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The addition of chloroquine and metformine to Metabloc induces a rapid drop of tumor markers in advanced carcinoma

Research Article

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Summary

Background: The combination of hydroxycitrate and lipoic acid has been demonstrated to be effective in reducing murine cancer growth. Early reports suggest a major efficacy in advanced human cancer.

Patients and Methods: Three patients with advanced, chemoresistant cancer were treated by a combination of lipoic acid and hydroxicitrate (Metabloc™) followed by the addition of metformin and chloroquine. Another patient was treated with a combination of Metabloc and cycloserine

Results: Side effects of metabolic treatment are mild. Treatment with Metabloc resulted in a transient drop in tumor marker. The addition of chloroquine and metformin resulted, within one week, in further decrease in tumor marker level. Whether this drop in marker will be sustained is an open question.

These results are in line with published animal data. They also put in evidence the extreme reactivity and variability of cancerous cells. Randomized clinical trials are being defined to confirm the major efficacy of metabolic treatment.

I. Introduction:

The alteration of glucose metabolism in cancer was first described by Warburg almost 90 years ago (Warburg, 1956). 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. The pentose phosphate shunt is necessary for the synthesis of DNA and RNA (Abolhassani et al, 2012; Israël and Schwartz, 2011; Schwartz et al, 2010; Gatenby and Gillies, 2004; Bui and Thompson, 2006; Israël and Schwartz, 2005; Pelicano et al, 2006; Moreno-Sánchez et al, 2007). In cancer cells, the Krebs cycle is also abnormal, with citrate flowing outside the mitochondria to contribute to lipid synthesis (Warburg, 1956; Abolhassani et al, 2012; Israël and Schwartz, 2011).

A combination of lipoic acid (α-LA) and hydroxicitrate (HCA) designated as MetablocTM has been shown to decrease the speed of tumor growth in various animal models with an efficacy similar to that of conventional chemotherapies (Abolhassani et al, 2012).

Phase I trials demonstrated only mild side effects (Guais et al, 2012; Baronzio et al, 2012).

In a subsequent preliminary study, low dose naltrexone was added to a combination of lipoic acid and hydroxycitrate. There were ten patients with very advanced cancer. The toxicity was limited to transient nausea (Schwartz et al, 2014; Schwartz et al; Van der Heiden et al, 2009). Two patients died of progressive disease within two months. Two other patients had to be treated again by conventional chemotherapy combined with metabolic treatment; one of them had a subsequent dramatic tumor regression. Disease in the other patients was either stable or very slowly progressive compared to expected development. The goal of this study is to assess if further improvement in metabolic treatment could result in tumor decrease.

II. Patients:

These four consecutive patients had advanced chemoresistant cancers. They were not offered any alternative chemotherapy but best supportive care. The details of the previous chemotherapy are given later.

They all received as a first line metabolic treatment 1,600 mg oral lipoic acid (Tiobec Laborest Italy), 500 mg hydroxycitrate (Garcinia Cambodgia extract) t.i.d. (Solgar Marne la Vallée France) and low-dose naltrexone (5 mg, Revia, Bristol-Myers Squibb, Rueil- Malmaison, France) at bedtime.

At time of relapse, the patients continued metabolic treatment and received 500 mg metformin t.i.d. (Glucophage Merck Lyon France) and chloroquine 100 mg (Nivaquine Sanofi-Aventis Paris France).

One patient was treated with cycloserine (Mac Leods Pharmaceutical India) 200 mg b.i.d.

II.A. Case 1

This 72-year-old man has metastatic adenocarcinoma of the colon diagnosed thirteen years ago. He had failed three different lines of chemotherapy most recently, Capecitabine and Bevacizumab. In late december 2013, CT scan demonstrated massive local recurrence with a 6 by 6 cm tumor mass with invasion of the sacrum, the bladder and the surrounding soft tissue. The CEA level had been between 32 and

36 ng/ml. He started metabolic treatment at the end of 2013 and within one week the level of CEA had dropped to 10. The level remained stable for two and a half months when it started to climb again to 15.

The addition of Metformin and Chloroquine induced further drop in CEA. (**Figure 1**)

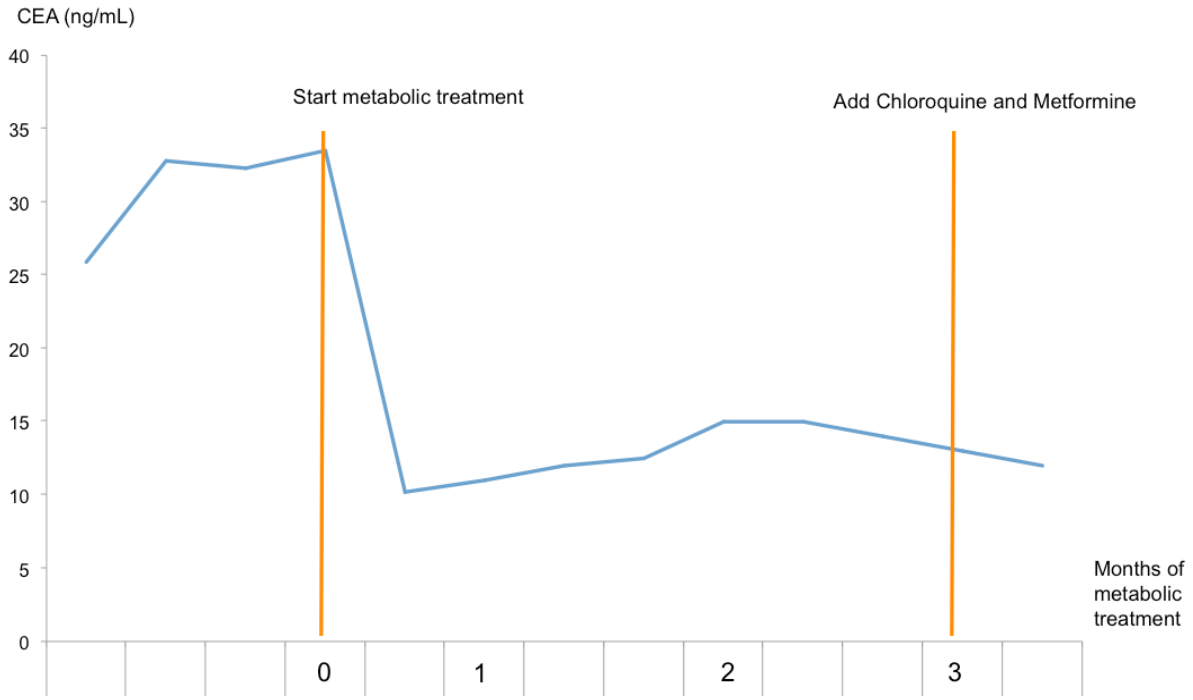

Figure 1. Case 1 – Metastatic adenocarcinoma of colon (diagnosed 2001)

II.B. Case 2

This 77-year-old lady has metastatic adenocarcinoma of the ovary diagnosed in 2010 because of voluminous ascites. She failed four different lines of chemotherapy. She stopped Gemcitabine in November because of tumor progression. The level of CA 125 dropped from 175 to 104 but to resume an increase in mid-January, after two months. The addition of Gemcitabine to metabolic treatment was ineffective and was stopped at the end of January. At the end of February 2014 the CA 125 had risen to 189, when metformin and chloroquine were added to metabolic treatment. The CA 125 level dropped to 150 within one week. (**Figure 2**).

II.C. Case 3

This 71-year-old lady was diagnosed as a stage IV adenocarcinoma of the ovary in 2012. Chemotherapy with Placlitaxel and Carboplatin resulted in a marked decrease in the tumor marker CA 125. Further chemotherapy with Betuximab and Doxorubicin did not prevent a massive pleural effusion and ascitis. In December 2013, she started with low dose Naltrexone, Metabloc and Cycloserine. She has been stable since. The tumor marker has been unchanged. (**Figure 3**)

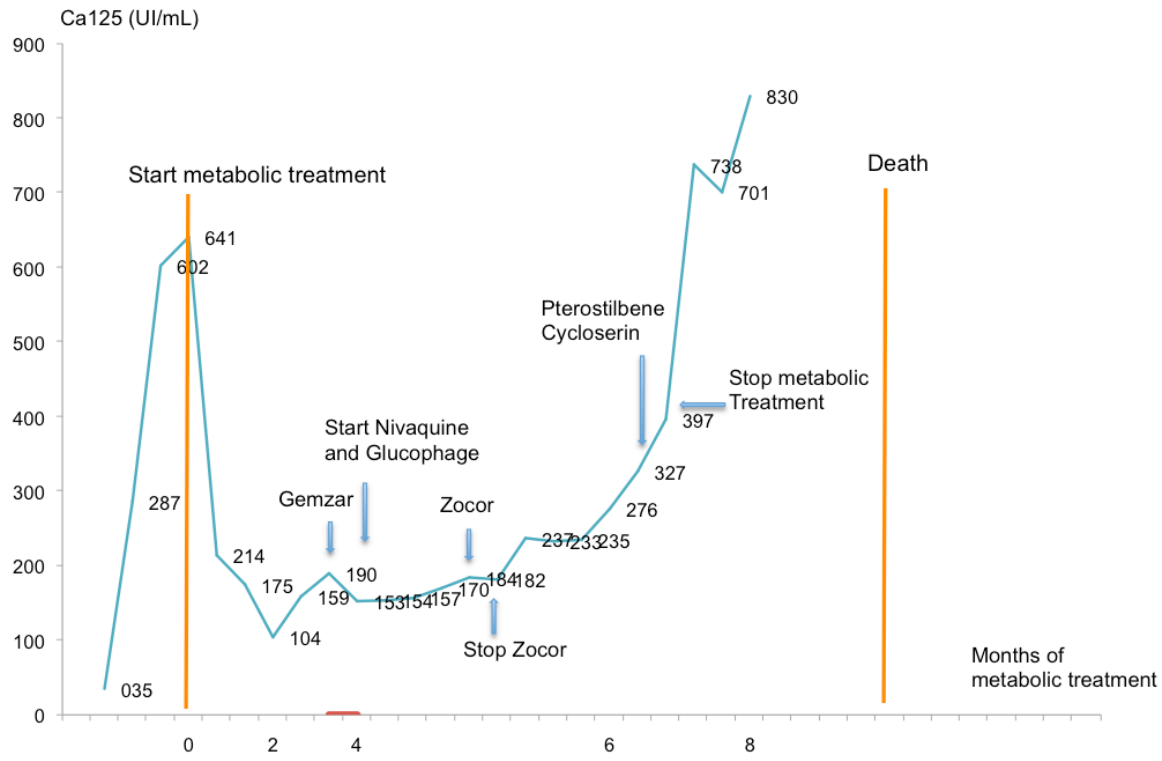

Figure 2. Case 2 – Metastatic adenocarcinoma of the ovary (diagnosed 2010)

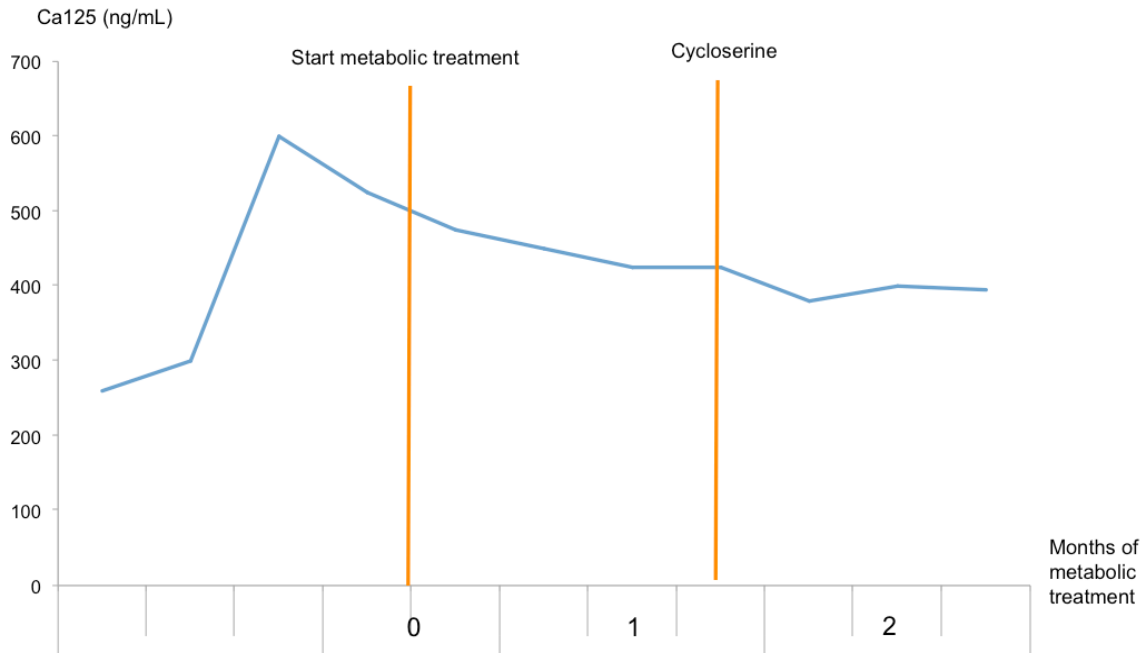

Figure 3. Case 3 – Stage IV adenocarcinoma of ovary (diagnosed 2012)

II.D. Case 4

The last patient, a 56-year-old female, was diagnosed in 2008 with metastatic adenocarcinoma of the colon to the liver. She was treated with multiple surgical procedures to remove liver metastasis by radiofrequency ablation of lesions as well as three different lines of intravenous chemotherapy. Carcino embryonic antigen (CEA) has been considered as a reliable tumor marker in her case. Because of tumor progression, she started metabolic treatment in July 2013. The CEA dropped from 234 ng/ml to 210 in October. CT scan showed stable disease. Along November, CEA level had risen from 390 to 590 in December. At that stage, Capecitabine was added. The tumor responded briefly with a drop to 348 before an increase to 866 in early February 2014. At that stage Capecitabine was stopped and within two weeks the CEA had risen to 2156. At that stage the patient had become febrile and bed ridden. There was no sign of infection. She started Metformine and Chloroquine in addition with the metabolic treatment. Within a few days, there was a clear and rapid drop in tumor marker: fever disappeared. Moreover, within a week of inception of treatment CRP dropped from 255 mg/l to 41. There was no side effect of metabolic treatment. The CEA fell down to 328 but two weeks later --- when writing this report --- has climbed to 466. (**Figure 4**)

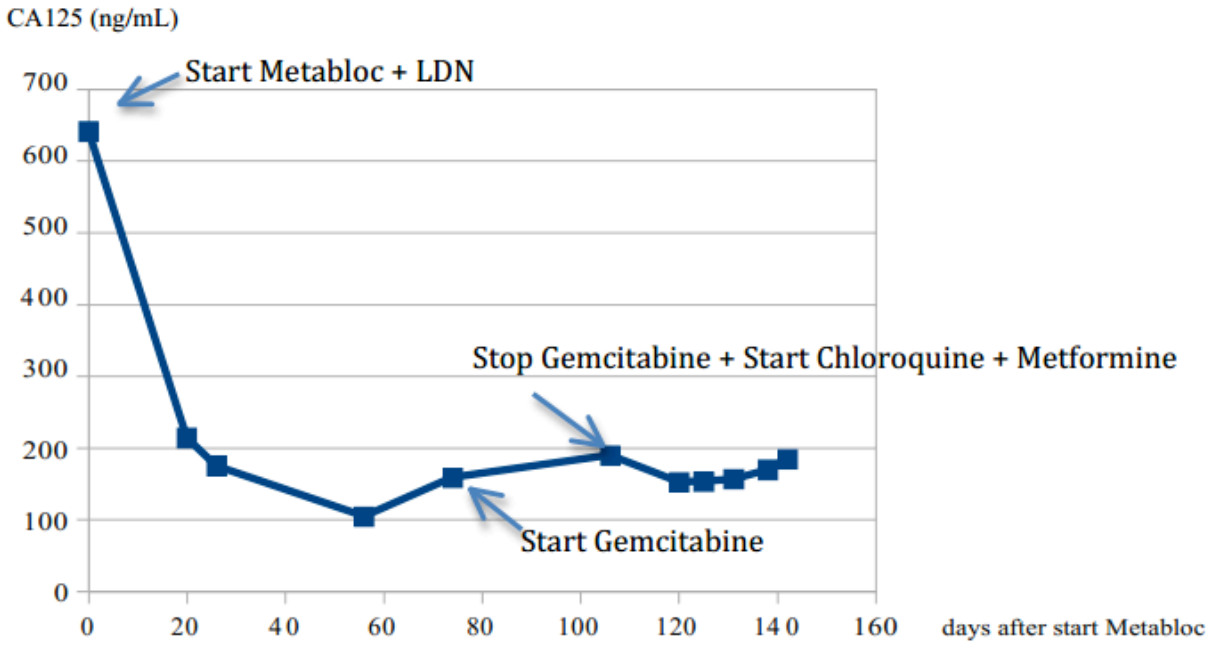

Figure 4. Case 4 – Metastatic adenocarcinoma of colon + liver (diagnosed 2008)

III. Discussion:

Cancer is not only a disease of the genome but also a disease of the metabolism. Since the work of O. Warburg, we know that the metabolism of cancerous cells clearly differs from that of normal cells (Israël and Schwartz, 2011; Schwartz et al, 2010; Van der Heiden et al, 2009). Previous

studies suggest that a combination of hydroxycitrate and lipoic acid slows down human tumor growth (Schwartz et al, 2014; Schwartz et al; Van der Heiden et al, 2009).

In a previous study we showed (Van der Heiden et al, 2009) that a treatment with these food suppléments induced a rapid fall in PSA in advanced prostate cancer. To our surprise, we notice a similar drop of tumor marker in advanced colon and ovarian cancers. It is uncommon to notice such as a speedy decline in chemotherapy treated patients. Most protocols request measurement of tumor marker usually every three months. This quick response suggests that the level of tumor marker could be used to adapt metabolic treatment within days of inception of treatment.

The logic for the combination of lipoic acid and hydrocitrate has been explained elsewhere (Israël and Schwartz, 2011; Israël and Schwartz, 2005). Briefly α-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 α-LA and HCA target two major enzymes of the metabolism of glucose, namely pyruvate dehydrogenase kinase (PDK) for α-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, α-LA will increase the activity of pyruvate dehydrogenase (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 α-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 (Israël and Schwartz, 2011; Schwartz et al, 2014).α-LA is a drug approved in several countries for the treatment of diabetic polyneuropathy. It is also sold over the counter as an antioxidant (McIlduff and Rutkove, 2011).

Hydroxycitrate is sold over the counter for weight loss, although its efficacy for this purpose was not demonstrated in a well-conducted clinical trial (Heymsfield and Allison, 1988). Metformin is a well known drug widely prescribed in the treatment of diabetes. Recently, Metformin has been demonstrated to be active as a cancer drug (Rizos and Elisas, 2013). Its mechanism of action remains unclear (Mc Carthy, 1998; Letteri et al, 2014). It increases the action of HCA and like HCA decreases tumor lipid synthesis.

Chloroquine is a widely prescribed anti-malarial drug. It has been shown to have a strong anti-cancer activity mostly in glioblastoma (Briceno et al, 2007). It inhibits phospolipase A2 (Zidovetzki et al, 1993).Cycloserine (Mary et al, 1972; Cinatl et al, 1999) is an inhibitor of the alanine transaminase, thus decreasing the amount of Oxaloacetate. It is commonly used in the treatment of tuberculosis and has been

shown to decrease the growth of tumor cells (Israël, 2014).

IV. Conclusion

In this short study, we demonstrate that tumor marker can drop quickly after the start of metabolic treatment. This metabolic treatment can be improved by the addition of Metformin and Chloroquine. The exact pathways still need to be explored. Nevertheless it is highly probable that citrate lyase and pyruvate deshrogenase play a key role in cancer proliferation. It is too early to tell whether it is a universal phenomenon and whether the efficacy of treatment will last.

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

Acknowledgements

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

Association Cancer et Métabolisme

Association Face Au Cancer Ensemble – FACE 44

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