TOWNSEND LETTER

The Examiner of Alternative Medicine

Integrative Cancer Treatment – Combination of Nutritional Ketosis and Hyperoxygenation Therapies

Dr. Santhosh John

Introduction

Cancer is a multifactorial disease, where various types of cancers exhibit varying mechanisms, pathways, genetic, and cellular defects. However, there are two phenomena that are common to almost all cancers, either causative and/or developmental, namely hypoxia and upregulated glycolysis.

Hypoxia, the absence of enough oxygen in the tissues, is a critical hallmark of solid tumors, which involves increased tumor survival, angiogenesis, glycolytic metabolism, metastasis, resistance to standard treatments and mortality rate. The presence of hypoxia in human tumors has been strongly demonstrated by histopathological study of vascular insufficiency, direct oxygen measurements in tumors, and by physiological imaging and mapping by clinicians and researchers.[1,2]

Glycolytic metabolism is a consistent feature of most tumor cells across all tissue types. In 1930, Otto Warburg (Nobel Laureate) observed that all cancers express high rates of fermentation, which cause cancers to rely heavily on glucose for energy.[3] Mitochondrial defects, overexpression of glycolytic genes, and oncogenic mutations in the tumor microenvironment (TME) contribute to the increased glucose consumption by cancer cells.

Nutritional ketosis and hyper-oxygenation therapies are very effective, non-toxic interventions to target hypoxia and glycolysis.

Nutritional Ketosis

Ketosis is a metabolic condition of the body when it is deprived of carbohydrates, in which ketone bodies are the primary source of energy, instead of glucose. Cancer cells mainly rely on glucose for their energy and, at the same time, normal cells, including brain cells, can survive with ketone bodies in the absence of glucose. Thus, elimination of carbohydrates can slow down the tumor growth and progression.

Nutritional ketosis can limit the growth of the tumor, protects healthy cells from damage by chemotherapy or radiation, accelerates chemotherapeutic toxicity toward cancer cells, and lowers

inflammation, which acts as a precursor to cancer.[4-7] A dietary regimen called Ketogenic Diet (KD) and ketone supplements are efficient in producing nutritional ketosis in the system.

Ketogenic Diet

The KD is a high-fat, low-carbohydrate diet with adequate protein and calories originally developed in the 1920s as a treatment for intractable epilepsy. The traditional KD is a 4:1 formulation of fat content to carbohydrate plus protein. KD delivers 90% calories from fat, 8% from protein and only 2% from carbohydrate.

Studies in mice models with cerebral tumor and malignant gliomas showed ketosis, enhanced the survival rate and reduced the tumor growth and tumor energy metabolism. The inflammation and angiogenesis found in the TME [toxic metabolic encephalopathy] and the process of apoptosis are greatly influenced by ketosis, which results in the reduction of tumor growth. It is found that ketosis stimulates some complex interactions amongst a number of gene networks that regulate the important intracellular signalling cascades and cellular homeostatic mechanisms for tumor reduction in addition to lowering blood glucose.[8-10] The above results are reobserved in the animal studies of prostate cancer, colon cancer, and gastric cancer.[11-14] Ketosis potentiated the chemotherapy effects, concurrently healed the side effects of chemotherapy in normal cells.[15]

KD improved the quality of life in patients with advanced metastatic cancer and also improved cancer patients' quality of sleep, emotional health, and mood.[16,17]

Ketone Supplementation

Therapeutically ketone supplements like 1, 3-butanediol or ketone esters are administered to elevate ketone bodies in the blood without the need of severe dietary restriction. These agents serve as ketogenic precursors and are either enzymatically cleaved or metabolized to produce ketones. Ketone supplements can be administered along with standard diet or with KD. Ketone supplements with KD offer more profound results.[18]

Hyperoxygenation Therapies

Hyperoxygenation therapies help to increase the O_2 level of the TME to target hypoxia. Hyperbaric oxygen therapy and ozone therapy are studied by many researchers in regards to cancer due to its efficacy, safety, and wide usage in the health industry.

Hyperbaric oxygen therapy. Hyperbaric oxygen therapy (HBO_2T) involves the administration of 100% oxygen at elevated pressure (greater than sea level). HBO_2T increases plasma O_2 saturation, which facilitates oxygen delivery to the tissues, independent of haemoglobin O_2 saturation.

Numerous animal studies confirm the anti-proliferative effect of HBO_2T. Both in vivo and in vitro study of murine osteosarcoma exposed to HBO_2T, shows significant reduction in tumor volume, metastasis, proliferation, and mortality rate. When HBO_2T combined with carboplatin, the chemotherapeutic effect was greatly accelerated.[19] In rat model studies of mammary tumors

and glioma, the HBO_2T reduced the tumor growth, angiogenesis, and increased the apoptosis. Mesenchymal-to-epithelial transition, induced by HBO_2T, reduced the aggressiveness of the tumor cells. Glycolysis, the signature cancer metabolism, has been shifted to oxidative phosphorylation, which results in tumor suppression.[20-23]

In a study of nineteen randomised control trials with 2286 patients, HBO_2T elicited anti-proliferative effects, especially with head and neck and uterine cervix cancers.[24] HBO_2T enhanced the effects of 5-fluorouracil (5-FU) in a mice study with sarcoma,[25] and also enhanced the chemotherapeutic effect of doxorubicin both in vitro and in vivo study of rat model metastatic lung cancer.[26] HBO_2T proved its strong anti-proliferative effect in mammary tumor as a stand-alone treatment in various animal studies.[27-30] HBO_2T with Radio Therapy (RT) has shown good result in patients with colon and rectal cancer.[31] In vitro studies of leukemia and prostate cancers treated with HBO_2T elicited profound anti-cancer properties along with improving the drug sensitivity.[32-35]

Intravenous ozone therapy. Ozone therapy refers to the process of administering ozone gas into the body to treat a disease or wound. Ozone is a colorless gas made up of three atoms of oxygen (O_3). Ozone therapy can be comfortably administered in cancer due to its profound anti-cancer properties.

Human cell culture studies of lung, breast, uterine, colon tumors and neuroblastoma, when treated with O_3, exhibited inhibition of tumor cells through apoptosis. O_3 also potentiates the effect of 5-FU and chemotherapy drugs like cisplatin and etoposide.[36,38,39] In vitro study of ovarian cancer, colon cancer, lung cancer and sarcoma, when treated with O_3, decreased the tumor metastasis and proliferation, and increased the cytotoxicity of radiation, cisplatin and 5-FU.[37,40,41] In a rabbit model study with metastatic squamous cell carcinoma, when treated with medical O_3/O_2 gas mixture intra peritoneally has shown complete disappearance of primary tumor along with prevention and/or remission of local and distant metastases.[42]

In addition, the potentiation of CT and RT by O_3 could be of higher clinical relevance. Animal studies with rat model sarcoma and tongue cancer and mice model peritoneal cancer, when treated with adjuvant O_3 therapy, report super anti-tumor effects along with greater survival rates.[43-45]

Some human clinical trials on O_3 therapy in cancer shown fantastic results. Patients with pelvic tumor, head and neck tumors, non-small cell lung cancer treated with O_3 with or without RT, showed good results, which includes improved quality of life, less aggressive tumor behavior, and fast tumor regression with minimal side effects of radiation.[46-49]

Combination of Nutritional Ketosis and Hyperoxygenation Therapies

Combining these therapies produces potent, synergistic anti-cancer effects by targeting several overlapping metabolic pathways that are critical to cancer progression and are especially prominent in metastatic cells.

In a mouse model study of metastatic tumor by Angela Poff, et al., (i) mice group treated with KD, (ii) mice group treated with KD and ketone supplements and (iii) mice group treated with KD, ketone supplements and hyperbaric oxygen therapy exhibited a 44.6%, 65.4% and 103.2% increase in mean survival time compared to controls (mice group fed with standard diet alone), respectively. Combination group has shown significant reduction in tumor burden and metastatic spread compared to other groups. This study strongly suggests that combining nutritional ketosis with HBO_2T may be an effective non-toxic therapy for the treatment of metastatic cancer.[50]

Maurer GD, et al., who studied the utilization of ketone bodies by glioma cells, suggest that, along with nutritional ketosis, a co treatment – an antiangiogenic agent like hyperoxygenation therapy can potentiate the anti-tumor effect by synergistic action.[8] In a double blind control study, 54 critically ill cancer patients with 6 different metastatic tumors (liver cancer, colorectal cancer, kidney cancer, brain metastatic tumors, breast cancer, and lung cancer) were treated with the combination of KD and intravenous ozone therapy (IOT). After three months, an average of 58% reduction in the tumor size was recorded.[51] This study continued with 31 patients for 180 days with an addition of HBO_2T and several supplements after 90 days and resulted in 98.8%

reduction in the tumor size, which warrants the development of non-toxic, non-invasive cancer treatment protocol with the substantial inclusion of above mentioned therapeutic components.

References

1. Vaupel P, Höckel M, Mayer A. Detection and characterization of tumor hypoxia using pO2 histography. *Antioxid Redox Signal.* 2007;9:1221–1235.
2. Thomlinson RH, Gray LH, Br J. Cancer. 9:539–549 (1955). THOMLINSON RH, GRAY LH. The histological structure of some human lung cancers and the possible implications for radiotherapy. *Br J Cancer*. 1955;9(4):539-549. doi:10.1038/bjc.1955.55
3. Warburg O. On the origin of cancer cells. *Science.* 1956;24;123(3191):309–314.
4. Klement RJ. Calorie or carbohydrate restriction? The ketogenic diet as another option for supportive cancer treatment. *Oncologist.* 2013;18(9):1056.
5. Klement RJ. Fasting, Fats, and Physics: Combining Ketogenic and Radiation Therapy against Cancer. *Complement Med Res*. 2018;25(2):102–113.
6. Klement RJ. The influence of ketogenic therapy on the 5 R's of radiobiology. *Int J Radiat Biol*. 2019;95(4):394–407.
7. Youm YH, Nguyen KY, Grant RW, et al. The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory disease. *Nat Med*. 2015;21(3):263–269.
8. Maurer GD, Brucker DP, Bähr O, et al. Differential utilization of ketone bodies by neurons and glioma cell lines: a rationale for ketogenic diet as experimental glioma therapy. *BMC Cancer.* 2011;11:315.
9. Stafford P, Abdelwahab MG, Kim DY, Preul MC, Rho JM, Scheck AC. The ketogenic diet reverses gene expression patterns and reduces reactive oxygen species levels when used as an adjuvant therapy for glioma. *Nutr Metab (Lond).* 2010;7:74.
10. Seyfried TN, Sanderson TM, El-Abbadi MM, McGowan R, Mukherjee P. Role of glucose and ketone bodies in the metabolic control of experimental brain cancer. *Br J Cancer.* 2003;89(7):1375–1382.
11. Freedland SJ, Mavropoulos J, Wang A, et al. Carbohydrate restriction, prostate cancer growth, and the insulin-like growth factor axis. *Prostate.* 2008;68(1):11–19.
12. Mavropoulos JC, Buschemeyer WC 3rd, Tewari AK, et al. The effects of varying dietary carbohydrate and fat content on survival in a murine LNCaP prostate cancer xenograft model. *Cancer Prev Res (Phila)*. 2009;2(6):557–565.
13. Beck SA, Tisdale MJ. Nitrogen excretion in cancer cachexia and its modification by a high fat diet in mice. *Cancer Res*. 1989;49:3800–3804.
14. Otto C, Kaemmerer U, Illert B, et al. Growth of human gastric cancer cells in nude mice is delayed by a ketogenic diet supplemented with omega-3 fatty acids and medium-chain triglycerides. *BMC Cancer.* 2008;8:122.
15. Lee C, Raffaghello L, Brandhorst S, et al. Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. *Sci Transl Med.* 2012;4(124):124ra27.
16. Schmidt M, Pfetzer N, Schwab M, Strauss I, Kämmerer U. Effects of a ketogenic diet on the quality of life in 16 patients with advanced cancer: A pilot trial. *Nutr Metab (Lond).* 2011;8(1):54.

17. Nebeling LC, Miraldi F, Shurin SB, Lerner E. Effects of a ketogenic diet on tumor metabolism and nutritional status in pediatric oncology patients: two case reports. *J Am Coll Nutr.* 1995;14(2):202–208.
18. Poff AM, Ari C, Arnold P, Seyfried TN, D'Agostino DP. Ketone supplementation decreases tumor cell viability and prolongs survival of mice with metastatic cancer. *Int J Cancer.* 2014;135(7):1711–1720.
19. Kawasoe Y, Yokouchi M, Ueno Y, Iwaya H, Yoshida H, Komiya S. Hyperbaric oxygen as a chemotherapy adjuvant in the treatment of osteosarcoma. *Oncol Rep*. 2009;22(5):1045–1050.
20. Raa A, Stansberg C, Steen VM, Bjerkvig R, Reed RK, Stuhr LE. Hyperoxia retards growth and induces apoptosis and loss of glands and blood vessels in DMBA-induced rat mammary tumors. *BMC Cancer*. 2007;7:23.
21. Stuhr LE, Raa A, Oyan AM, et al. Hyperoxia retards growth and induces apoptosis, changes in vascular density and gene expression in transplanted gliomas in nude rats. *J Neurooncol*. 2007;85(2):191–202.
22. Moen I, Øyan AM, Kalland KH, et al. Hyperoxic treatment induces mesenchymal-to-epithelial transition in a rat adenocarcinoma model. *PLoS One*. 2009;4(7):e6381.
23. Stuhr LE, Iversen VV, Straume O, Maehle BO, Reed RK. Hyperbaric oxygen alone or combined with 5-FU attenuates growth of DMBA-induced rat mammary tumors. *Cancer Lett.* 2004;210(1):35–40.
24. Bennett M, Feldmeier J, Smee R, Milross C. Hyperbaric oxygenation for tumour sensitisation to radiotherapy: a systematic review of randomised controlled trials. Cancer *Treat Rev.* 2008;34(7):577–591.
25. Takiguchi N, Saito N, Nunomura M, et al. Use of 5-FU plus hyperbaric oxygen for treating malignant tumors: evaluation of antitumor effect and measurement of 5-FU in individual organs. *Cancer Chemother Pharmacol*. 2001;47(1):11–14.
26. Petre PM, Baciewicz FA Jr, Tigan S, Spears JR. Hyperbaric oxygen as a chemotherapy adjuvant in the treatment of metastatic lung tumors in a rat model. *J Thorac Cardiovasc Surg*. 2003;125(1):85–95.
27. Granowitz EV, Tonomura N, Benson RM, et al. Hyperbaric oxygen inhibits benign and malignant human mammary epithelial cell proliferation. *Anticancer Res*. 2005;25(6B):25:3833–3842
28. Moen I, Jevne C, Wang J, et al. Gene expression in tumor cells and stroma in dsRed 4T1 tumors in eGFP-expressing mice with and without enhanced oxygenation. *BMC Cancer*. 2012;12:21.
29. Moen I, Tronstad KJ, Kolmannskog O, Salvesen GS, Reed RK, Stuhr LE. Hyperoxia increases the uptake of 5-fluorouracil in mammary tumors independently of changes in interstitial fluid pressure and tumor stroma. *BMC Cancer.* 2009;9:446
30. Jevne C, Moen I, Salvesen G, Reed RK, Stuhr LEB. A reduction in the interstitial fluid pressure per se, does not enhance the uptake of the small molecule weight compound 5-fluorouracil into 4T1 mammary tumours. *Drug Ther Stud*. 2011;1(1):10–14.
31. Dische S, Senanayake F. Radiotherapy using hyperbaric oxygen in the palliation of carcinoma of colon and rectum. *Clin Radiol*. 1972;23(4):512–518
32. Chen YC, Chen SY, Ho PS, et al. Apoptosis of T-leukemia and B-myeloma cancer cells induced by hyperbaric oxygen increased phosphorylation of p38 MAPK. *Leuk Res*. 2007;31(6): 805–815.

33. Ohgami Y, Elstad CA, Chung E, Shirachi DY, Quock RM, Lai HC. Effect of hyperbaric oxygen on the anticancer effect of artemisinin on molt-4 human leukemia cells. *Anticancer Res*. 2010;30(11): 4467–4470.
34. Kalns J, Krock L, Piepmeier E Jr. The effect of hyperbaric oxygen on growth and chemosensitivity of metastatic prostate cancer. *Anticancer Res*. 1998;18(1A):363–367.
35. Kalns JE, Piepmeier EH. Exposure to hyperbaric oxygen induces cell cycle perturbation in prostate cancer cells. *In Vitro Cell Dev Biol Anim*. 1999;35(2):98–101.
36. Sweet F, Kao MS, Lee SC, Hagar WL, Sweet WE. Ozone selectively inhibits growth of human cancer cells. *Science*. 1980;209(4459): 931–933.
37. Karlic H, Kucera H, Metka M, Schönbauer M, Söregi G. Effect of ozone and ionizing radiation on an in vitro model–a pilot study of 4 gynecologic tumors. *Strahlenther Onkol*. 1987;163(1):37–42.
38. Zänker KS, Kroczek R. In vitro synergistic activity of 5-fluorouracil with low-dose ozone against a chemoresistant tumor cell line and fresh human tumor cells. *Chemotherapy*. 1990;36(2):147–154.
39. Cannizzaro A, Verga Falzacappa CV, Martinelli M, Misiti S, Brunetti E, Bucci B. O(2/3) exposure inhibits cell progression affecting cyclin B1/cdk1 activity in SK-N-SH while induces apoptosis in SK-N-DZ neuroblastoma cells. *J Cell Physiol*. 2007;213(1):115–125.
40. Simonetti V, Quagliariello V, Giustetto P, Franzini M, Iaffaioli RV. Association of Ozone with 5-Fluorouracil and Cisplatin in Regulation of Human Colon Cancer Cell Viability: In Vitro Anti-Inflammatory Properties of Ozone in Colon Cancer Cells Exposed to Lipopolysaccharides *Evid Based Complement Alternat Med*. 2017;2017:7414083.
41. Menéndez S, Cepero J, Borrego L. Ozone therapy in cancer treatment: State of the art. *Ozone Sci Eng.* 2008;30(6):398–404.
42. Schulz S, Häussler U, Mandic R, et al. Treatment with ozone/oxygen-pneumoperitoneum results in complete remission of rabbit squamous cell carcinomas. International *J Cancer.* 2008;122(10):2360–2367.
43. Hernuss P, Müller-Tyl E, Seitz W. Radiosensitizing effect of ozone in animal experiment. *Strahlentherapie*. 1974;147(1):91–96
44. Kızıltan HŞ, Bayir AG, Yucesan G, et al. Medical ozone and radiotherapy in a peritoneal, Erlich-ascites, tumor-cell model. *Altern Ther Health Med*. 2015;21(2): 24–29.
45. Dogan R, Hafız AM, Kiziltan HS, et al. Effectiveness of radiotherapy+ozone on tumoral tissue and survival in tongue cancer rat model. *Auris Nasus Larynx*. 2018;45(1):128–134.
46. Hernuss P, Müller-Tyl E, Dimopoulos J. Ozone-oxygen injection in gynecological radiotherapy. *Strahlentherapie*. 1974;148(3):242–245.
47. Clavo B, Ruiz A, Lloret M, et al. Adjuvant Ozonetherapy in Advanced Head and Neck Tumors: A Comparative Study. *Evid Based Complement Alternat Med*. 2004;1(3): 321–325.
48. Bocci V, Larini A, Micheli V. Restoration of normoxia by ozone therapy may control neoplastic growth: a review and a working hypothesis. *J Altern Complement Med*. 2005;11(2):257–265.

49. Emma B. Treatment of advanced non-small-cell lung cancer with oxygen ozone therapy and mistletoe: an integrative approach. *Eur J Integr Med.* 2012(4):130.
50. Poff AM, Ari C, Seyfried TN, D'Agostino DP. The ketogenic diet and hyperbaric oxygen therapy prolong survival in mice with systemic metastatic cancer. *PLoS One*. 2013;8(6):e65522.
51. Somayeh Zaminpira and Sorush Niknamian. "Evolutionary Metabolic Hypothesis of Cancer (EMHC)". EC Pulmonology and Respiratory Medicine 5.4 (2017): 167-179.

Published June 17, 2023

About the Author

Dr. Santhosh John is Ayush Medical Officer (Naturopathy & Yoga) at Government Primary Health Centre, Gudalur, Theni District, Tamil Nadu, India. E-mail: **manonehujeph@google.com**, Mob: 0091 8668161009