Mini Review
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Cancer immunotherapy and immuno nutrition

Abstract

Recently, immunotherapy has become a clinically validated treatment for cancer patients. Immunotherapeutic strategies include cytokines, cancer vaccines, adoptive cellular therapy, immune checkpoint blockade, Immunostimulatory antibodies and treatment methods used to restore or enhance the cancer cell antigen numbers. Studies also show that immuno nutrition, newly developed formulas containing arginine and/or glutamine, omega-3 fatty acids, and ribonucleic acids could modulate inflammatory and immune response in cancer patients. These reviews outline some of the main strategies in cancer immunotherapy and the role of immuno nutrition. The authors believe that the combination therapies with the support of immuno nutrition may provide new hopes to end cancer.

Keywords: cancer, immunotherapy, immunonutrition

Volume 3 Issue 4 - 2017

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Received: January 03, 2017 | **Published:** April 26, 2017

Abbreviations: ACT, adoptive cellular therapy; CAR, chimeric antigen receptors; CMP, cancer precision medicine; CTLA-4, cytotoxic t-lymphocyte associated protein 4; DCs, dendritic cells; PD1, programmed cell death protein 1; PD-L1, programmed cell death protein-ligand 1; TCR, t cell receptor

Introduction

Cancer is a disease where cells fail to die, and continue to multiply until it overwhelm the healthy cells and later the body. The oldest description of cancer was found in an ancient Egyptian text that dated back to 3000 B.C. The paper was called the Edwin Smith Papyrus and it was part of a textbook about trauma surgery, and states about cancer "There is no treatment".[1] Centuries later, the treatment of cancer becomes more advanced, and survival rates has steadily increased. Currently, we are on the path trying to find a more suitable treatment that does not involve the destruction of healthy non-cancerous cells.

The human immune system protects us against pathogens including cancer cells with innate and adaptive immunity. Innate immune system includes physical barriers, mononuclear phagocytes, macrophages, natural killer cells, and cytokines and so on. Adaptive immunity consists of B cells and T cells. Cancer immunology realizes that there are three different phases of cancer cells progression, the first is immune surveillance, in which the immune system efficiently eliminates the cancer cells. The second phase is immune equilibrium, in which the cancer cells clings to survival and when the immune cells fight back. Immune escape is the third phase, in which the immune system is defeated, and the tumor begins to grow, invade, and metastasize.[2] Immunotherapy is a reasonable treatment option that uses the body's very own immune system to help fight cancer cells. There are many different possible methods for immunotherapy with different levels of success and results.[3]

Discussion

The different approaches against already existing cancers include surgery, radiation therapy and chemotherapy, and immunotherapy to eliminate neoplastic cells. Regular immune system can suppress cancer cells, however but cancer cells are known to be efficient at suppressing or resisting the body's immune response, including local immune evasion, and systemic disruption of T cell signals. The immune system's immune editing, immune recognition of malignant cells are also suppressed. Over the years, people discovered different components of the immune systems that play a critical role in killing cancer. That includes various approaches such as the stimulation of effector mechanism to counteract inhibitory and suppressive mechanisms.[4]

Cytokines are a form of immunotherapy, in which IL-2 and IFN-alpha stimulate the host's immune system, but both have low response rates. IL-2 has a significant risk of serious systemic inflammation, and IFN-alpha has a high dose of toxicity.[5]

Treatments to activate effector immune cells involve vaccination with tumor antigens or augmentation of antigen presentation which can increase the ability of the patient's immune system and bolster immune response against neoplastic cells. While having only a small amount of toxicity and is able to be administered outpatient, the lack of universal antigens and ideal immunization protocols lead to poor efficacy and response.[6]

Another cell-based therapy besides vaccines is adoptive cellular therapy (ACT), which exploits the antitumor properties of lymphocytes to erase metastatic and primary tumors. The lymphocytes are isolated from patient's blood, tumor-draining lymph nodes or tumor tissues, expanded *ex vivo*, and are re infused back into the patient. ACT would hopefully circumvent the tolerance to tumor antigens and produces high avidity in effector T-cells, but is only currently restricted to melanoma, and has safety issues and serious adverse effects and lacks of long lasting responses. It is also an expensive treatment and requires time to develop the desired cell population.[7–9]

Another type of immunotherapy is immune checkpoint blockade, in which anti-cytotoxic T-lymphocyte-associated protein 4(CTLA-4) monoclonal antibodies, anti-programmed cell death protein 1(PD1) and anti-programmed cell death protein-ligand 1(PD-L1) antibodies are used. Anti-CTLA-4 monoclonal antibodies unleash previous existing anticancer T cell responses and prolongs the patient's survival, but it benefits only a small fraction of patients and has severe immune related adverse events that has been observed in 35percent of patients. The anti-PD1 and anti-PD-L1 antibodies are long lasting and have therapeutic responses in patients with a broad range of human cancer, and possesses reduced toxicity but only benefits a small fraction of patients.[4,10]

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Immunostimulatory antibodies are another class of agents that had been used as mono therapy or in combination. The goal of most of these antibodies is to activate their target receptors. Most of the target are members of the TNF receptor super family. 4-1BB is a type of membrane glycoprotein expressed on the surface of CD4+ and CD8+ T cells. Studies indicate that signaling via 4-1BB by binding to its ligand promotes T cell activation, growth, and survival.[11] OX40 is a receptor found on CD4+ and CD8+ T cells, and its engagement helps promote T cell activation, proliferation and cytokine production. These class of agents is still in its early stage, and needs more clinical investigation.[12]

The loss of antigens presents a major immune escape mechanism, and may precludes the efficacy of T cell-based immunotherapies and checkpoint inhibitors. There are a number of treatments that can be used in selected patients to restore or enhance the antigen numbers for the patient's immune system, for example, radiotherapy, chemotherapy, tyrosine kinase inhibitors, epigenetics modifiers (HDAC inhibitors and demethylation agents), cytokines, TLR agonists, and CD40 agonists.[13]

Since President Obama announced the Precision Medicine Initiative in his 2015 State of Union address, precision medicine had grown in popularity. The cancer precision medicine (CMP) system covers a wide range of cancer management service, like cancer screening, monitoring of relapse, and prediction of the most effective treatment and personalized immunotherapy. Neoantigens are newly formed antigens on oncogenic cells, which have not been previously recognized by the immune system. Shared antigen vaccines and adaptive T cell therapy, including chimeric antigen receptors (CAR) T cell and T cell receptor (TCR) engineered T cell, are other types of personal immunotherapy, in which exome and transcriptome analyses are used to identify neoantigens.[14]

Immunotherapy has demonstrated that the immune system is crucial to fight cancer. DCs, T and B lymphocytes, cytokines, antibodies, and interleukins, and other molecules interact with the immune system to create a response against the cancer. However, the patient's immune system would not only be spared, but also would be strengthened. Studies show some nutrition formulation containing defined quantities of essential amino acids, omega-3 fatty acids, and nucleotides could provide immune support in cancer patients. These products are called immuno nutrients indicating their special effects on immune system rather than the standard nutrient support. Arginine is an essential substrate for immune cells, specifically for lymphocyte. Omega-3 fatty acids have multiple anti-inflammatory effects, which can decrease oxidative injury. Glutamine can be a major fuel source for macrophages, lymphocytes, and enterocytes. Nucleotides participate in the maturation, activation, and proliferation of lymphocytes, stimulating the phagocytic function of macrophages, modulating delayed hypersensitivity response, response against tumor and grafts, immunoglobulin production, and response to infection. These new developed immuno nutrient formulas has been demonstrated to improve outcome in cancer patients receiving radio and chemotherapy. This improvement is related to the modulation of the inflammatory and immune response and decreases acute toxicity in cancer patients. Immuno nutrition is an emerging field in oncology, and further research is needed, especially focusing on the effects of immuno nutrition in cancer immunotherapy.[2]

Conclusion

Cancer immunotherapy is now emerging as an important addition to conventional therapies by bolstering the patient's immune system to fight cancer. Cancer is a complex condition, in which the cancer cells with different characteristics come from the normal cells. Figuring out the key therapeutic targets and supporting the patient's own immune system are the critical issues in cancer treatment. Immuno nutrition has been demonstrated to improve outcome in surgical or radical treatment in cancer patients. The best formulation and protocols which may aid in improving patient outcomes with immunotherapy needs to be further investigated. However, we believe that optimal combinations of regimes would be the final way to end of cancer.

Acknowledgements

This work was supported primarily by grants to Fen Wang from the National Natural Science Foundation of China (81573798 and 81001586).

Conflict of interest

Author declares that there is no conflict of interest.

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