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Chlorine dioxide as a possible adjunct to metabolic treatment

Laurent Schwartz
Assistance Publique des Hôpitaux de Paris, Avenue Victoria 75003 Paris, France

Article Info

*Correspondence:
Dr. Laurent Schwartz, M.D.
Assistance Publique des Hôpitaux de Paris, Avenue Victoria
75003 Paris, E-mail: dr.laurentschwatz@gmail.com

ABSTRACT

A first patient with metastatic adenocarcinoma of the pancreas has decided, on his own, to refuse chemotherapy but to treat himself with lipoïc acid, hydroxycitrate combined with oral ingestion of chlorine dioxide. His blood tests and radiological examinations have almost normalized and the disease is stable at 18 months. Another patient with hormone resistant metastatic prostate cancer has experienced a sharp drop in PSA level as well as improved medical condition. From extensive literature review, the mechanism of action of chlorine dioxide is unknown. It is our hypothesis (albeit unproven) that chlorine dioxide results in tumor cell acidification of the alkaline pH of cancer cells.

Introduction: Cancer is a fermentation process

In the early 1920's Otto Warburg demonstrated a unique feature of cancer cells, namely an increased uptake of glucose and secretion of lactic acid by cancer cells, even in the presence of oxygen (e.g. the aerobic glycolytic phenotype)[1,2]. This aerobic fermentation is the signature of cancer[3]. Warburg also noticed a concomitant decreased number of mitochondria (grana)[4]. In normal, differentiated cells, the yield of a molecule of glucose is 34 ATP. ATP is derived mostly from oxidative phosphorylation which takes place in the mitochondria[5,6]. In the absence of mitochondria the energy yield drops to two molecules of ATP per molecule of glucose[5,6]. As stated by Warburg in the 1920's, in cancer cells there is a decreased efficacy of the mitochondria resulting in lesser yield. Despite increased glucose uptake, there is a 50% drop in ATP level in human colon cancer cells compared to adjacent benign cells[7]. This decrease in ATP is a consequence of impairment of the oxidative phosphorylation[6–9].

To compensate for the decreased energy yield, the cell increases its glucose uptake[7,10]. The decreased activity of the mitochondria has many consequences, one of which is an increased secretion of lactic acid and another one is the activation of the pentose phosphate pathway (PPP). Another consequence is the activation of the glutaminolysis which is necessary for nucleic acid synthesis[6–9].

The activation of the Pentose Phosphate Pathway results from an increase in glucose uptake with a concomitant obstacle downstream of the pentose phosphate shunt, most probably at the level of pyruvate dehydrogenase and/or of pyruvate kinase[2,6,11]. The increased flux in the pentose phosphate pathway results in:

A shift toward anabolism due to increased synthesis of NADPH that plays a crucial role in NADPH/NADP+ ratio that determines

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the redox state of the cell via removal of reactive oxygen species (ROS) and so prevents cellular death and controls cellular fate[7,11].

The shift toward the pentose pathway also results in the production of ribose-5-phosphate, required for the synthesis of nucleic acids[5].

One other crucial consequences of the mitochondrial defect is intracellular alkalosis[7]. Tumors show a 'reversed' pH gradient with a constitutively increased intracellular pH that is higher than the extracellular pH. This gradient enables cancer progression by promoting proliferation, the evasion of apoptosis, metabolic adaptation, migration, and invasion[12–15].

There is evidence that an acidic extracellular pH promotes invasiveness and metastatic behaviour in several tumor models[14,16], proteolytic enzyme activation and matrix destruction[17–19].

In normal cells, the intracellular pH (pHi) oscillates during the cell cycle between 6.8 and 7.3[7]. The oscillation of the pH during the cell cycle matches the value of the decompaction of the histones, RNA polymerase activation, DNA polymerase activation and DNA compaction before mitosis[7,11].

The intracellular pH of the cancer cells has been less studied. During the cell cycle, it oscillates between 7.2 and 7.5. Intracellular alkalosis is probably a consequence of the decreased oxidative phosphorylation resulting in decreased secretion of carbon dioxide (CO_2) and the CO_2 reacts with water to create carbonic acid. Cell transformation or enhanced cancer cell division and resistance to chemotherapy are all associated with a more alkaline pHi[20–23].

The Warburg effect may be a direct consequence of the activation of oncogenes[6]. Infection by an oncogenic virus or exposure to a carcinogen inhibits the mitochondrial function and causes the Warburg's effect[24–29].

Reversing the Warburg inhibits tumor growth

The introduction of normal mitochondria into cancer cells restores mitochondrial function, inhibits cancer cell growth and reverses chemoresistance[30-35]. Also the fusion of cancer cells with normal mitochondria results in increased ATP synthesis, oxygen consumption and respiratory chain activities together with marked decreases in cancer growth, resistance to anti-cancer drugs, invasion, colony formation in soft agar, and « in vivo » tumor growth in nude mice[31].

As the Warburg aerobic glycolytic phenotype and its effects on metabolism are key to cancer, the obvious question is whether drugs can be designed to target it. To alleviate the Warburg effect, pyruvate should be converted into Acetyl-CoA, which would decrease the bottleneck that results in the activation of both the Pentose Phosphate Pathway and the glutaminolysis. The mitochondrial yield should be increased to stimulate the synthesis of CO_2 and the increased secretion of CO_2 would result in a decreased intracellular alkalosis.

The combination of α-lipoïc acid and hydroxycitrate[36–39] has been reported to slow cancer growth, in murine xenografts. This inhibition appears to be independent of the primary tumor site and has been reproduced in different laboratories[40,41].

The most likely mechanism of action for α-lipoïc acid in its reduction of tumor growth is the inhibition of pyruvate dehydrogenase kinase (the same target of Dichloroacetic acid (DCA)). This enzyme inhibits the activity of pyruvate dehydrogenase and is known to be up-regulated in cancer cells expressing the Warburg aerobic glycolytic phenotype. Pyruvate dehydrogenase catalyses the conversion of pyruvate to acetyl-CoA, the initial step of the final conversion of glucose to carbon dioxide and water in the TCA cycle, with the concomitant production of ATP. Therefore, it is reasonable to suggest that blocking the activity of pyruvate dehydrogenase kinase will at least partially restore the activity of pyruvate dehydrogenase, thereby increasing the flux of pyruvate through the TCA cycle in the mitochondria, while simultaneously reducing the production of lactic acid and most importantly decreasing the flux in the pentose pathway shunt[9].

There are several reports of metabolic treatment utilizing a combination of α-lipoïc acid and hydroxycitrate together with conventional cancer therapy. Starting in January 2013, metabolic treatment (α-lipoïc acid/ hydroxycitrate with low doses of chemotherapy plus Naltrexone) was offered to patients sent home after the failure of conventional cytotoxic chemotherapy for metastatic cancer (irrespective of the primary site) but with a Karnovsky performance status above 70 (quantification cancer patients' general well-being and activities of daily life)[42–46]. Of the first randomly selected eleven patients, five were alive and reasonably well 30 months after the start of treatment[43-45].

In the update of a subsequent study, patients with multiple brain metastasis (n=4) or glioblastoma (n=6) were treated with a combination of conventional and metabolic treatments (α-lipoïc acid/hydroxycitrate) as well as ketogenic diet. Five out of six patients with glioblastoma were alive and stable after two years, while two of the four patients with multiple brain metastases are alive and well three years later[46,47].

Cases reports

Patient number 1

The first case is a 65 year old French gentleman

with biopsy-proven unresectable well differentiated adenocarcinoma of the pancreas in June 2016 . The cholestasis was treated by a derivation in December 2016 which was effective in alleviating the obstruction. The tumor markers (CA 19-9 and CEA) were uninformative. The patient subsequently refused chemotherapy and decided by himself to start a treatment involving

1) Ketogenic diet

2) Lipoïc acid 800 mg twice a day and hydroxycitrate 500mg three times a day

3) Chlorine dioxide up to 32 drops per day. Chlorine dioxide was produced by the activation of NaCLO2 by 4% HCl. The activation time takes 3mn and a drop contains around 86 micromoles of CLO2 if the activation is total.

As of 9/2017, the patient was living normally, the blood tests were normal, the tumour mass such as seen on CT scan had grown from 3 to 5 cm. No side effects were noted. There was ne concomitant chemotherapy or radiation therapy.

Patient number 2

Having heard of the first case, a second patient started a similar treatment. He is a 67-year-old man. He was diagnosed in 8/16 with Gleason 8 adenocarcinoma of the prostate responsible of a cord compression that was successfully treated by laminectomy and post op radiationtherapy. At the start of disease PSA was 1320. Degarelix was started in 8/16 with concomitant ketogenic diet. Because of partial responds chemotherapy with Docetaxel (150mg IV) was started in December 2016. Chemotherapy was discontinued after two cycles because of poor tolerance. Simultaneously, starting In mid November metabolic treatment with lipoïc acid as well as hydroxycitrate. He performs weekly assessment of his PSA.

End of march, the PSA had dropped to 27 and stayed at this value up to beginning of June, but started increasing,
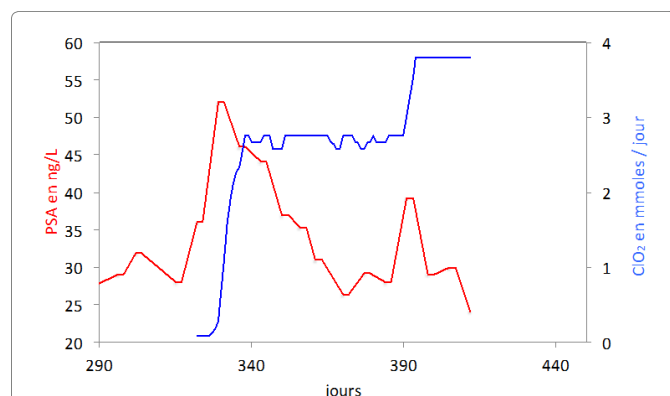

Figure 1: Evolution of the PSA following ClO2 intake in micromole/day in combination with Metabolic treatment.

in three weeks from 27 to 52 (figure 1). Metastatic pain increased and was responsible of Karnovsky of 70. At that stage the patient started to take chloride dioxide. The PSA dropped linearly for eight weeks to 26. The patient took eight times a day, 344 micromoles of chlorine dioxide. After these eight weeks of decrease, the PSA started to increase in three weeks from 26 to 39. At that stage, metastatic pain, which has almost completely disappeared, was responsible of insomnia. He started to take chlorine dioxide drops not only during the daytime but also every 90 minutes at night. Nightly metastatic pain decreased drastically from day one, and the second part of the night was practically pain free. The PSA decreased again linearly from 39 to 24.

Discussion and conclusion

Chlorine dioxide is a poorly studied chemical entity. The mechanism of action of ClO2 is poorly understood. It is our hypothesis that chlorine dioxide decreased the intracellular pH. We are currently running experiments to confirm/infirm this hypothesis. Correcting the intracellular pH may be an alternative or an adjunct to a metabolic treatment as there is extensive literature that many effective cancer treatments decrease the intracellular pH (pHi)[2,23,47]: literature on increased survival support for the combined use of antacids (which prevent proton extrusion from the tumour cells) with standard chemotherapy[15,48–50].

Today, cancer is thought to be a set of very complex diseases with thousands of different mutations. That apparent complexity has led to personalized medicine. However, modern biology has confirmed the universality of the Warburg aerobic glycolytic phenotype. Furthermore, the fact that the combination of α-lipoïc acid and hydroxycitrate slows down cancer growth in every tumor model studied to date suggests that at least some targets are the same in a large spectrum of tumors.

It is possible that the addition of chlorine dioxide increases the response to metabolic treatment.

Acknowledgement

Conflict of interest

None

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