

A Simple Method to Optimize the Effectiveness of Chemotherapy: Modulation of Glucose Intake During Chemotherapy

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Abstract. *Background/Aim:* Cancer cells consume high amounts of glucose to produce ATP and molecules entering biosynthesis. Numerous experimental studies have demonstrated that glucose deprivation and/or glycolysis inhibition arrest cancer cell growth and may increase the efficiency of cytotoxic drugs. In contrast, increasing glycolysis in tumor-infiltrating lymphocytes (TILs) activates these cells that destroy cancer cells. We propose to increase the efficiency of chemotherapy by modulating glucose intake during the course of chemotherapy. *Materials and Methods:* Glucose and caloric intake should be drastically reduced the day before and during chemotherapy administration to deprive cancer cells of ATP and molecules required to repair cytotoxic lesions. Few hours after chemotherapy, glucose and caloric intake should be drastically increased for few days to promote the activation of TILs that reinforce the destruction of cancer cells. *Results:* This strategy could improve the results of chemotherapy by first enhancing cytotoxic stress against tumor cells and then promoting activation of the anti-cancer immune response. *Conclusion:* The modulation of glucose intake during chemotherapy should be tested clinically. The proposed scheme is simple, surely easier to follow than a strict chronic diet, and should avoid weight loss.

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Cancer cells consume large amounts of glucose (10 to 15 times more than normal cells) in order to produce molecules (ribose, serine), needed for biosynthesis and replication (1, 2). At the same time, tumor cells produce lactic acid, either because they lack oxygen and/or because they down-regulate their mitochondria to reduce the production of molecules (citrate, CO₂, ATP, and reactive oxygen species (ROS)) in adequate range for proliferation (3-6). Due to the involvement of the "Warburg effect", a large part of the pyruvate no longer enters the tricarboxylic (TCA) cycle to produce CO₂ and ATP, but is instead transformed into lactic acid. Since glycolysis can deliver ATP up to 100-times more rapidly than mitochondria (7), cancer cells may use this pathway to rapidly adjust their concentration of ATP into an adequate range for active proliferation. This "disconnection" between glycolysis and mitochondria is promoted by hypoxia-inducible factor (HIF) (8) and supported by various oncogenes and aberrant signaling pathways, in particular Myc, K-ras, and STAT-3 (9-12).

Numerous experimental studies have shown that strategies promoting the inhibition of glycolysis and/or the deprivation of glucose, arrest cancer cell growth while increasing sensitivity to chemotherapy (13-15). It is noteworthy that the disconnection of glycolysis from the mitochondria can be partially compensated with the increase of glutamine consumption, especially when glucose is limited (9, 16). The waste-products rejected by cancer cells in their microenvironment, such as lactate, promote cancer cell invasiveness, in particular through inhibition of the immune response (17-19). Importantly, recent studies have shown that cancer cells escape immune destruction, because they divert glucose for their own benefit (20). This process inhibits the use of glucose by tumor-infiltrating lymphocytes (TILs)

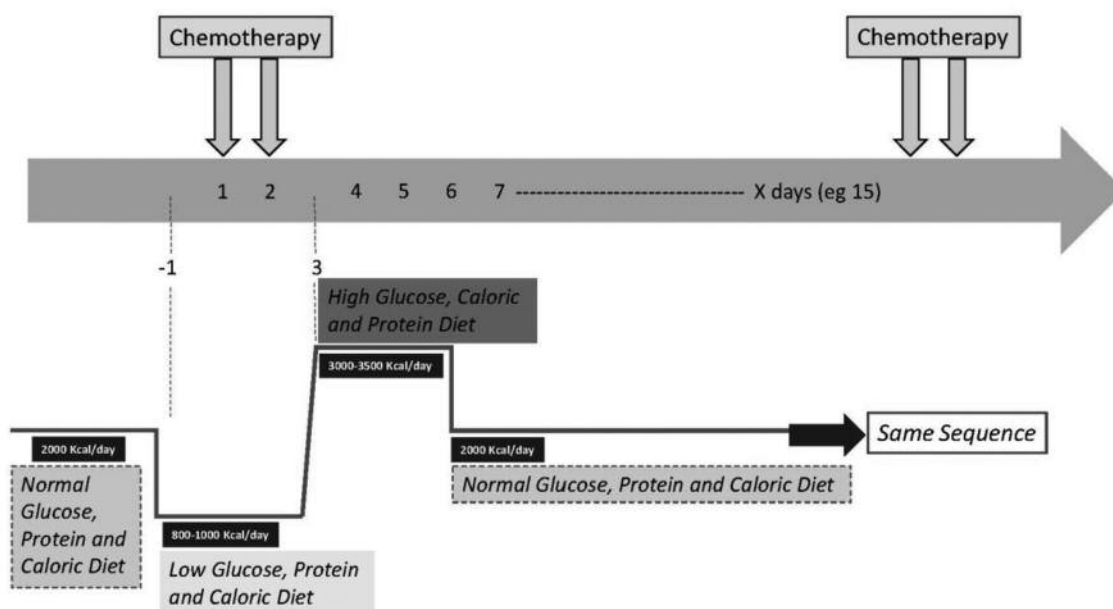


Figure 1. A protocol of diet could be the following: i) First, a severe restriction in glucose and proteins with high caloric restriction (800-1,000 Kcal/day) beginning the day before chemotherapy and finishing in the hours following drug administration; ii) then, a high intake of glucose and proteins (3,000-3,500 Kcal/day) during the next 3 days, in order to promote the activation of immune cells, destroying cancer cells.

promoting their inactivation. In contrast, glycolysis activates TILs which rapidly multiply and destroy cancer cells through acute inflammation and secretion of interferon γ (20-22). Current immunotherapy is based on the competition between cancer cells and TILs: PD-1 ligand (PD-L1) stimulates glycolysis in cancer cells through the activation of the Akt/mTOR pathway (20, 23). Therefore, the inhibition of PD-L1 stimulates glycolysis in cytotoxic CD8⁺ T lymphocytes, promoting acute inflammation and secretion of interferon γ (20, 23). Furthermore, competitive uptake of glucose by activated T cells can starve Dendritic cells (DCs), and promote the stimulation of pro-inflammatory DCs which enhance the immune response (24).

Thus, as demonstrated in experimental models (13-15), the efficacy of chemotherapy drugs could be increased by depriving cancer cells of the energy and molecules needed to repair cytotoxic lesions, whereas CD8⁺ T cells destroying cancer cells could be stimulated by increasing their glucose utilization (20-23). Thus, an optimal metabolic strategy should consist in starving the cancer cells in glucose while increasing the consumption of glucose in the CD8⁺ T lymphocytes. We propose here a simple method aimed at this dual objective of increasing the effectiveness of chemotherapy and promoting an acute activation of the immune system destroying cancer cells. This method relies on modulating the intake of glucose and calories during chemotherapy.

Materials and Methods

As consequence of these experimental facts and explanations, we propose a simple method to improve the efficiency of cytotoxic drugs: - first, the intake of sugar and proteins should be drastically reduced the day before, during the administration of chemotherapy to deprive cells of molecules (glucose, glutamine) and ATP required for repairing cytotoxic drug damages, and to activate dendritic cells; -few hours after the end of chemotherapy administration, the intake of glucose and proteins should be drastically increased for 3-4 days to activate the acute immune response to reinforce the cytotoxicity of chemotherapy drugs.

To test this hypothesis, we propose a protocol of diet that could be: (i) a severe restriction in glucose and proteins with severe caloric restriction (800-1,000 Kcal/day) that begins the day before chemotherapy and finishes in the hours following drug administration; - then, a high intake of glucose and proteins (3,000-3,500 Kcal/day) should be implemented during the next 3 days, in order to promote the activation of TILs, destroying cancer cells. Apart this short period of 6 to 7 days surrounding chemotherapy, the patient has no special diet to follow (Figure 1).

Results

To confirm or refute this hypothesis, clinical studies should compare the administration of chemotherapy (for example that of cisplatin, one of most frequently used drugs in cancer therapy), with or without the association of this sequential diet protocol modulating the intake of glucose and proteins during the course of chemotherapy as aforementioned.

Knowing that the metabolic response can be rapidly evaluated by positron emission tomography (PET scan) in the days following cytotoxic drugs administration (25), this examination should be advantageously performed within the week after the end of the protocol, to make a comparison between the groups.

Discussion

If our hypothesis is confirmed, the modulation of glucose and caloric intake during and after chemotherapy can be a new strategy for increasing the action of cytotoxic drugs, while promoting the activation of immune cells. The dietary scheme we proposed is simple and likely much easier to follow than a chronic diet such as a ketogenic diet (for review see 26), because it is sequential and intermittent. Although duration of the first hypocaloric phase is brief (2 or 3 days), such short term fasting can be efficient to reduce side effects of chemo and radiation therapy while improving their results, as demonstrated in animal models (26-30). These beneficial effects would be mediated in part by hypoglycemia and reduction in insulin-like growth factor 1 (IGF-1) level (31, 32). Because the second phase of our diet protocol is hypercaloric, weight loss should be avoided or limited while promoting the immune response against cancer. This stimulation of anti-tumoral immunity is surely a key element of an effective therapeutic strategy, as demonstrated by the better prognosis of cancers with activated TILs (33, 34), while it could also improve the efficiency of immunotherapy.

Finally, apart from the short period of time surrounding chemotherapy (approximately 6 days), the patient has no special diet to follow. A great advantage of this intermittent diet should be the maintenance of a stable weight. Case studies should be undertaken to verify the accuracy of the concept, while use of PET may help determine the level of caloric intake that has a favorable impact on the efficacy of chemotherapy, maybe even able to overcome resistance to chemotherapy in some cases. This new strategy, simple and inexpensive, aimed both at increasing the effectiveness of chemotherapy while strengthening the immune response against tumor cells, could have a major influence in the field of cancer treatment.

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