Metabolic Oncology™: Exploration, Understanding, and Application of this Emerging Field in Whole Patient Oncology Care

Nasha Winters ND FABNO, Ahmed Elsakka MD, Abdul Slocum, MD

Introduction

Since 1914, thanks to the work of Dr. Theodore Boveri, we have towed the Somatic Mutation Theory (SMT) line in the treatment of cancer.[1] SMT remains the dominant theory, study, research focus and therapeutic intervention in oncology standard of care today. Though many important discoveries and victories have come from this dominant theory, we still fall short of changing cancer outcomes from prevention to treatment, to survivorship. There is a resurrected and emerging field known as Metabolic Oncology building on the 1920's Nobel Prize winning work of Dr. Otto Warburg picking up momentum in research institutions across the globe.

With metabolic reprogramming as a hallmark of malignancy, we have gained a new appreciation of the complexity of tumor metabolism and the tumor microenvironment. As such, we are learning how to identify and exploit these metabolic vulnerabilities. And, in doing so, bringing integrative oncology via provocative testing, patient-centered care, and vetted metabolic integrative therapies to the table alongside current standard of care practices.

Historically being viewed as a disorder of proliferation, cancer is increasingly being considered a metabolic disease. As tumors grow, they can rewire their metabolic pathways to meet the energetic demands of continuous cell growth.[2] Increased consumption of fuel sources such as glucose and glutamine, begs the questions of why do cancer cells shift their metabolism in certain ways, are these changes a consequence of the changes in proliferation or a driver of cancer progression, and can targeting these metabolic pathways change patient outcomes?[3] Cancer has long been considered a genetic disease characterized by a myriad of mutations that drive cancer progression. Recent accumulating evidence indicates that the dysregulated metabolism in cancer cells is more than a hallmark of cancer but may be the underlying cause of the tumor. Most of the well-characterized oncogenes or tumor suppressor genes function to sustain the altered metabolic state in cancer. Here, we review evidence supporting the altered metabolic state in cancer including key alterations in glucose, glutamine, and fatty acid metabolism. Unlike genetic alterations that do not occur in all cancer types, metabolic alterations are more common among cancer subtypes and across cancers. Recognizing cancer as a metabolic disorder could unravel key diagnostic and treatments markers that can impact approaches used in cancer management.

With cancer overtaking heart disease as the number one cause of death and the World Health Organization expecting worldwide doubling of cancer rates by 2030, perhaps it is

time to consider the Metabolic Theory in addition to SMT, as a role in and target for cancer treatment and prevention.

Below, several case examples are presented where a metabolic approach, alongside standard of care, was incorporated as part of the patients' treatment plan to the benefit of the each patient.

A case of Glioblastoma

The first case is of a 38-year-old man who presented with chronic headache, nausea, and vomiting accompanied by left partial motor seizures and upper left limb weakness in February 2016.[4] The enhanced MRI revealed a solid cystic lesion in the right partial space suggesting GBM. Prior to subtotal tumor resection and standard of care (SOC), the patient fasted for 3 days and then initiated a 21-day vitamin/mineral-supplemented ketogenic diet (ketogenic metabolic therapy). Post-surgical histology confirmed the diagnosis of GBM. Reduced invasion of tumor cells and thick-walled hyalinized blood vessels were also seen suggesting a therapeutic benefit of pre-surgical ketogenic metabolic therapy. In addition to radiotherapy, temozolomide chemotherapy, and the Ketogenic diet, the patient received supportive medications and dietary supplements and hyperbaric oxygen therapy (HBOT) (60 min/session, 5 sessions/week at 2.5 ATA). No steroid medication was given at any time. After 9 months of treatment with the modified SOC and complementary ketogenic metabolic therapy (KMT), seizures and left limb weakness resolved.

This is the first report of a confirmed GBM where KMT was the initial treatment which was then followed by a modified SOC together with KMT and HBOT, and other targeted metabolic therapies. As rapid regression of GBM is rare following subtotal resection and SOC alone, it is possible that the response observed in this case resulted in part from the modified SOC and other novel treatments.

A case of Triple Negative Breast Cancer

The second case summary describes the metabolic oncology approach used for an overweight 29-year-old woman with stage IV (T4N3M1) triple-negative invasive ductal carcinoma of the breast2.[5] The patient presented with an observable mass in her left breast in December 2015. In August 2016, MRI revealed a BI-RADS 5 tumor and multiple lymphadenomegaly in the left axilla, and a Tru-Cut biopsy led to the diagnosis of triple-negative nuclear grade 2 invasive ductal carcinoma. The patient was admitted to ChemoThermia Oncology Center, Istanbul, Turkey in October 2016. A PET Scan confirmed the primary tumor in left breast, lymph node involvement and with metastases to liver and abdomen.

The patient received a treatment protocol consisting of MSCT, KD, HT and HBOT. She received MSCT on the first and eighth day of a 21-day cycle and following each MSCT session she received local 60 minutes sessions of HT and HBOT together. She was also encouraged to consume a ketogenic diet. After 12 sessions of MSCT, HT and

HBOT a repeat PET scan, in February 2017, was performed which revealed a complete therapeutic response. The patient continued to receive 6 additional sessions and in April 2017 underwent a mastectomy. Pathology confirmed a complete pathological response consistent with the response indicated by her PET-CT imaging. This single case study presents evidence of a complete clinical, radiological, and pathological response following a six-month treatment period using a combination of MSCT and a novel metabolic therapy in a patient with stage IV TNBC.

A case of Stage IV Breast Cancer

The third case is that of a 47-year-old woman with stage IV (T4N3M1) grade 3, ER +, PR +, and HER2- breast cancer which had metastasized to the brain, lungs, mediastinum, liver, abdomen, and bones.[6] It was determined that she was ineligible for standard conventional treatment due to advanced disease, poor performance status, and life expectancy of less than one month. She was admitted to the ChemoThermia Oncology Center, Istanbul, Turkey, in November of 2018 where she received 17 rounds of metabolically supported chemotherapy (MSCT); along with hyperthermia (HT) and hyperbaric oxygen treatments (HBOT) on the same day as and the day following receiving MSCT. A ketogenic diet (KD) along with supportive medications and dietary supplements were used during the entire treatment period and following her return home. The treatment resulted in a complete and enduring response spanning two years at present (2021).

These cases highlight the benefits of integrating a combination of modalities targeting multiple vulnerabilities of tumor cells with standard chemotherapeutic drugs administered using an MSCT protocol along with other metabolic therapies. With disease regression as the goal, patients can achieve a complete and durable response to the administered treatment, extend their lives and experience an enhanced quality of life.

References

1. Seyfried, T. N., Flores, R. E., Poff, A. M. & D'Agostino, D. P. Cancer as a metabolic disease: implications for novel therapeutics. *Carcinogenesis* **35**, 515–527 (2014).
2. Coller, H. A. Is Cancer a Metabolic Disease? *Am. J. Pathol.* **184**, 4–17 (2014).
3. Gyamfi, J., Kim, J. & Choi, J. Cancer as a Metabolic Disorder. *Int. J. Mol. Sci.* **23**, 1155 (2022).
4. Elsakka, A. M. A. *et al.* Management of Glioblastoma Multiforme in a Patient Treated with Ketogenic Metabolic Therapy and Modified Standard of Care: A 24-Month Follow-Up. *Front. Nutr.* **5**, 20 (2018).

5. İyikesici, M. S. *et al.* Efficacy of Metabolically Supported Chemotherapy Combined with Ketogenic Diet, Hyperthermia, and Hyperbaric Oxygen Therapy for Stage IV Triple-Negative Breast Cancer. *Cureus* (2017)
6. İyikesici, M. S., Slocum, A. K., Winters, N., Kalamian, M. & Seyfried, T. N. Metabolically Supported Chemotherapy for Managing End-Stage Breast Cancer: A Complete and Durable Response. *Cureus* (2021)