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Improving 21st Century Cancer Therapy: Correcting Treatment Paradoxes and Combining Integrative and Conventional Oncology

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Abstract

Recently there have been many advances in cancer treatment, however, treatment results would be much better if clinical oncologists were educated on the research of cancer metabolism and basic cancer immunology. Many medical oncologists have deficiency in these areas and are devoted to treatment protocols and totally against integrative oncology. One neglected problem is a lack of attention to the cancer patient's host immunity, which should be evaluated at diagnosis. This huge barrier between integrative and conventional oncology should be eliminated for the benefit of the cancer patient. This communication is an attempt to resolve these important treatment details and bring awareness to this problem.

Keywords

Cancer Immunotherapy, Lymphocyte Count, Gut Microbiome, Metabolic Therapy

1. Introduction

In the past 50 years, there have been many advances in cancer detection, imaging, staging, genetic testing, and exciting new treatments. The big 3, surgery, chemotherapy, and radiation still play an important role in cancer treatment; but fortunately, now the 4th modality cancer immunotherapy has finally arrived in the cancer therapy arena. It is now playing a vital complementary role in the management of cancer.

The advances in cancer treatment have improved survival in some cancers,

however, the overall cancer free survival in Stage IV cancer still has much room for improvement. This improvement will require surgical, medical and radiation oncologist to make important changes in their approach to treating and managing cancer.

These important changes should be implemented the moment the patient is advised their diagnosis is cancer. This task is usually done by the surgeon that performed the diagnostic biopsy. The diagnosis is a tremendous shock to the patient and immediately has a devastating immunosuppressive effect on their host immune system. When a patient is told they have cancer a cascade of fear, stress, anxiety, anger and death thoughts which initiate severe host immunosuppression that might impact the overall therapeutic result [1].

This communication is an attempt to bring awareness to the importance of host immunity at diagnosis, knowledge of metabolic therapy, eliminating lymphocyte depleting prechemotherapy cocktails, importance of maintaining good absolute lymphocyte counts, role of the gut microbiome; and how to improve response to checkpoint inhibitors by applying techniques to activate effector T-lymphocytes and maintain great absolute lymphocyte counts.

This will be a complicated and difficult task, but we will try to address each topic and its role on cancer patient therapy. Then we will discuss how each one relates to the others and how used together they synergize, complement, and improve cancer therapy response with less toxicity. Hopefully, this article will stimulate all oncologists to adopt detail treatment protocols that will improve cancer therapy and better patient quality of life and survival.

2. Importance of Host Immunity in the Cancer Patient

Although certain cancer immunotherapies are now available, there is still a serious problem of patient host immunity being ignored in clinical oncology. The concept of cancer immunotherapy is not new and was promoted by William Coley more than a century ago [2]. Unfortunately, it has taken too long for it to become a mainstream treatment modality for cancer, and results could be much better if patient host immunity is activated and healthy. The strong patient host immunity is critical for how the patient tolerates therapy and is directly related to the response of therapy.

We published an article in 2005 about this problem. It was entitled "Host Immunity Ignored in Clinical Oncology: a Medical Opinion" [3]. Now 15 years later it is still a serious problem that should be corrected at the time of diagnosis, or we are denying the best treatment response. The patient probably got cancer because of host immunosuppression. The reason for depressed immunity may be different in each patient, but if not addressed it will be further insulted by cancer treatment. The effects of surgery, chemotherapy, and radiation are all very stressful and immunosuppressive.

The clinical oncologist needs to evaluate host immunity while they are directing their attention to the disease, tumor type, staging, tumor biology, genetic-

testing, and treatment options. This work-up and consultation period have a tremendous negative effect on patient host immunity. However, if it's addressed it gives the oncologist time to improve host immunity before the cancer treatment phase.

The progression of depressed host immunity in the cancer patient is uniquely described by Urosevic and Reinhard as cancer immunoediting. They state there are 3 stages: 1-elimination, 2-equilibrium, and 3-escape [4]. The escape phase leads to clinical cancer which is probably initiated by an acute or chronic stressful event or illness.

There are 5 important phases of host immunosuppression during the cancer treatment journey. These phases require different approaches and treatment that should start at diagnosis. The 5 phases and approaches to each for immune support are described in our paper on "Psychoneuro-Immunooncology" [1]. The 5 stages are: 1) stress at diagnosis, 2) stress and anxiety during staging work-up, 3) stress involved with treatment decisions, 4) preoperative, operative, and postoperative period, 5) period of adjuvant treatment: a) chemotherapy, b) radiation, c) hormonal treatment. These all affect host cancer immunosuppression by different mechanisms. This paper is highly recommended for those interested in these important critical details. Hopefully, this section has stimulated some oncologist to evaluate and address host immunity with their cancer treatment protocol.

3. Importance of Maintaining a Great Absolute Lymphocyte Count

The value of lymphocytes in supporting host immunity cannot be overemphasized. They are involved in innate and adaptive immunity. There are 3 different groups of lymphocytes: 1) T-cells, 2) B-cells and 3) Natural killer T-cells (NK-T); and they have different roles to protect the host from invaders and prevent overactive immunity that can cause autoimmunity. The T-cell is involved in cell medicated immunity and the B-cell plays a role in antibody production and stimulation of plasma immunoglobulins. The (NK-T) cell is a major player in innate immunity and protects the host from bacteria, parasites, viruses, andcancer. Each lymphocyte group has different subsets that perform effector or suppressive functions. Healthy and great host immunity requires a delicate balance of effector and suppressive functions.

The goal of this section is to emphasize the valuable role of total number of healthy lymphocytes in the cancer patient's journey of cancer diagnosis and treatment. A major mistake is the medical oncologist ignoring the lymphocyte count during chemotherapy. They monitor the neutrophil counts for neutropenia to prevent sepsis. However, they not only ignore lymphocyte counts, but actually eliminate their numbers and function by adding steroids to their pre-chemotherapy intravenous cocktails. This may reduce side effects but totally decreases the goal of irradicating the tumor and preventing recurrence.

Chemotherapy produces a cytotoxic or necrotic effect on tumor cells; however, a better response occurs if healthy lymphocytes can invade the damaged tumor microenvironment (TME) and augment the chemotherapy effect. These (TME) lymphocytes can process peptides and proteins (tumor antigens) from cells of the dying tumor and this induces antigenic presentation to produce more tumor directed T-cells which may induce an immunogenic response and autovaccination.

Riesco has reported more evidence on the importance of the lymphocyte in cancer. He reported that the pretreatment lymphocyte count predicted the overall survival of cancer patients. He found it to be a major independent prognostic factor above all others [5]. Great strong evidence of lymphocyte importance was reported by Fumagalli *et al.* [6]. This group reported that lymphocyte counts predict overall survival independently in advanced cancer patients and should be a biomarker for interleukin-2 (IL-2) therapy. They emphasize that not only response of the tumor, but proper immune performance of the host is measurable by lymphocyte change which can be improved by IL-2 treatment and if not improved, is a very negative immune factor. They also stated that cancer-associated lymphopenia is related to endogenous IL-2 inhibition and assessment of lymphocytes is a biomarker for IL-2 treatment is peripheral rebound lymphocytosis and from a clinical view is a predictor of long term survival which is the goal of anticancer treatment [7].

Unfortunately, all the above data and documentation on the lymphocyte role in cancer survival is still ignored in clinical oncology. This is genuinely concerning because our paper and others are all over 15 years; yet mainstream clinical oncology has not implemented careful monitoring of lymphocytes during chemotherapy. They do not monitor, nor do they institute treatment to correct severe lymphopenia. If this was done, we would be seeing better treatment and survival results. Some simple methods are to support lymphocyte numbers and health is placing these patients on a good probiotic and mushroom supplements, and monitor lymphocyte counts during therapy. It is important to reemphasize the importance of the (TME) during chemotherapy. Chemotherapy produces cytotoxic and necrotic effects on tumor cells; however, a better result occurs if healthy activated lymphocytes can then invade the damaged tumor microenvironment (TME). The chemotherapy response will be augmented. These (TME) activated lymphocytes can engulf and process tumor peptides and antigens of the dying tumor cells to induce antigenic presentation to induce more tumor directed T-cells. This effect can induce an immunogenic response and autovaccination.

4. Importance of the Gut Microbiome in Host Immunity and Cancer Immunotherapy

The gut microbiome initiates birth of healthy host immunity. The gut is loaded with tremendous amounts of lymphoid tissue referred to as Gut Associated

Lymphoid Tissue (GALT). Its role in general health, host immunity and cancer therapy are now much more appreciated; and great researchers are actively studying and reporting exciting roles of the microbiome in health, host immunity and disease. Dr. Martin J. Blaser has made a tremendous contribution to understanding the human microbiome and its importance in human health. This was discussed in detail in his book entitled "Missing Microbes: How the Over usage of Antibiotics is Fueling our Modern Plagues" [8].

Severe damage to the microbiome is done by cancer chemotherapy and this can affect the therapeutic result. Cancer patients on chemotherapy frequently are prescribed antibiotics which cause further damage to the gut microbiome, and damage mitochondria in the patient's normal cells. This damage adds to toxicity, fatigue, mitochondrial oxidative damage and decreases therapeutic effect. This is evident because mitochondria are evolutionary bacteria and they share very similar ribosomes to their relatives, good bacteria, in the microbiome and also pathogenic bacteria. The details of this effect and damage are discussed in our paper entitled: "Antibiotics Friend or Foe: From Wonder Drug to Causing Mitochondrial Dysfunction, Disrupting Human Microbiome and Promoting Tumorigenesis" [9]. Oncologist can help prevent this microbiome and mitochondrial oxidative damage by making sure their patients are on a very good probiotic and strong antioxidant when they have to use an antibiotic.

The cancer immune checkpoint inhibitor therapy response depends on a healthy gut microbiome that contains certain organisms and absence of others. Routy *et al.* have evaluated interactions and response to anti-PD-1 therapy in patients with several carcinomas and found that patients on antibiotics taken during cancer therapy for infections had a negative response to anti-PD-1 treatment. This was thought to be due to disruption of microbiota. Microbial diversity was important, and responders had an abundance of *Akkermansia muciniphila* in the fecal microbiota. Other important organisms in responding patients were immune-regulatory bacteria (Akkermansia, Bifidobacterium and Faecalibacterium). These observations showed tremendous interaction of antitumor PD-1 blockade and intestinal bacteria [10].

Matson *et al.* also showed that responding patients had abundance of certain microbial species especially *Bifidobacterium longum* [11]. Routy *et al.* compared the fecal microbiota of non-responders to responders that revealed responders had an abundance of *Akkermansia muciniphila* in the microbiota. They suggest giving fecal transplants to improve anti-PD-1 cancer therapy [10].

Other investigators have reported also on the fact that CTLA-4 anticancer immunotherapy blockade depends on the gut microbiota. They emphasize the importance of distinct Bacteroides species. Some of the organisms stressed for good response were B. fragilis and B. thetaiotaomicron. The consensus was that there was a key role for Bacteroides to get positive effects of CTLA-4 blockade [12] [13] [14]. The bacterial population of the human gut microbiome is extremely important in host immunity, cancer immunotherapy and health. There

are now suggestions that gut bacteria could be linked to neurodegenerative disease, depression, mental well-being, and especially ALS.

A serious existing problem is that we still see many patients on chemotherapy and checkpoint inhibitors therapy that are not on a probiotic and have very low effector lymphocyte counts. Frequently, they are on antibiotics and not on a probiotic or an antioxidant. The correct probiotic is important for efficacy of checkpoint blockade therapy and the antioxidant protects normal cells from antibiotic induced oxidative damage to healthy cellular mitochondria.

5. Cancer Metabolism and Metabolic Therapy

The importance of cancer metabolism and the "Warburg Effect" in cancer cells has recently been revisited. However, the efficacy of metabolic therapy for cancer as an adjunct to conventional cancer therapy has essentially been ignored by medical oncology. The importance of cancer as a metabolic disease was described in detail in our paper entitled: Want to Cure Cancer? Then Revisit the Past; "Warburg was Correct," Cancer is a Metabolic Disease [15].

We owe much appreciation for the renewed interest in cancer metabolism and metabolic therapy of cancer to Thomas Seyfried. He and Shelton published a great paper on cancer as a metabolic disease [16] and later Seyfried' s book on Cancer as a Metabolic Disease released by Wiley [17]. In order to improve cancer treatment, we need to know what is common to all tumors and not just all of the genetic mutations which can be numerous. There is now strong evidence that a main problem in all cancers is defective cellular energy metabolism no matter the cellular or tissue of origin. Normal cells produce energy by oxidative phosphorylation while cancer cells ferment glucose to lactic acid by aerobic glycolysis.

Otto Warburg, in the 1930's, described a link between tumorigenesis and mitochondrial dysfunction. He noticed a marked increase in glycolysis with increased lactate production in the presence of oxygen and a decrease in oxidative phosphorylation. This became known as the "Warburg Effect" [18] [19]. Hanahan and Weinberg described six essential alterations in cancer they designated as the hallmark of cancer [20]. We believe that the "Warburg Effect" aerobic fermentation is a robust metabolic hallmark of most tumors [21]-[26].

Aerobic glycolysis "Warburg Effect" can be impacted and reversed by the metabolic therapy of cancer. However, mainstream oncology has not embraced metabolic therapy and it has virtually been ignored. Metabolic therapy involves preventing the fermentation of glucose. This can be done by placing patients on a rigid Ketogenic diet. It is important to monitor the patient's glucose and ketones daily. Ketosis inhibits glycolysis, cancer cell proliferation and sensitizes cancer cells to standard chemotherapy. This means if a patient is in ketosis; the oncologist can cut the dose of chemotherapy, reduce toxicity, and still achieve the same cytotoxic chemotherapy effect. The decreased dose will then produce less adverse events on lymphocytes and general host immunity. Metabolic ther-

apy can be enhanced by other glycolysis inhibitors, such as, metformin, dichloroacetate (DCA) and 3-bromopyruvate. These agents can produce serious side effects and patients need to be monitored carefully. Glutamine should also be avoided as it can be a substrate for energy production through another cancer cellular metabolic pathway.

For the readers that want to learn extensive details of metabolic therapy; I highly recommend Seyfried's book "Cancer as a Metabolic Disease" (on the origin, management, and prevention of cancer) [3] [17].

Tumor cellular iron metabolism is another abnormal metabolic defect that is common to all cancers. Iron is an essential micronutrient for DNA synthesis and utilized by the important enzyme in DNA synthesis *Ribonucleotide reductase*. Cancer cells are rapidly proliferating which requires rapid DNA synthesis. Therefore, cancer cells express numerous transferrin receptors to endocytose transferrin bound iron into the cancer cell to be used for DNA synthesis. Cancer cells take in more iron than can be metabolized and the excess iron is bound by ferritin. If not for ferritin, the cancer cell would have severe oxidative damage caused by the excess iron. The iron exporter protein ferroportin is absent in cancer cells as the iron greedy cancer cell wants to retain iron for DNA synthesis. Tumor iron metabolism is complicated and beyond the scope of this communication. For those very interested in the topic, I highly recommend our paper entitled "Cancer: Tumor from Metabolism, Mitochondrial Dysfunction and Tumor Immunosuppression; a Tight Partnership-Was Warburg Correct?" [26].

6. Conclusions and Some Solutions

It is hard to understand why conventional oncology has not embraced the important cancer treatment protocols discussed in this communication to obtain better treatment results.

Integrative oncologists are already accepting these important treatment modifications, but the mission is not yet accomplished. The problem has been emphasized in our commentary entitled "21st Century Cancer Treatment "What's Missing? Wake up Oncology" [27]. There is still a huge disconnect between integrative and conventional oncology.

There are several important points in this communication: 1) Importance of host immunity in the cancer patient, 2) Importance of maintaining a good absolute lymphocyte count, 3) Importance of the Gut Microbiome in host immunity and cancer immunotherapy, 4) Cancer metabolism and metabolic therapy. We have described important methods of how to address each one of these points in each different section. We must start supporting the patient's host immune system, attention to maintaining a good lymphocyte count during treatment, stop the liberal use of steroids and implement metabolic therapy, meditation, proper supplements, exercise, and nutrition. We should have a combined immune-metabolic oncology approach along with a modified conventional therapy regimen, and remember low effector lymphocytes inadequate PD-L1 and CTLA-4

checkpoint response.

We believe if these treatment details are implemented at the beginning of the cancer patient's journey and through their treatment period; the patient will have a better trip and will have a better experience on this very difficult, anxious, fearful and unknown final destination. This is a plea for all cancer patients and the time is now!!

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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