

Immunotherapy in Cancer Treatment

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Abstract

Various kinds of immunotherapy treatment for cancer are either available to the public or are in the process of clinical trials. Immunotherapy treatments have the potential to treat cancer with significantly less toxicity than chemotherapy and radiation treatments. An emphasis on cellular infusion as a method of either enhancing the immune system by creating an environment for sequestering the host immune system to attack cancer cells or more directly inserting cells to directly attack cancer cells will be provided in this review. Various forms of cancer vaccines are also discussed in this paper as an important aspect in immunotherapy. This review seeks to describe various methodologies associated with administering immunotherapy in the treatment of cancer.

Keywords

Immunotherapy, Cancer, T-cell, NK Cell, Dendrite, CIK, Nano Particles, Exosomes

1. Introduction

The three traditional methods of treating cancer are surgery, chemotherapy, and radiation. These methods may fail to completely remove or eradicate neoplastic cells or cancer stem cells. These methodologies are not specific and have the potential to damage healthy tissue which can lead to morbidity and even mortality. The immune system itself can be greatly impacted by chemotherapy and radiation, leaving the immune system response to cancer degraded.

The ability to restock or enhance the immune response to cancer is very important following chemotherapy and radiation. The immune system protects against cancer in a few ways. One way is the ability of the immune cells to fend off pathogens that are also known carcinogens. Nearly 20% of all cancers are caused by carcinogenic microorganisms. Some of these pathogens, if unregulated by the immune system, can lead to cancers that include but are not limited to Hepatitis B and C, Epstein Barr virus, chlamidia pneumonia, merkel cell polyovirus, and salmonella typhi-1. The immune system can also regulate inflammation which is associated with the development of cancer. Lastly, the immune system can regulate cancer cells themselves through tumor immune

surveillance. This involves the immune system recognizing precancerous and cancerous cells and eliminating them before they become harmful.

There can be a balance of the immune system response to cancer and cancer development called cancer immunoediting. This is a dynamic process where the immune system regulates cancer in one of three different phases. These phases include elimination, equilibrium, and escape. The elimination phase is where the cancer or precancerous cells are detected by the immune surveillance and essentially eliminated [1]. If the cancer cells cannot be completely eliminated, then an equilibrium occurs where the immune system essentially keeps the cancer in check by eliminating as much as it can while the cancer develops. At some point the cancer cells either mutate to avoid immune surveillance [2] [3], fight back with various chemicals that can inhibit the immune response, and/or create a tumor microenvironment where the acidity surrounding the cancer further inhibits the immune response.

Innate immune response is an important factor in controlling the spread of cancer. The innate response involves the use of natural killer cells, macrophages, dendritic cells (DC), and DC/T-cell response. Natural killer cells include CD3⁻, CD16⁺, and CD56⁺ and have the potential to recognize and eliminate tumor cells via perforin/granzyme, and can induce apoptosis in a variety of cell lines. Macrophages, in particular M1 macrophages, have the capacity to kill tumor cells by secreting inflammatory cytokines which can exert cytotoxic activity in addition to tumor-destructive reactions [4]. DCs are responsible for generating a tumor specific effect or immune responses and are an essential link between the innate and adaptive immune response. DCs interact with naive T lymphocytes in a process involving different cellular signals to establish effector T-cells [5]. The process involves four steps and includes antigen presentation, co-stimulatory molecules, cytokine signaling, and chemokine signaling.

The adaptive immune response involves the recognition of antigens presented by MHC-1 and MHC-2 by several kinds of T lymphocytes which include CD8⁺ cytotoxic T lymphocytes (CD8⁺ CTL) and CD4 T helper (T_H) cells. Adaptive immune responses are longer lasting with regard to remembering antigens presented to them by MHC-1 and MHC-2 respectively. CD8⁺ T-cells secrete IFN- γ , perforin, and granzyme B which enact cytolytic activity on cancer cells in addition to playing an important role in immune surveillance. CD4⁺ T-cells are divided into several subtypes and into T_H1 T_H2 phenotypes. T_H1 cells collaborate with CD8⁺ T-cells in addition to secreting IFN- γ , TNF- α , and IL-2 [6], promoting the presentation on MHCI and MHCII and the up regulation of antigen processing. T_H2 fosters humoral immune response by associating with B-cells [7].

1.1. Genetically Modified Dendritic Cells

There are several reasons why the immune system's protection against cancer is so challenging. This includes aberrantly tumor associated antigens [8]-[12] which are associated with natural immunological tolerance of cancer cells and tumor induced immune suppression [13]. Dendritic cells are major regulators of the immune system [9] [14] [15] as well as stimulators or inhibitors of T-cells and B-cells [16]. Constructing dendritic cells to recognize and support an immunological response against cancer cells is challenging and involves changing the intercellular responses to tumor associated antigens and the relaying a signal to T-cells and B-cells. Lentiviral constructs are used to present dendritic cells with new genes that can alter the intracellular pathways associated with creating a robust immune response. Antigen presentation of cancer associated antigens involves a 3 signal model [17] [18]. The mechanism involves the binding of T-cells to form a complex associated with antigen presentation by major histocompatibility molecules and antigen peptides found on dendritic cells as well as responding to co-stimulatory molecules is significant for recognition of self and non-self epitopes. The selection of co-stimulatory molecules in dendritic cells are a major target for enhancing an immune response against cancer since without the co-stimulatory molecules, T-cells will automatically be programmed for apoptosis, anergy, or exhaustion.

Modulation of T-cell response by selective targeting of intracellular signaling pathways is complicated and often results in a new phenotype of dendritic cells. Activation of MAPK/IRF3 increased the secretion of immunosuppressive cytokines [14]. Subcutaneous vaccination of modified dendritic cells by expressing p38 or JNK1 activators significantly increased the CD8 and CD4 cellular expansion [14]. Although p38-activated dendritic cells take approximately 7 days to activate T-cell, complete regression was evident with the caveat of having some of the tumors grow back after dendritic cells lost expression of OVA [14]. Lentiviral constructs to promote a blockade of PD-L1/PD-1 interaction in DC has a stimulatory effect with regard to the interaction of T-cells in

addition to increasing the infiltration of T-cells in tumors [19] [20]. The combination of expressing p38 in addition to PD-L1 silencing in DC yielded an increase IFN- γ T-cell expansion in addition to a decrease in tumor size while increasing survival time [21]. After 3 months, the cure rate was about 80% for the EG7 lymphoma model [20] [22].

1.2. Stem Cell Immunotherapy

Immunotherapy through the use of stem cells remains in its infancy and has yet to become as focused as other forms of immunotherapy. The pluripotent characteristics allow stem cells to become virtually any kind of cell. Some stem cell therapies include inducing stem cells to produce dendritic cells, natural killer cells, and antigen specific T-cells. The differentiation of dendritic cells has been accomplished in both mouse and human ES cell lines [23] [24]. These dendritic cells were functional but had limited ability for cross presentation of antigens to CD8+ T-cells MHC. Differentiation of ES cells to form antigen specific naïve T-cells has been produced by a combination of transcription factors and the introduction of fetal thymus organ culture in order to provide an environment conducive for the formation of diverse CD4+ and CD8+. There have also been reports of successfully differentiated induced pluripotent stem cells to form antigen specific T-cells that can recognize the epitope of melanoma antigen MART-1 [25]. Natural Killer cells have been derived from induced pluripotent stem cells in a two stage culture system [26]. One of the advantages of creating NK cells from stem cells is that it does not require the cell sorting associated with acquiring NK cells in *ex vivo*. NKT cells have also been differentiated from iPS cell lines. Although these cell lines certainly play a role in the immune system response to fight cancer cells, these cell lines have not been introduced to patients in clinical trials.

2. Tumor Infiltrating Lymphocyte Immunotherapy

Tumor infiltrating lymphocytes (TIL) are a heterogeneous mixture of lymphocytes that are found growing within a tumor. TILs are predominately ineffective for killing the cancer cells within the tumor for a number of reasons including a high number of immunosuppressive T regulatory cells, a low number of anti-tumor cells, or anti-tumor cells that have become deactivated or anergic.

Immunotherapy using TIL involves the removal of the TILs from the tumor microenvironment before inducing the growth of these cells *in vitro* and then delivering them back into the body to combat the cancer. Lymphodepletion is thought to increase the activity of the TILs in addition to removing immunosuppressive T-reg cells in order to create an environment that is more conducive for the TILs to combat cancer [27] [28]. This process may even reduce the competition of IL-7 and IL-25 [29] and create space for the proliferation of TILs including NK cells.

Treatment involving TIL therapy has shown itself to be one of the most effective forms of immunotherapy [30]-[32]. The objective response rate varies between 51% - 72% for patients in the advanced stage of melanoma following aggressive treatment involving chemotherapy and often radiation [33] [34]. The TILs effectiveness involves the clinical response time, with regard to the time it takes to culture the TILs which subsequently affects the length of telomere of TILs [35]-[39]. In addition to younger TILs with longer telomeres, they also have higher levels of costimulatory molecule including CD27 and CD28, which is associated with greater persistence *in vivo* [37]-[41].

2.1. Natural Killer Cell Immunotherapy

Natural killer (NK) cells, also known as CD56+ and CD3+, are lymphocytes with cytotoxic potential against anti-self cells. NK cells can be activated and inhibited via several receptor-ligand interactions depending on whether the cells encounter self or anti-self MHC antigens [42] [43]. Licensing via KIR receptor is an important step with regard to how NK cells recognize anti-self cells before they can be fully activated [44]-[46]. NK cells have anti-cancer characteristics but can also be attenuated by either molecules secreted by cancer cells or the cancer micro-environment acidity can paralyze the cells [47] [48].

Autologous NK cell infusion is clinically ineffective with regard to its cancer fighting ability even in the presence of interleukin IL-2 [49]-[51]. However, allogenic NK transfusion has shown some promise with minimal cytotoxicity [52]. CD3-depleted NK lymphocytes with prior doses of cyclophosphamide and fludarabine with additional IL-2 injections following the CD56+ infusion resulted in five out of 19 patients with a poor prognosis

of acute myeloid leukemia had remission [53]. A study containing 10 children with AML were treated with T-cell depleted CD56+ after being treated with chemotherapy and all of the children were in remission for at least 2 years [54].

2.2. Natural Killer T Cell Immunotherapy

Natural Killer T (NKT) cells are able to bridge the gap between the innate and adaptive immunity by establishing memory responses in addition to improving protective immune response. NKT cells are characterized by their antigen receptor $V\alpha 14j\alpha 18$ in mice and $V\alpha 24j\alpha 18$ in humans [55]-[57]. The NKT cell is activated by the α -galactosylceramide (α -GalCer) ligand which results in the expansion of NKT cells which in turn inhibit the growth of metastatic lung cancer and liver metastasis in melanoma *in vivo* mouse models [58] [59]. Mice with induced liver metastasis and treated with α -GalCer/DCs resulted in complete remission of liver metastasis a week after treatment [60]. After surgery, chemotherapy, and radiation, seventeen non-small cell lung cancer patients, who had their peripheral blood mononuclear cells (PBMC) cultured for a week before being pulsed with α -GalCer, were administered their autologous and induced NKT cells twice in the period of a week [61]. Of the 17 patients who underwent this treatment, 10 patients had prolonged their median survival time to 29.3 months as compared to the group without IFN- γ producing cells who had a median survival time of 9.7 months even though either group did not show significant tumor regression [62]. The clinical study had remarkably low levels of toxicity.

2.3. Cytokine Induced Killer Cell Immunotherapy

Cytokine induced killer (CIK) cells, CD3+ and CD56+, are rare in peripheral blood mononuclear cells and are typically expanded *in vitro* derived from T-cells [63]. These cells co-express T-cell markers for CD3 and the NK marker CD56. CIK cells are a heterogeneous that include CD3- CD56+ NK cells, CD3+ CD56- effector T cells, and CD3+ CD56+ cells [64]. *In vivo*, CD3+ and CD56+ interact with NKG2D receptors and MHC-related ligands which mediate the tumor-killing activity [65].

CIK cells' ability to grow rapidly *in vitro*, in the presence of cytokines, with a robust antitumor activity and the ability to attack various kinds of cancer make CIK cells an attractive form of immunotherapy [66]. CIK cells also have the capacity of strengthening the immune system in patients with cancer [67]. The ability to travel to tumor site *in vivo* models with its various chemokine receptors makes CIK cells targeting more efficient [68] [69]. Autologous and allogeneic CIK cells have been studied in phase I/II clinical trials. In these trials, CIK cell immunotherapy has shown evidence of anti-tumor activity and limited toxicity [70]-[74].

2.4. Oncolytic Viruses

Viruses naturally produce a robust immune response including antigen presentation, inflammatory cytokines, and co-stimulation [75]. Viruses are typically recognized as foreign or non-self via pattern recognition receptors like toll receptors (TLR) of the innate immune response. Such recognition drives an immediate immune response of type 1 interferons which involve IFN- α and β [76]-[78] and which in turn enhance the expression of CD40, CD80, CD83, and CD86 [79]-[81]. The pro-inflammatory response is then associated with expression of MHC and co-stimulatory molecules including IFN- α which is involved in stimulating CD8 cells associated with the activation of T-cells.

The recognition of antigens translated and presented after cell lysis has had limited effects on treating cancer thus far. Antigens associated with tumor cells have the potential to recruit innate and adaptive immune responses when presented after cell lysis. Jx-594 is an example of an oncolytic virus that infects hepatocellular carcinoma (HCC) in order to present cellular signals for an innate or adaptive immune response in addition to causing cell lysis [82]. The virus causes the expression of β -galactosidase which is a surrogate marker associated with viral detection in addition to being a granulocyte-macrophage colony-stimulating factor (GM-CSF) [83] [84]. Jx-594 also requires the activation of EGFR/RAS pathway for replication, essentially using the oncogenic metabolism to replicate in a manner that leads to cell death and presentation of the translated immunogenic antigens [83] [84].

2.5. Monoclonal Antibody Immunotherapy

Monoclonal antibodies (mAB) have been used in various ways to treat various cancers. The first FDA approved

mAB was rituximab in 1997. Rituximab targets the CD20 of malignant B-cells and is also known to treat Hodgkin's lymphoma, neuroblastoma, and prostate cancer. Rituximab is a nmAB that binds to tumor-associated antigens (TAA) and is associated with antibody dependent cell-mediated cytotoxicity (ADCC) [85] and complement dependent cytotoxicity [86] [87]. Other mABs like catumaxomab are bispecific and can crosslink to two different antigens in a manner that retains the capability of activating immune effector functions to treat malignant ascites in patients with epithelial cell adhesion molecules (EPCAM) tumors with specificity to CD3 [88] [89]. Y-ibritumamabtrixetan and I-tositumamab are mAB coupled with toxins or radionucleotide which can recognize CD20 targets [90] [91]. These antibodies are used to shuttle the toxins or radionucleotides in a way that can reduce the overall toxicity of drug administration by targeting specific cancer cells. Cetuximab is a chimeric IgG1 that has antigen specificity toward epidermal growth factor receptor (EGFR) and is used to inhibit cancer cell ability to transduce metabolic pathways associated with proliferation and/or survival in colorectal carcinoma [92] [93]. TRAILR2 or DR5 are targets of conatumumab which has the potential to initiate apoptosis of cancer cells by activating cytotoxic receptors of cancer cells [94]. It is currently in phase II clinical trial to treat colorectal carcinoma, lung cancer, and pancreatic cancer.

3. Peptide Vaccines

Peptide vaccines are short or long chains of amino acids which present an epitope to the immune system. These epitopes can include antigens expressed by various cancers which are used to stimulate an immune response that eventually targets cancer cells. The majority of peptide vaccines for cancer are designed stimulate CD8+ which has been associated in the eradication of tumors [95]-[99]. Other peptide vaccines induce an immune response by targeting CD4+ helper T lymphocytes with some anecdotal success with melanoma reactive CD4+ T cells [100].

The administration of peptide vaccines vary with regard to the length of the peptide and how many different varieties of peptides are used. Peptides are easy to make especially when compared to other forms of immunotherapy in addition to being well received in patients. Short peptides are usually 8 - 10 amino acids in length are recognized by CD8+ and eventually presented to class I MHC [101]. Long peptides are range from 13 - 18 amino acids long and are recognized by CD4+ T lymphocytes and presented to class II MHC [101]. Multiple peptides of various lengths are often used simultaneously to induce a more robust immune response and are immunogenic in 100% of the patients [102].

Although most peptides are able to induce an immune response in most patients, the effect on the immune system to attack tumor cells is limited with clinical response rates of 3% - 5% [103]. Presence of T-cells that recognize the antigen is no guaranty of a positive clinical outcome [102] [104]. This might have to do with the tumor micro environment not being hospitable to tumor associated immune response. In addition, many peptide vaccines lack secondary or tertiary structures and have the potential to be eradicated by proteases.

4. Exosomes

Exosomes are small membrane vesicles that usually range between 30 - 100 nm in diameter. They are typically in a saucer shape consisting of a lipid bilayer membrane with an internal compartment [105]. There are many different intercellular functions associated with exosomes including, exosome secreted by B cells can stimulate CD4+ T-cells [106]. There is also evidence to support that tumor antigens can be delivered from dendritic cells by exosomes to be presented to T cells *in vivo* and *in vitro* [107]-[109]. Cancer cells have the capacity to use exosomes in order to induce T-cell apoptosis associated with the CD95 ligand [110] [111]. Exosomes can essentially be used as a shuttle for antigen presentation to a host of immune cells. Clinical trials for inducing the immune system to target cancer cells involving exosome shuttling of granulocyte-macrophage colony-stimulating factor to induce an antitumor cytotoxic T lymphocytes [112] [113] was successful in inducing cytotoxic T-cell response [113].

4.1. Gold Nanoparticle Vaccine

Gold nanoparticles can specially accumulate within lymphocytes in addition to other tissues for delivering immune therapies like vaccines [114]-[117]. They come in a variety of sizes which have different properties with regard to absorption and localization of the nanoparticles [118]. The antigens and cytokines that are presented on

the gold nanoparticles are protected from degradation [119]. Modulation of dendritic cells and T-cell activation in addition to other humoral responses is a function of gold nanoparticle mediated adjuvant delivery [119] [120]. Gold nanoparticles offer a persistent and strong immunological response and have been used deliver large payloads of antigens to given sites associated with the size of the nanoparticle [121]-[125]. It is important to note that the size of the nanoparticle with conjugated antigens increases the diameter substantially. A 30 nm in diameter gold nanoparticle conjugated with a peptide increases to a size of 80 nm [126]. This nanoparticle in particular was able to stimulate T cells at approximately 4 times that of free antigen peptide [126]. Gold nanoparticles of 10 nm, with their associated antigen OVA, have the capacity to deliver a strong immune response after absorption into the skin in mice models, stimulating the anti-OVA IgG response [127]. Clinical studies at this moment are both limited in the amount in process as well as the low number of participants in the trials.

4.2. IL-27 in Immunotherapy

Interleukin 27 (IL-27) is in the IL-12 family of cytokines. IL-12 cytokines, secreted by DC and macrophages, are important in promoting cytotoxic T-cells (CTL) response in addition to differentiating T helper (Th) cells to type Th1 [128] [129]. DC secretes IL-27 when exposed to stimuli including type I or type II interferons and CD40 [130]-[132]. IL-27 acts to stimulate NK cytotoxicity and make tumor cells more vulnerable to cytotoxicity from NK cells [133] in addition to inducing tumor specific antibody response [134]. IL-27 works primarily through CD8+ cells to hinder tumor growth and metastasis. There is potential for tumor promoting activity by promoting Tr1 cells, from T cells, to further induce IL-10 which acts as a negative feedback for pro-inflammatory immune response [135] [136]. IL-27 can also repress DCs from producing cytokines in addition to its antigen-presenting abilities [137].

IL-27 has been shown to have anti-proliferative and anti-angiogenic properties for various kinds of cancers including melanoma [138] [139], acute myeloid leukemia [140], B acute lymphoblastic leukemia [141], multiple myeloma [142], and B cell lymphoma [143]. IL-27 has tertiary effects associated with its immune-stimulatory activity with regard to its anti-tumor characteristics in colon carcinoma [144] [145], lung cancer [146], melanoma [147], neuroblastoma [148], and head and neck squamous cell carcinoma [149]. These studies also remarked on the low level of toxicity.

5. Discussion

There are many forms of effective immunotherapy for cancer with new forms coming out each year. The specificity and the toxicity when compared to chemotherapy and radiation is a significant improvement. While all immunotherapies are not created equal, there is still room to enhance each methodology respectively. As biomarkers become available targets and cancer biology becomes more in focus, the ability to target cancer cells without harming the rest of the body is becoming a reality. Although some immunotherapies did not effectively reduce the size of the tumor, many of them significantly increased the median survival time of the patient. The potential of using more than one form of immunotherapy per patient might become as popular as a patient being prescribed more than one drug to treat cancer.

Unfortunately, a significant amount of promising treatments are still in either phase I or phase II clinical trials and will not be available to the public for years to come. Another issue may involve the price associated with growing various lymphocytes before infusion. Many of the techniques associated with isolating and culturing cells require significant training and expertise to cultivate and administer the treatment. In addition, many hospitals are not equipped to handle the attention required for preserving lymphocytes. The storage and transfer from a lab bench to a hospital is also problematic.

As expressed in this article, there are many different modes to present antigens for cancer vaccines to aid the immune system in recognizing epitopes associated with various cancers. Cancer vaccines in particular are very intriguing and could serve as a method of treating cancers before they occur. Although that is not the current function of the cancer vaccines since they are targeted to the cancer that already exist in the patient, specific and common antigen biomarkers could be presented in a way that can harbor the memory of a common cancerous biomarker.

It is very difficult to rank the various forms of immunotherapy against each other since the clinical data is limited. The methodologies can vary greatly from each form of immunotherapy, and the types of cancers are not uniform when comparing each study. More research is needed to see which set of circumstances immunotherapy

works for a given patient with a specific type of cancer since a similar cancer diagnosis does not provide adequate information of the specific biology of cancer itself. Biopsy of the cancer should be examined to see which biomarkers are present and cross reference that information to either identify which immunotherapy would work or to make those antigens specific to that form of cancer for a cancer vaccine.

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