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Review Article

Antimetabolites in the Treatment of Solid Tumors: Competitive Inhibition by Structural Analogs

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Summary

Cancer cells rely heavily on a few nutritional metabolites. The pronounced functional asymmetry between cancerous cells and normal cells with an intact OXPHOS can be exploited in the clinical setting through pharmacological and nutritional interventions, non-toxic to the host. Neoplastic tissues overexpress glycolytic and glutaminolytic enzymes such as HK2, LDH-A, GLUD, as well as other rate-limiting enzymes and transporters for both energy-producing reactions and the provision of biosynthetic building blocks within tumors. Providing stereometrically similar molecules with no intrinsic activity has already been employed successfully in the clinical setting by several medical groups. The intravenous injection of structural analogs of sugars, amino acids, vitamins or their metabolites is selectively cytotoxic to cancer cells without harming the host. Competitive inhibition of said enzymes using structural analogs of their naturally occurring substrates is a safe and effective complementary approach to the treatment of solid tumors as well as of hematological malignancies.

Enzymatic Inhibition with Structural Analogs

Antimetabolites such as methotrexate -a folate analog- have been used to halt tumor progression or disrupt embryogenic growth since the 1950s. 2-deoxy-D-glucose (2DG) -an undegradable pseudo-sugar with antiproliferative effects- has served routinely in cancer diagnosis through Positron Emission Tomography, combined with ^{18}F as radiotracer, and is both safe and effective in humans when used on its own [1]. Sodium ascorbate (which happens to be a hexose or six-carbon glucose analog) is widely recognized for its strong antimicrobial and antineoplastic properties, when properly applied in pharmacological doses [2]. Intravenous D-Glucosamine has been shown to induce tumor hemorrhage, halt cell proliferation and prolong survival since 1970 [3].

In one form or another, the principle of Enzymatic Inhibition with Structural Analogs (EISA) for the treatment of solid tumors is being deployed in many clinics to induce an acute energy constriction in neoplastic tissues, usually as an adjunct to known chemotherapeutic regimes such as R-CHOP-21. Such an approach requires the implementation of carefully engineered dietary restrictions, as suitable to the host, coupled with metabolic disruptors. This is routinely accomplished through intravenous injections of structural analogs of glutamine, glucose and pyruvate, administered under deep physiological ketosis.

In the clinical setting, physiological ketosis is defined as: ketonemia ≥4 mM/L, glycemia ≤3 mM/L, and pH 7.4 (±0.1). This state is arrived at by way of a low-calorie ketogenic diet, or short-term water-only fasting (usually 72 hours), and has been extensively proven to optimize chemotherapy regimens of any type [4-7].

In the last two decades, this author and many other researchers and clinicians have acquired deep functional knowledge on the use of the glucose analog 2-deoxy-D-glucose as an adjuvant in the treatment of highly glycolytic tumors [1, 8]. As stated, the intravenous use of pharmacological doses of sodium ascorbate has proven to be selectively cytotoxic for cancer cells of multiple tumor types, both *in vitro* [9] and *in vivo* [10], as well as *in Homo*, including pancreatic adenocarcinoma [11-13].

Safe and effective metabolic interventions intended to optimize standard therapeutics such as tumor-reducing surgery, cytotoxic chemotherapy, immunotherapy and radiotherapy are readily

available. The intended purpose of these adjuvant metabolic interventions is to increase the therapeutic index (TI) of orthodox treatments. However, there are many reports of tumor remissions and substantial improvements in five-year survival rates when employed on their own as a sole form of treatment in individuals deemed non suitable for cytotoxic chemotherapy [14-17].

Rationale: Exploiting the functional asymmetry of cancer cells with structural analogs

It has long been established that virtually all solid tumors that constitute metastasis have a high Standardized Uptake Value or SUVmax in Positron Emission Tomography scans [18]. All manner of cancers exhibit a hypermetabolic phenotype, proven to be quantitatively predictive of invasiveness and survival [10-21]. Adding labeled nutritional substrates to cell cultures and experimental animals in countless studies has shown that substantial amounts of carbon donors metabolized by neoplastic cells require transmembrane carriers, as well as an oversized enzymatic machinery. There is, for instance, unmistakable evidence of a proportional, direct correlation (r 0.83) between GLUT1 and cancer invasiveness [22-24]. Key rate-limiting enzymes such as glutamate dehydrogenase (GLUD), hexokinase II (HK2), and isoenzyme 5 in the lactate dehydrogenase family (LDHA) are intensely overexpressed in neoplastic cells, dwarfing its enzymatic expression in normal cells by an order of magnitude [25-29]. Tumor avidity for glutamine, glucose and pyruvate, as well as the overexpression of their catalyzing enzymes and transporters is already being exploited therapeutically by hundreds of doctors from multiple countries in a systematic manner [30-33].

Such approach takes advantage of the compensatory increase of fermentative glycolysis and glutaminolysis in neoplastic cells. This aberrant form of fermentative metabolism takes place even under high partial pressure of oxygen in the tissue ($ptiO_2$), hence named the "facultative" anaerobiosis of cancer cells [34]. Although in vivo, the actual yield of oxidative phosphorylation (~28 molecules of ATP) is somewhat lower than the theoretical yield (~36 molecules), this functional asymmetry has profound implications. It is deemed that the relative inefficiency in the energetic yield of glucose fermentation is approximately 14-fold lower than that of respiration (2 moles and 28 moles of ATP per mole of glucose, respectively). Poor ATP output induces cancer cells to an over-expression of GLUT transporters [23], hexokinase-II [26], and isoenzyme "A" (LDHA) also named LDH-5 [29]. Therefore, blocking these metabolic pathways has strong disruptive effects on neoplastic tissues (sometimes inducing acute tumor necrosis) while sparing the host.

The extensive reprogramming of energy metabolism undergone by cancer cells explains the intense glucose and/or glutamine uptake shown by solid tumors and is, as mentioned, the basis for the Positron Emission Tomography (PET). Using ^{18}Fluoro-Deoxy-D-Glucose or ^{18}Fluoroglutamine as a radiotracer, the absorption of these substrates reveals hypermetabolic tissues. In PET-positive tumors, with a Standardized Uptake Value equal to or higher than 3 (SUVmax $\geq$ 3), glycolysis and glutaminolysis are known to be overexpressed by a factor of 10, 30, or higher, even under a ptiO2 high enough to sustain oxidative phosphorylation [35]. Despite their clinical heterogeneity, this central feature of cancer, the Warburg effect, is a universal phenotypical hallmark of all malignant tumors [36].

Ongoing research and challenges

To date, several thousand technical papers on a vast array of metabolic approaches have been published [37]. As per the peer-reviewed literature, over the last two decades multiple medical centers and clinical research groups in several countries have acquired experience and functional knowledge on the use of structural analogs of glutamine, glucose, and pyruvate as non-toxic metabolic disruptors [38, 39]. A summarized list of these antimetabolites includes 2DG, ascorbate, D-glucosamine, telaglenastat, piperazine erastin, L-asparaginase, DON, 3BP, EGCG and oxamate. Several other compounds are being tested preclinically.

Applying the principle of competitive inhibition with structural analogs as an adjunct -or even as a sole form of treatment, with no other concomitant therapeutic interventions- has proven effective in at least 12 types of malignancies, including kidney, bladder, breast, stomach, colon, lung, prostate, and pancreatic cancer, as well as lymphoma, sarcoma, and melanoma [40-46].

Unexpected findings in the clinical setting following adjuvant or palliative interventions, i.e. tumor remissions and doble- or even triple-digit percentual increases in overall survival time (OS), have led clinicians to conclude that functional constrictions induced by antimetabolites are an effective, non-toxic, economical method to improve the therapeutic index of standard cancer treatments. By our calculations, as of March 2026, in just a few medical centers across Latin America and Spain, well over 1.007.000 metabolic treatment sessions have been administered on ≈7.900 cancer patients over the course of 10 years.

As of this writing, 13 prospective, phase three clinical studies concerning some form of metabolic therapy are registered in http://www.clinicaltrials.gov . Although hundreds of doctors already employ different modalities of metabolic therapy due to their safety and simplicity, more clinical trials are necessary to test emerging molecular candidates and to assess the efficacy of combinatorial metabolic approaches to cancer.

Conclusion

Standard treatments of cancer can be substantially improved by the adjunct introduction of antimetabolites of glutamine, glucose, pyruvate and possibly other nutritional substrates. The competitive inhibition of several rate-limiting enzymes within neoplastic cells using already available structural analogs may improve therapeutic outcomes in a non-toxic, cost-effective way.

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