid) as a potential antiobesity agent. *JAMA: The Journal of The American Medical Association* 280-288, 1998.

- 29 Soni MG, Burdock G a, Preuss HG, Stohs SJ, Ohia SE and Bagchi D: Safety assessment of -hydroxycitric acid and Super CitriMax, a novel calcium/potassium salt. *Food and Chemical Toxicology: an International Journal Published for the British Industrial Biological Research Association (no pubmed indexation) 42*: 1513-1529, 2004.
- 30 Zagon IS and McLaughlin PJ: Naltrexone modulates tumor response in mice with neuroblastoma. *Science (New York, NY) 221*: 671-673, 1983.
- 31 Koo KL, Tejwani GA and Abou-Issa H: Relative efficacy of the opioid antagonist, naltrexone, on the initiation and promotion phases of rat mammary carcinogenesis. *Anticancer Res 16(4A)*: 1893-1898, 1996.
- 32 Abou-Issa H and Tejwani GA: Antitumor activity of naltrexone and correlation with steroid hormone receptors. *Biochemical and Biophysical Research Communications 175*: 625-630, 1991.
- 33 Donahue RN, McLaughlin PJ and Zagon IS: The opioid growth factor (OGF) and low dose naltrexone (LDN) suppress human ovarian cancer progression in mice. *Gynecologic Oncology 122*: 382-388, 2011.
- 34 Donahue RN, McLaughlin PJ and Zagon IS: Low-dose naltrexone suppresses ovarian cancer and exhibits enhanced inhibition in combination with cisplatin. *Experimental Biology and Medicine (Maywood, NJ) 236*: 883-895, 2011.
- 35 McLaughlin PJ and Zagon IS: The opioid growth factor-opioid growth factor receptor axis: homeostatic regulator of cell proliferation and its implications for health and disease. *Biochemical Pharmacology 84*: 746-756, 2012.
- 36 Chopra P and Cooper MS: Treatment of Complex Regional Pain Syndrome (CRPS) Using Low Dose Naltrexone (LDN). *Journal of NeuroImmune Pharmacology: the Official Journal of the Society on NeuroImmune Pharmacology 8*: 470-476, 2013.
- 37 Ahmed MI, Duleba a J, El Shahat O, Ibrahim ME and Salem A: Naltrexone treatment in clomiphene resistant women with polycystic ovary syndrome. *Human Reproduction (Oxford, England) 23*: 2564-2569, 2008.
- 38 Guido M, Pavone V, Ciampelli M, Murgia F, Fulghesu a M, Apa R *et al*: Involvement of ovarian steroids in the opioid-mediated reduction of insulin secretion in hyperinsulinemic patients with polycystic ovary syndrome. *The Journal of Clinical Endocrinology and Metabolism 83*: 1742-1745, 1998.
- 39 Zangeneh FZ, Mohammadi A, Ejtemaieimehr S, Naghizadeh MM and Fatemeh A: The role of opioid system and its interaction with sympathetic nervous system in the processing of polycystic ovary syndrome modeling in rat. *Archives of Gynecology and Obstetrics 283*: 885-892, 2011.
- 40 Arcidiacono B, Iiritano S, Nocera A, Possidente K, Nevolo MT, Ventura V, Foti D and Brunetti A: Insulin resistance and cancer risk: an overview of the pathogenetic mechanisms. *Experimental Diabetes Research 2012*: 789174, 2012.
- 41 Atzori F, Traina TA, Ionta MT and Massidda B: Targeting insulin-like growth factor type 1 receptor in cancer therapy. *Target Oncol 4*: 255-256, 2009.
- 42 Rodon J, Dienstmann R, Serra V and Taberero J: Development of PI3K inhibitors: lessons learned from early clinical trials. *Nature Reviews Clinical Oncology 10*: 143-153, 2013.
- 43 Yang W, Zheng Y, Xia Y, Ji H, Chen X, Guo F *et al*: ERK1/2-dependent phosphorylation and nuclear translocation of PKM2 promotes the Warburg effect. *Nature Cell Biology 14*: 1295-1304, 2012.
- 44 Kariv R, Tiomny E, Grenshpon R, Dekel R, Waisman G, Ringel Y *et al*: Low-dose naltrexone for the treatment of irritable bowel syndrome: a pilot study. *Digestive Diseases and Sciences 51*: 2128-2133, 2006.
- 45 Sharafaddinzadeh N, Moghtaderi A, Kashipazha D, Majdinasab N and Shalbafan B: The effect of low-dose naltrexone on quality of life of patients with multiple sclerosis: a randomized placebo-controlled trial. *Multiple Sclerosis (Houndmills, Basingstoke, England) 16*: 964-969, 2010.
- 46 Cree B a C, Kornyeveva E and Goodin DS: Pilot trial of low-dose naltrexone and quality of life in multiple sclerosis. *Annals of Neurology 68*: 145-150, 2010.
- 47 Younger J, Noor N, McCue R and Mackey S: Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. *Arthritis and Rheumatism 65*: 529-538, 2013.
- 48 Younger J and Mackey S: Fibromyalgia Symptoms Are Reduced by Low-Dose Naltrexone: A Pilot Study. *Pain Medicine 10*: 663-770, 2009.
- 49 Frech T, Novak K, Revelo MP, Murtaugh M, Markewitz B, Hatton N *et al*: Low-dose naltrexone for pruritus in systemic sclerosis. *International Journal of Rheumatology 2011*: 804296, 2011.
- 50 Israël M and Schwartz L: *Cancer: A Dymethylation Syndrome*. John Libbey Eurotext, 2005.

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