Combination cancer immunotherapy “Expanding Paul Ehrlich’s Magic Bullet Concept”

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The concept of cancer immunotherapy is not new and investigators have tried to stimulate the immune system to fight cancer for over a hundred years. However, success has been limited, inconsistent and very disappointing, thus preventing cancer immunotherapy from becoming a mainstream modality of cancer therapy. In order to improve results of cancer immunotherapy, and catapult it into the mainstream of cancer treatment, an aggressive individual combined approach must be considered and attempted. This communication is admittedly an opinion commentary about a very complex subject and is not a review article. It is important that the reader appreciates this while contemplating the ideas presented.

Paul Ehrlich’s magic bullet theory has inspired many generations of scientists to explore numerous molecular cancer therapeutics. He connected chemistry to biology and medicine; and predicted the existence of specific cell receptors [1]. However, for cancer immunotherapy to be efficacious, it will take out of the box thinking, and applying a multiple magic bullet approach. Most cancer immunotherapy protocols and trials have only evaluated monocancer immunotherapy. Many of these studies have only been vaccine trials, and attempts to attack all arms of the immune system and escape mechanisms in the tumor microenvironment have not been explored at the same time. It is well known that cancer immunotherapy works better when there is less tumor burden, and that is and will be the role of cancer immunotherapy in the adjuvant setting. However, for Stage IV disease we must be more creative and use multiple approaches of cancer immunotherapy in combination with other modalities, such as chemotherapy, radiation, and targeted therapy. I have attempted to explore some of these ideas and concepts in this opinion communication. An effort has been made to describe areas important to address in combination cancer immunotherapy while utilizing the complementary roles of chemotherapy, radiation, and targeted therapy.

Cancer immunotherapy is not a new concept and was initiated in the late 1800s by William Coley [2]. However, even today, cancer immunotherapy is considered to be in an early stage of development; when, in fact, there has been an abundance of research and numerous clinical trials of cancer immunotherapy [3]. The problem is that many trial results of cancer immunotherapy have been disappointing and the field of cancer vaccines has been on a roller coaster ride with much disillusionment and frustration. Today cancer immunotherapy is still considered experimental and this attitude is deep and lingers within the medical oncology community. There are no FDA approved true therapeutic cancer vaccines. The cervical cancer vaccine Gardosil is really a preventative vaccine directed at antigens to the Human Papilloma Viruses. Unfortunately, cancer immunotherapy is not part of the mainstream of cancer therapy and is not on the Big 3 Therapeutic team of surgery, chemotherapy and radiation. The medical oncology community has been too involved with tumor biology and stage of disease and has ignored the host with the disease. The evaluation of individual host immunity has been neglected in clinical oncology, and treatment protocols. However, it is very important and definitely impacts survival.

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Now the future of cancer immunotherapy is more optimistic because of recent advances in cellular and molecular immunology. This has allowed a much better understanding of the complexity and high rate of interactions between tumor cells and the immune system. These interactions can result in tolerance to tumor-associated antigens (TAAs) available in many ways. They cause apoptosis and necrosis, which can be remiss and do an injustice to this communication if I did not mention the excellent and elegant article by Gilboa published 2004 in *Nature Reviews—Cancer* [5]. The article was entitled “The Promise of Cancer Vaccines.” It was an opinion in the perspectives section. He does a tremendous job discussing the complexity of cancer immunotherapy, but also leaves you with optimism that this hurdle can be overcome with a combined approach. He stated, “There are four important issues to consider in designing effective cancer vaccines: how to identify potent tumor rejection antigens; how to stimulate an effective antitumor immune response; how to avoid autoimmune pathology; and how to prevent immune evasion.” He addresses all four areas in detail and also discusses the importance of the tumor stroma and microenvironment in immune suppression and escape mechanisms. He emphasized a combined approach and using chemotherapy and radiation to assist in potentiating the immune response. The goal of this communication is to stimulate interest in combination cancer immunotherapy and discuss some of the many areas that need to be addressed to achieve a better tumor immunotherapeutic efficacy.

This commentary is mainly concerned with adaptive immunotherapeutics and not with passive or adoptive immunotherapy. Passive cancer immunotherapy is available and the monoclonal antibodies Herceptin (trastuzumab) and Avastin (bevacizumab) are impacting cancer therapy favorably. Recent studies of adoptive cell transfer have shown promising results in patients with selected metastatic cancers [6], and this research should continue. However, this therapy is labor intensive, expensive, and requires special dedicated laboratories making it impractical in most community settings. Therefore, manipulating the adaptive immune system and tumor microenvironment in the cancer patient is more challenging and practical.

I believe for cancer immunotherapy to be efficacious and ultimately accepted as the fourth modality of cancer treatment, it will take a very innovative combined individual approach. There will be no set routine protocols. It will take the evaluation of host immunity, tumor biology, genomics and proteomics to design a plan of treatment for each patient. For the cancer immunotherapy to be effective, all areas of the immune system and the tumor must be exploited. The innate and adaptive immune systems must be addressed and used as partners, along with disrupting the numerous and complex tumor escape mechanisms in the tumor and tumor microenvironment. We also need to take advantage of the immunogenic properties of chemotherapy and radiation, which are mainly known to be immunosuppressive. However, these partners with proper dosing and critical timing can be very immunostimulatory [7,8]. Chemotherapy and radiation assist the host immune system in many ways. They cause apoptosis and necrosis, which can produce a large pool of tumor-associated antigens (TAAs) available for crosspresentation to dendritic antigen presenting cells (APCs). They also cause inflammation, produce danger signals, and plasma membrane exposure of calreticulin creating pre-existing immunity for better Toll-like receptor 4 responses, which produces far better antigenic expression by tumor cells, (4) nitric oxide and reactive oxygen species, (5) down regulation of antigenic expression by tumor cells, (6) expression of transforming growth factor beta (TGFB), and Interleukin-6, (7) arginase, (8) indolamine 2,3 dioxygenase, (9) HLA-G, (10) STAT-3, and (11) the interaction of numerous different adhesion molecules. However, we need to attempt it, in hopes of eliciting the right immune cascade, if even in only a few patients.

Cancer immunotherapy protocols in the adjuvant setting will be much different than those for patients with advanced disease. Actually, there have been few studies (trials) of cancer vaccines in the adjuvant setting compared with vaccine protocols in patients with advanced disease. This communication addresses mainly the need for a very sophisticated combined immunotherapy approach for patients with stage IV disease. This will require a new way of thinking and teamwork. All areas of the immune system must be exploited sequentially at the same time. The innate and adaptive systems must be stimulated and manipulated concurrently. They are much more connected than previously thought, and work as a continuum with many important bridging immune cells carrying receptors for both systems [10]. Both sides of the adaptive system must be manipulated. The effector system should be stimulated and the suppressor system inhibited. At the same time the very complex tumor immunosuppressive mechanisms in the tumor and tumor microenvironment have to be reversed. This will be a difficult and very complicated task as there are many tumor microenvironment immunosuppressive mechanisms. Some of the most important are: (1) hypoxia, (2) FOXP-3 regulatory T-cells, (3) myeloid derived suppressor cells, (4) nitric oxide and reactive oxygen species, (5) down regulation of antigenic expression by tumor cells, (6) expression of transforming growth factor beta (TGFB), and Interleukin-6, (7) arginase, (8) indolamine 2,3 dioxygenase, (9) HLA-G, (10) STAT-3, and (11) the interaction of numerous different adhesion molecules. However, we need to attempt it, in hopes of eliciting the right immune cascade, if even in only a few patients.

We have to elicit the biological barriers to generating effective tumor immune responses, improve methods of immunological monitoring, and improve inter-laboratory and inter-trial comparisons. Personal communication with an European colleague (G. Gaudernack) working with the Biotherapy Development Association stated that they have posed a number of general solutions, such as: “(1) better patient selection, (2) Use of multi-modal treatments that affect several aspects of the immune system at once, (3) a requirement for the development of good biomarkers to stratify patients for selection prior to trials and as surrogates for clinical responses, and (4) harmonization of standard operating procedures for immunological monitoring of clinical trials.” [11]

This is a very complex topic, but it is time we begin thinking about a combined cancer immunotherapy approach just as we have done for years with chemotherapy. I believe the goal is to selectively make the tumor an autoimmune disease, and by using these concepts along with targeting foreign antigens to the tumor our lab has made significant progress towards that goal (data not reported).

Hopefully, this communication will stimulate a renewed interest in cancer immunotherapy and initiate protocols of combination cancer immunotherapy in association with chemotherapy, radiation, and targeted therapy. It is only by applying new ideas and concepts that cancer immunotherapy will reach its full potential and become the fourth modality of cancer therapy. There is no doubt that host immunity impacts survival in the cancer patient [12]. We must explore all possibilities to afford the cancer patient better palliation and survival. This will be accomplished only by new creative approaches. I challenge those in this field to expand their thinking, start this journey and network with other teams. The journey will be difficult, but exciting and could yield dramatic results.

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