

New cancer paradigm and new treatment: the example of METABLOC

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Abstract

Hyperthermia has long been known to interfere with the tumor metabolism. The goal of this presentation is to review the potential of metabolic therapy and to suggest that its combination with hyperthermia may be of interest.

Objective

In a landmark article, John Bailar published in the “New England Journal of Medicine” in 1997 the article: Are we losing the war on cancer? We recently confirmed that is still the case. We obtained mortality from the World Health Organization time-series data of 20 countries over 45 years (1961-2005). During these 45 years the age standardised cancer death rate has varied little (-4%). There has been a slight decrease in breast cancer (-6.5%), lung cancer in men (-2.5%), prostate cancer (-1.7%) but there was a sharp decrease for stomach cancer (-77%). These data confirm the preliminary results of Bailar and contradicts the notion of a breakthrough in cancer prevention, early detection and cancer treatment (Summa 2012). Today, as before, metastatic cancer to the notable exception of some childhood malignancies and of lymphoma remains almost universally fatal.

Today cancer is thought to be an invasion by malignant cells which deserve to be killed either by surgery, radiation therapy or chemotherapy. The screening of new drugs is done by assessing their efficacy in killing cancer cells. Modern drugs target one specific pathway in order to kill the malignant cell. But the logic is still the same: killing the cancer cell. None of these new drugs can be credited in having significantly changed the survival pattern. For example, the overall response rate to Herceptin (a so called magic bullet) when administered alone is less than 5%.

In the meantime the cost of cancer drugs has been increasing exponentially. It is highly probable that we are witnessing a “bubble” based more on goodwill, and hope than on results.

There is an obvious need for change of paradigm. This change is not only scientific (in reassessing what cancer really is) but we also need to change the way we conduct clinical trials. This change of paradigm will be a dramatic change in medical strategy and in the financial cost to society.

Cancer is widely thought to be the consequence of genetic abnormalities such as oncogene activation or tumor suppressor inactivation. This is correct but it is only a partial view of the disease. For example, there is oncogene activation in normal cells or during development of benign inflammation. There are alternative ways to understand cancer. The most promising is considering cancer as a metabolic disease, as a disease related to diabetes.

Metabolic aspects of cancer: Otto Warburg

Cancer is not only a genetic disease but also a disease of the metabolism. Since the work of Nobel Prize winner Otto Warburg, we have known that the metabolism of cancerous cells clearly differs from that of normal cells (Warburg 1956; McKnight 2010). Cancerous cells consume higher amounts of glucose than they are able to fully degrade (Van der Heiden et al. 2010). This is the actual basis for PET scan imagery, in which the intravenous injection of a radioactive substance similar to glucose is used to visualize the cancer and its metastases. This fact, which had long been forgotten, is starting to surface again. A considerable amount of recent work, including our own, shows that this metabolic disorder could be the source of the cancer development process (ref in Israel & Schwartz 2011).

Otto Warburg, published his observations regarding a metabolic alteration frequently observed in cancer cells in the 1920's (Warburg). Warburg reported that the cancer cells he investigated metabolized glucose directly to lactic acid, as opposed to the pyruvate being converted to water and carbon dioxide in the mitochondria via the tricarboxylic acid (TCA) pathway. This metabolic property of cancer cells bears his name, that is, the Warburg effect. It is also referred to as aerobic glycolysis, as it takes place in cancer cells even under normoxic conditions.

Interest in the Warburg effect has been waning 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 actually

the cause of cancer and that the most likely explanation for his observation was the damage to the mitochondria (Warburg). 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 means damage to the mitochondria and it is not the explanation for why many cancer cells adopt aerobic glycolysis as the principal pathway for glucose metabolism (Robey, Moreno-Sanchez). However, during the last 15 years or so, there has been a considerable increase in interest regarding the Warburg effect and its role in cancer. As a result, some seminal publications have elucidated the role that the Warburg effect plays in cancer, and there are a number of recent excellent reviews as well (Van der Heiden, Feron, Kroemer). Warburg understood that there is a prevalent defect in the anabolic pathway. He did not understand that the oxidative pathway (catabolism) is also flawed.

Change in metabolism explain prominent features of cancer such as carcinogenesis and response to chemotherapy

There is a wide consensus today on the importance of metabolism in cancer (Van der Heiden, Feron, Kroemer). Prominent features of cancer can probably be summarized by metabolic changes. For example the oncogene targets the metabolic pathway (for review see Israel and Schwartz: cancer as a dysmethylation syndrome). A retrovirus can capture a gene, from a host cell and transmit it to a new host. Retroviral oncogenes disturb a major signaling pathway: the MAP kinases mitogenic pathways while the different steps of PI3 kinase pathway are targets for DNA viruses. Oncogene can thus be seen as metabolic perturbator.

To confirm the role of metabolism in carcinogenesis, we exposed normal melanocytes (from adolescent's foreskin) to high dose glucose and insulin. The proliferation increased (doubling time: 2.7 vs 5.6 days). After 3 weeks of exposure to glucose or after 3 weeks followed by 4 weeks culture in standard medium, melanocytes were able to grow in soft agar colonies, a feature of cancer cells (Morvan 2011).

Most anticancer drugs target the DNA, but their precise mechanism of action is debated. It is clear that even when the treatment is effective in patients with large metastatic disease, there are no signs of cell death. Minutes after the beginning of a small cardiac infarct, there is an increase of intracellular protein in the circulating blood. This is not the case after chemotherapy. However, the first sign of response of treatment is a decrease of glucose uptake as demonstrated by the PET scan. Cancer drugs can kill cancer cells (it is what they are selected to do), but when a cell survives it stops to grow for days or weeks. This resting phase has not been studied deeply, it is technically difficult (only a few cells survive) and time consuming. We were able to demonstrate that this growth arrest was because of a switch in metabolism (Guenin 2007).

Targeting cancer metabolism: background

There is considerable logic in targeting metabolic changes as an approach to the development of pharmaceutical agents to treat cancer despite the fact that these changes are not causal in nature. A relatively recent publication has shown that the genes involved in glycolysis are over-expressed in at least 24 different types of cancers that correspond to approximately 70% of all cancers (Altenberg). It has been hypothesized that this widespread prevalence is because aerobic glycolysis provides a competitive advantage to cancer cells, allowing the synthesis of compounds (ribonucleotides and lipids) required for proliferation (Gatenby 2004, Bui, Gatenby 2006).

A number of specific inhibitors of key enzymes involved in the aerobic glycolytic pathway have been evaluated as potential anti-cancer drugs (see reviews Yeung, Pelicano, Michelakis). However, with rare exceptions none of these compounds has been used clinically. Michelakis reported that treatment of five patients with glioblastoma multiforme using dichloroacetate, an inhibitor of pyruvate dehydrogenase kinase, resulted in tumour regression in three individuals. Berkson treated four pancreatic cancer patients with a combination of lipoic acid and naltrexone with excellent results. The first patient treated was still alive and well 78 months after presentation. Somewhat coincidentally, α -lipoic acid is also known to be an inhibitor of pyruvate dehydrogenase kinase just like dichloroacetate.

Naltrexone, on the other hand, is an opioid receptor antagonist and is primarily used for the treatment of alcohol and opioid dependence, although there are limited data suggesting its potential role in cancer inhibition.

This relative lack of success suggested to us 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. We adopted a strategy to use compounds already proven to be nontoxic in humans.

Screening for a “universal” metabolic combination

In 2004, we started collaborating with other scientists, among them was Dr. Maurice Israel, we focused their efforts to discover a way to take advantage of one of the weaknesses of cancer: its poorly effective metabolism. Instead of targeting the mitotic process, they chose to target the metabolism of the cell (Israel & Schwartz, 2005).

In June 2007, the second phase of this work began with the selection of about a hundred molecules potentially active from literature analysis. Focusing on the metabolic alterations of cancer cells, we identified molecules that have been described to act on enzymes which activities are known to be affected in cancer. Our second selection criteria was the existence of data on human administration for these molecules. This approach allowed us to select 27 different molecules.

In the first animal study (Schwartz 2010), a detailed literature analysis was conducted from which the first library of twenty-seven drugs that are known to target pathways potentially implicated in cancer was developed. We conducted in vitro tests on these molecules to determine their antiproliferative capacity on four cells lines at concentrations consistent with published human plasma levels. The data, summarized in Table 2, showed that 5 molecules were not effective, 11 molecules were weakly effective, while 11 molecules were significantly effective.

Thus, this preliminary study (see Schwartz et al. 2010 for details) suggested that a combination of ALA with HCA may have a high antitumoural potential. This efficacy was similar on whatever the cell line was tested. Our group tested 15 combinations of two drugs based on the seven effective and least toxic molecules. Seven combinations showed a strong antiproliferative effect (< 20% of viable cells after 24 hours). They were: acetazolamide and hydroxycitrate, lipoic acid and dichloroacetate, lipoic acid and hydroxycitrate, acetazolamide and miltefosine, albendazole and dichloroacetate, dichloroacetate and hydroxycitrate, lipoic acid and miltefosine.

In vivo antitumoural effect

We then proceeded to test these seven most effective combinations in vivo using mice bearing syngeneic MBT-2 bladder carcinoma. The majority of the combinations were not or only weakly effective (data not shown). The most effective treatment was the hydroxycitrate and lipoic acid (designated as METABLOC™) (Schwartz 2010). The efficacy of this combination was confirmed in B16-F10 melanoma and LL/2 Lewis lung carcinoma. This combination both drugs slowed growth of the tumour and increased survival with an efficacy was similar to conventional cytotoxic chemotherapy. This combination is effective whatever the tumor model is like, suggesting that these metabolic pathways are crucial for cancer survival.

The compositions were tested against different murine tumour models (MBT-2 bladder carcinoma, LLC Lewis lung carcinoma and B16F10 melanoma implanted in syngeneic C3H mice (MBT-2 cells) or C57Bl6 (LLC and B16F10 cells). Tumour cells were inoculated in the flank of the mice and the tumour developed for few days before the beginning of the treatment. After randomization, the combination and also the control compositions were administered intraperitoneally, for 21 days. The change in tumour development was monitored by measuring the size of the tumours with a Vernier caliper and monitoring the survival of the animals during the experiment. The mice used in this study were treated in accordance with the ethical regulations in force. In the described results, the following doses and schedule of administration were used: alpha-lipoic acid 10 mg/kg, twice a day; hydroxycitrate 250 mg/kg, twice a day.

The combination was used to treat mouse syngeneic cancer models: MBT-2 bladder transitional cell carcinoma, B16-F10 melanoma and LL/2 Lewis lung carcinoma. The efficacy of this combination appears to be similar to conventional chemotherapy (cisplatin or 5-fluorouracil) as it resulted in significant tumour growth retardation and enhanced survival (see Figure 1.) (for details see article by Schwartz 2010).

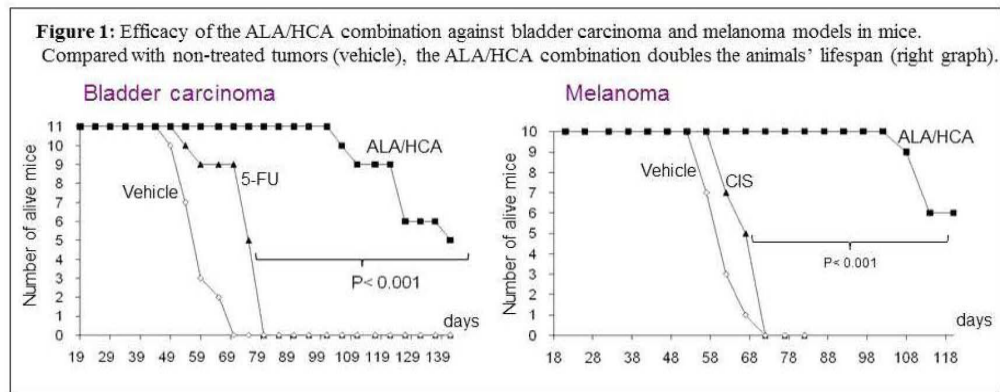


Figure 1.

These complementary studies suggest that combination of ALA and HCA is efficient against cancer cell proliferation.

The addition of a fourth molecule (see Figure 2.), capsaicin was responsible for tumor regression (Schwartz invest New Drugs 2012). None of these four different compounds is known to target the DNA. They all interfere with the metabolism.

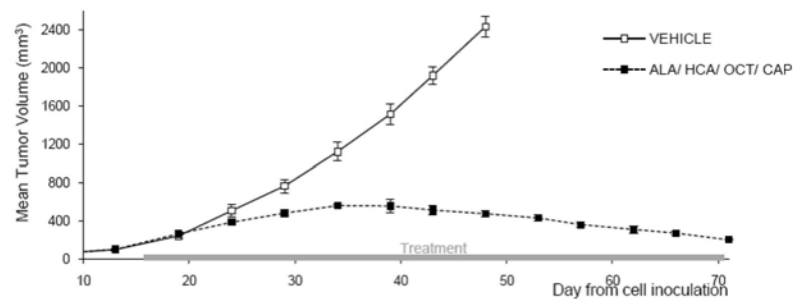


Figure 2. Anti-tumor activity of the alpha-lipoic acid, hydroxycitrate, capsaicin and octreotide combination in the melanoma model

Clinical data obtained with metabloc

At this stage, there is only preliminary data on the combination of these two molecules. The toxicity trials were conducted using increasing dosage of oral lipoic acid and hydroxycitrate. This treatment was added to standard anti-cancer cytotoxic chemotherapy. There is no trial using intra-venous combination of these drugs.

Eleven patients, five males and six females, were treated according to the standard protocol in use for their cancer type and stage between January 2009 and July 2011.

In addition to the normal chemotherapeutic regimen, a combination of ALA and HCA was administered to patients, after the informed consent was obtained, and both the results and side effects were registered. All patients had a histologically proven malignant disease. Follow-up data on patients was collected at a mean interval of 65 days, with a large range (40-90 days) for those patients with disease stabilization.

The minimum oral dose administered for ALA was 0.4 g/day, and the maximum dose was 1.8 g/day. The minimum dose for HCA was 1.2 g/day and the maximum dose was 3g /day.

The recorded side effects were related to the respective chemotherapies administered except for gastrointestinal disorders of mild intensity. Three patients (1 male, 2 females) out of 5 (3M, 2 F) treated with higher doses of ALA 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, nausea, and in 2 cases weight loss.

These side effects disappeared on using proton pump inhibitors, such as esomeprazole or lansoprazol, or by decreasing the dose. Seven patients (3M, 4F) tolerated the ALA 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 treatments. The minimum duration of a treatment was two months while the maximum duration was 21 months.

The patient affected by a pancreatic adenocarcinoma with liver metastases displayed tumour regression during a few months. She then spontaneously stopped her treatment and subsequently died. However, her survival was prolonged up to 18 months (Guais et al. 2010 for detailed description). Another patient with widely metastatic colon adenocarcinoma four years after the start of the treatment (Schwartz, 2012 submitted); however, the cancer finally recurred. Most of the patients receiving treatment for more than 6 months displayed partial regression or stabilization. Of the eleven patients, 5 were characterized by partial regression, 3 by a stable disease, and 3 by disease progression.

The combination of oral ALA and HCA with chemotherapy is well-tolerated. Side effects are primarily restricted to the gastrointestinal tract and can be avoided by decreasing the doses or preferentially by using proton pump inhibitors. The optimum dosage remains to be established by more clinical cases and a controlled clinical trial. However, these preliminary treatments support that METABLOC™ can be used safely with various common standard chemotherapeutic regimens (Baronzio 2011).

Conclusion

Since the work of Nobel Prize winner Otto Warburg, we know that the metabolism of cancerous cells clearly differs from the normal cells. Cancerous cells consume higher amounts of glucose than they are able to fully degrade. The changes in metabolism are universal features of cancer. This is the actual basis for PET scan imagery, in which the intravenous injection of a radioactive substance similar to glucose is used to visualize the cancer and its metastases. While Warburg described the effect that now bears his name, he did not understand the very reason behind it. We have probably understood it. It is probable that cancer is a simple metabolic disease closely related to diabetes.

To this day, we have outlined the enzymatic anomalies responsible for the Warburg effect and determined the therapeutic targets. We have devised a strategy against cancer by blocking the few metabolic pathways that feed its development.

Our work (theoretical and experimental) demonstrates that restoring the normal fluxes decreases tumor growth. This work conducted over the past eight years has enabled us to identify therapeutic targets and active molecules. Combinations of two of these compounds have revealed to be efficient in murine tumor models: alpha lipoic acid and hydroxycitrate. There is, as of today, no resistant cell line both in vivo and in vitro. Accordingly this combination slows tumor growth in every tumor model (lung cancer, bladder cancer and melanoma). These data were confirmed in an independent second laboratory. These molecules have an excellent safety profile that has already been approved for other medical applications than cancer. Early clinical work confirms an excellent safety profile and strongly suggests efficacy.

The long forgotten cancer metabolism, is now reaching headlines with tens of new molecules being developed, one at a time, both by the industry and by the academia. Our approach is different. We focus on the combination of well established and inexpensive drugs or food supplement in order to speed the clinical development. If effective the treatment should not be limited to a peculiar primary tumor site.

An other way to interfere with metabolism is oncothermia. It is highly probable that the combination of these non toxic approaches will yield great results.

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