American Institute of Integrative Oncology
RESEARCH & EDUCATION

Foundations of Integrative Oncology
COURSE

GRAND ROUNDS CALL
With Dr. Nalini Chilkov
August 9th, 2017

Second Wednesday of Every Month
5:30 PM Pacific / 6:30 PM Mountain / 7:30 PM Central / 8:30 PM Eastern

Clinical Pearl: Glutamine & Cancer Metabolism

Reference Article: https://www.hindawi.com/journals/omcl/2015/964321/
Key Roles of Glutamine Pathways in Reprogramming the Cancer Metabolism

Complete summary notes below.

Questions & Answers

Follow-up Question [Judy Pruzinsky]:
Prior Case Study presentation "LS" - Post-breast cancer chemo and on aromatase inhibitors (estrogen-receptor positive) is still suffering a lot from neuropathy. It presents as: numb, can go from feet up through calves, feels very swollen and tight, occasional shooting pain but not the common presentation. She was on Letrozole and now on Exemestane. Her doctor has her going off medications for a little while to let the symptoms abate. She is on everything suggested when the case was reviewed.

Is it possible to monitor certain markers to see how important the AIs are? Would adding something like FemGuard help enough to add more supplements to her regimen?

Recommendation:
Is this neuropathy only, or is she also experiencing pain as a side effect of the AI therapy? If she takes a real break from AI, if some symptoms are relieved, then we know some are related to AI, and maybe she also has neuropathic pain from the chemo. In my experience, AI pain is more from the fascia, ligaments and joint linings, so the prescription for repairing nerves isn't effective. We need to figure out if she is having two sources of pain. If a patient has had significant damage during chemo, it can take a long time to for pain relief.

Regarding monitoring, AI is in the tissue, not the blood, so there isn't a way to measure.

FemGuard is a Designs for Health formulation for estrogen metabolism that is systemic, not in the tissue. Application is for woman with estrogen dominance because she is no longer ovulating or has poor clearance or microbiome is causing recirculation of estrogen. It will not affect aromatase.

Natural Aromatase Inhibitors:
- Chrysin (bioflavanoid, very safe) - about 100 mg/day
- Resveratrol - 2000-3000 mg/day (powder)
- Nettle Root - Tincture/botanical extract - 2 tsp/day

AI therapy is a nice insurance policy, but can be poorly tolerated by patients. I will often recommend to patients to adjust the doses down in order to maintain some level of AI therapy for at least 2 years if they aren't tolerating the full doses well. Utilize this psychological milestone of 2 years (versus the standard 5 years) to help patients overcome barriers to trying aromatase inhibitors. Let's give AI a try for two years and then see how well you're tolerating the therapy.

Keep in mind:
- Vitamin D should be between 55-80

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- Adequate mineral status - in particular Magnesium and supporting bone health
- Patients need to stretch (yoga, tai chi) - often relieves musculoskeletal complaints from AI

Follow-up Question [Judy Pruzinsky]:
Prior Case Study presentation - Colorectal cancer patient is still not utilizing chemo or surgery. Patient reports that his oncologist has indicated that regardless of how small the tumor were to be, he would have to cut a 12" section to remove the total blood supply. Does this sound common practice in your experience?

Recommendation:
No, this seems to be overly aggressive, especially if the 12-inch segment were close to the rectum, placing control of rectum or bowels at risk, but we don't have enough information. It is important at this juncture since we don't have the complete picture of the tumor or the blood supply to strongly encourage a second and even a third surgical consult from well-regarded oncologists. In order to get a true second opinion, you need to go outside this oncologist's community, because they otherwise tend to stand behind one another and/or maintain like-minded medical opinions.

Case Takeaways from Dr. Chilkov's Clinic

Patient 63 yo Stage 3 Lung Cancer
Extensive nodal involvement in her upper body
Overwhelmed and anxious - single, lives alone, not high income
Watched her mother die of the same diagnosis - in 6 weeks from date of diagnosis

Recommendations:
Important to take a good patient history to understand the full picture.

With these significant stressors, it's important to ensure that our treatment plan doesn't add to the overwhelm, and at the same time she needed an aggressive treatment plan to give her a sense of progress and control.

With high-stress patients, it's important to consider the patient - beyond the tumor microenvironment. Recommended adaptogenic herbs to support the body in modulating the stress response:

- Hawthorne Berry
- Magnesium
- Ashwaganda

Patient 40's Stage 3 Colorectal Cancer
Neoadjuvant Chemotherapy and Radiotherapy
Oncologist recommending surgery and second round of chemo
Extreme pain in GI tract, rectal bleeding, ulcer

Restored health over three months
Tumor micoenvironment testing every three months with good results
Highly compliant patient with diet and recommendations
Scan came back clear
Sigmoidoscopy results were shocking for radiologist and oncologist - tissue was so healthy
Determined very low risk, but oncologist still recommending surgery and chemo
Circulating tumor cell test came back positive - may have micrometastasis

Recommending cytotoxic therapy IV Vitamin C, Artesunate, Curcumin, Mistletoe because chemo was so toxic for his body before.

CLINICAL PEARL: L-GLUTAMINE (an amino acid)

KEY POINTS

Food Sources Wheat, corn, barley, peanuts, soybeans, egg whites, and milk

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Physiology

- L-glutamine (Gln) is the most abundant free amino acid in human body[5], with its concentration higher than that of all other 19 amino acids combined.
- Most tumor cells consume Gln at a much higher rate compared to normal cells
- Gln is converted into L-glutamate (Glu) and ammonia through glutaminolysis[9].

L-glutamine (Gln) may play an essential role in cancer cell growth through enzymatic release of ammonia for acid resistance

Glutamine is produced by the body. It is found in high amounts in muscle.

Potential mechanisms of glutamine effects

- maintenance of mucosal integrity
- improved immune competence
- inhibition of cell proliferation
- increased apoptosis rate
- increased synthesis of glutathione
- induction of heat shock protein synthesis
- increased synthesis of glucagon-s-like peptides

Glutamine is the major fuel source of enterocytes and is therefore essential for the maintenance of intestinal mucosal integrity and function [(1)].

Maintains immune function by serving as the principle metabolic fuel for lymphocytes and macrophages, and acts as a precursor for protein synthesis

With cysteine and glycine, is involved in glutathione (GSH) synthesis.

Intravenous glutamine preserves liver and intestinal glutathione stores in animal models of oxidant damage.

Glutamine is also involved in nitrogen exchange, as it neutralizes and eliminates excess ammonia formed during protein catabolism.

As a nitrogen donor, it contributes to the synthesis of other non-essential amino acids, including the purines and pyrimidines, and is therefore essential for the proliferation of most cells [(15)].

It also plays a supportive role during biochemical stress and sepsis.

Although the mechanism in treatment of cachexia is unclear, it is thought that glutamine, a modulator of protein turnover, enhances net protein synthesis [(3)]. Clinical evidence suggests that total parenteral nutrition supplemented with glutamine improves nitrogen balance, maintains the intracellular glutamine pool, enhances protein synthesis, and prevents deterioration of gut permeability in post-surgery patients [(4)].

Glutamine may potentiate the tumoricidal effect of methotrexate (MTX) since polyglutamation of MTX impairs its efflux from tumor cells and may reduce its accumulation in the gut. Rats fed a glutamine-enriched diet while receiving MTX chemotherapy exhibit less enterocolitis, improved hematologic parameters, decreased sepsis, and improved survival [(16)]. The supplemental intravenous form leads to increases of GSH in the gut, but not in tumors, in a sarcoma-bearing rat model.

However, recent findings show that glutamine transporters are upregulated in tumor cells and that glutamine acts as a mitochondrial substrate and promotes protein translation. This indicates tumor cell dependence for growth and

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maintenance [17]. And a recent study demonstrated that glutamine helps cancer cells survive acidic stress, rather than provide nutrition, through enzymatic deamidation [24].

Drug Interactions

Methotrexate: Glutamine may preferentially increase tumor retention of MTX, thereby increasing its therapeutic efficacy.

Therapeutic Applications

- Physical stress (long distance running, surgery, burns)
- Fast Dividing Cells Deplete Glutamine
- Peripheral Neuropathy
    - Chemotherapy induced peripheral neuropathy
    - Taxanes Paclitaxel
    - Platinum Drugs cisplatin, oxaliplatin, carboplatin
- Immunity
    - Promotes Phagocytosis, Neutrophil and Eosinophil activity
- Radiation Enteritis
- Mucositis
- Gastroenteritis
- Post Surgical Repair
- Bone Marrow Transplant
- Catabolic states Sarocpenia-Muscle Wasting-Cachexia-Sepsis-Surgery-Bone Marrow Transplant

L GLUTAMINE DOSING

- Mouth Rinse for oral mucositis: ½ tsp :¼ cup of water Swish, Hold in the mouth, swallow
- Oral Glutamine for catabolic syndromes 15-20g per day
- Oral Glutamine for gastroenteritis 5 grams 3-4 /day

Glutamine and Glutaminolysis Dependence in Cancer Cells

- Glutamine dependency and tumor invasiveness is established in ovarian cancer.
- Glutamine maintains the high-invasive phenotype by regulating STAT3 signaling.
- High-invasive ovarian cancer (OVCA) cells are glutamine dependent in contrast to low-invasive cells that are glutamine independent.
- Glutamine regulates STAT3 activation in high-invasive cancer cells.
- Glutamine's entry into TCA cycle modulates the invasive potential of high-invasive cancer cells.
- The ratio of glutamine catabolism over glutamine anabolism is associated with worse overall survival in OVCA patients. Glutamine plays an important role in cellular growth in several cancers. In this study, a further link between glutamine dependency and tumor invasiveness is established in ovarian cancer. Glutamine maintains the high-invasive phenotype by regulating STAT3 signaling.

Wise DR, Thompson CB. Glutamine addiction: a new therapeutic target in cancer. *Trends Biochem Sci.* 2010 Aug;35(8):427-33.

Huang W, Choi W, Chen Y, Zhang Q, Deng H, He W, Shi Y. Cell Res. 2013 May;23(5):724-7. doi: 10.1038/cr.2013.15. Epub 2013 Jan 29.

A proposed role for glutamine in cancer cell growth through acid resistance

Cancer cells exhibit a greatly increased level of aerobic glycolysis with accumulation of lactic acid, a phenomenon known as the Warburg effect. Apparently, survival of cancer cells requires an elaborate system for acid resistance. L-glutamine (Gln) has long been known to be essential for cancer cell growth, which is generally thought to relate to the nutritional value of Gln as carbon and nitrogen source.
We hypothesized that the primary role of Gln in cancer cells is to fight acid, rather than provide nutrition, through enzymatic deamidation. We demonstrate that **Gln helps cancer cells survive acidic stress**, which is compromised by inhibition of specific glutaminase activity.

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Cancer cells must be able to efficiently neutralize lactic acid to ensure normal growth.

L-GLUTAMINE Opinion and Review By Paul Andersen ND

Reference: Michalak KP, et.al. Key Roles of Glutamine Pathways in Reprogramming the Cancer Metabolism. Oxidative Medicine and Cellular Longevity. Volume 2015, Article ID 964321, 14 pages. http://dx.doi.org/10.1155/2015/964321

Practice Implications:
l-Glutamine the amino acid is one of the most widely used therapeutic substances in natural and integrative clinics as well as some allopathic practices. It has benefit in gastrointestinal illnesses and repair, post-surgical care, renal support, muscle mass maintenance, cachexia and a number of other conditions.

Given its wide use in the integrative medical community the concern regarding potential for any adverse or untoward event associated with its use is significant. The primary potential issue is the “feeding” of cancer cells and another related issue is increasing glutathione stores and thereby inactivating standard therapies.

Likely the most concerning of all potential adverse events is potentiation of cancer in a person using therapeutic l-Glutamine (GLN). As with many considerations in medicine it is not a simple answer. The authors state “In analyzing GLN intake as a possible positive or negative factor supporting the cancer growth and/or cancer treatment, one must take into consideration the differences between the metabolism of healthy and cancer cells. The main problem of this analysis is the variety of metabolic changes characterizing different cancer types. Individual types of cancer metabolism should be analyzed with regard to the possible positive or negative effect of glutamine supplementation. Some methods of metabolic analysis of cancer cells are available.” They then proceed to elaborate on many of the variations in cancer cells that may cause a difference in metabolism in the presence of GLN.

The authors take an exhaustive look at GLN metabolism in normal and cancerous cells, outlining and elucidating differences in GLN metabolism. What they clearly show is that a simplistic view of the role of GLN in oncology just cannot do justice to the topic.

Factors which may alter considerations in the patient with cancer include dose, timing, tumor type and patient depletion.

Potential GLN benefits include but are not limited to:

- Post-surgical healing
- GI repair and maintenance
- Immune system recovery and maintenance
- Muscle cell maintenance and recovery
- Glutathione pool restoration
- HIF-1 alpha inhibition
- and others

In cancer metabolism there is a deterioration of Pyruvate dehydrogenase complex (PDHC) and oxidative phosphorylation (OXPHOS) leading to safety when GLN is in the system. Broadly speaking there are few tumor types that oppose this metabolic change. The availability of GLN even in a supplemented person is often too low to do much more than feed the deficient GI cells, so peripheral use is limited with oral doses. The one common exception is glioblastoma multiforme (GM). In the case of GM, it is theoretically possible that amounts of GLN that were able to cross the GI barrier could be metabolized in a manner promoting of GM energy and health.

In the case of GM the authors point out that restricting carbohydrates would likely make the GLN effective in an anti-GM biology. They state: “Thus, the supplementation of GLN as the source of NADH2/FADH2 for the impaired OXPH chain producing many ROS can be potentially beneficial in this case. It should be, however, accompanied with the strong

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carbohydrate reduction in the diet and/or with the glycolysis inhibition therapy and/or with the increase in amino- and fatty acids in the diet that supports TCA cycle and in this way the oxidative stress in the cell."

Take home points for practice:

1. GLN oral supplementation is likely safe across most tumor types in patients with cancer.
2. In cases of GI damage (during or after chemotherapy and radiation) GLN is indicated.
3. In patients with post oncology therapy depletion or cachexia restoration of the GLN pool is critical to survival.
4. In active cancers, especially those with active PDHC and OXPHOS, carbohydrate restriction improves the safety of GLN supplementation.
5. In our clinics the standard uses of GLN in the oncology patient are as follows:
    a. During and after chemotherapy and radiation GLN powder in liquid or a soft food 1-3 grams BID-TID and HS
    b. In cases of post GI surgery recovery 4-6 grams PO TID
    c. In active cancer therapy where GLN supplementation is indicated:
        i. Dietary carbohydrate restriction
        ii. Other metabolic therapies (DCA, LAMC etc.)
    d. In cachexia we will replete the patient using oral and IV protocols.

The authors quote "Based on the analysis of GLN metabolism, it can be concluded that if the OXPH chain is deteriorated, GLN cannot be an effective source of ATP for the cancer cell regardless of the metabolic pathway." As well as my clinical experience indicates that l-Glutamine used appropriately is an excellent adjunctive therapy in the oncology setting.

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