CANCER IMMUNOTHERAPY – AN EMERGING FIELD

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ABSTRACT
Immunotherapy directed at activating the body's immune system against cancer cells is an exciting field in oncology. In order to circumvent many pitfalls in the area, ongoing research has used monoclonal antibodies, cytokines and cancer vaccines to specifically target and destroy tumor cells. Clinical trials have been conducted with success that use immunotherapies alone or with conventional chemotherapies to address various types of cancers. This short review mentions the significant improvements in the area, as well as remaining challenges to be addressed. Cancer immunotherapy is a developing area that holds many promises. Future years will show if efficient and durable anti-tumor action is provided through these novel approaches.

Keywords: cancer, immunotherapy, monoclonal antibodies, cytokines, vaccines.

INTRODUCTION

Harnessing the body's immune responses to fight against its cancer is an attractive concept in medical research. In principle, antibodies and immune cells that specifically recognize cancer antigens and cells and subsequently destroy them, would provide defense against cancer. This concept has lead to the exploration of several avenues of cancer immunotherapy till date. Some success has been encountered in the past with monoclonal antibodies, immunostimulatory cytokines and vaccine strategies. Most recently the promising clinical trial results for Ipilimumab has spurred great interest in this area for future endeavors (1).

Historically, the concept of cancer immunotherapy was first identified and tested by a surgeon from New York named William B. Coley in 1891 (2). His strategy of injecting live or killed bacteria to sarcoma patients, led to regression of tumors in some of them. The concept was to boost the body's immune responses against the bacterial antigen, which would then provide bystander protective effect against existing cancer cells. Since that time, much improvement has occurred in our understanding of immune cells in the body, and more robust and sophisticated strategies have been devised to approach the concept of cancer immunotherapy.

This short review will discuss the different venues of cancer immunotherapy currently being pursued. It will describe roadblocks encountered in this area that have limited its success, and touch upon possible areas for future research and development.

BOTTLENECKS TO CANCER IMMUNOTHERAPY

A few of the main concerns in the field of cancer immunotherapy are highlighted in a concise manner below. Research and review articles for further study have been mentioned.

1. Tumor antigens are generally closely related to self-antigens, and hence may escape immune recognition (3).
2. Tumor antigens derived from the cancer cells that are mutated proteins or preferentially expressed proteins, have to be encountered by dendritic cells. At this time, the dendritic cells should be also receiving proper signal for its activation and differentiation to mediate an immune response. This is crucial as without the dendritic cell activation signal,

the processing of tumor antigens may lead to development of immune tolerance (4) (5).

3. The lymphoid organs is where the dendritic cells carrying tumor antigens generate desired immune responses mediated by either CD8z T cells, antibodies, natural killer (NK) cells or T cell associated NK cells. Here again, if the proper maturation of dendritic cells have not been achieved, it would lead to the tolerance via regulatory T cells (Tregs).

4. The tumor environment is where immunosuppression occurs through multiple modes (6). Tumors are known to

a) suppress dendritic cell maturation,
b) help accumulate Tregs that would oppose immunity,
c) downregulate the expression of MHC class I molecules and its expression of tumor antigens,
d) cause T cell anergy through the expression of surface molecules (e.g. PD-L1, PD-L2) that bind with T cell receptors,
e) release immunosuppressive agents such as indoleamine 2,3-dioxygenase (IDO), myeloid derived suppressor cells,
f) maintain hypoxia in their micro-environments that produce substances such as adenosine, CCL28 that oppose anticancer immunity, and
g) harbor stromal cells (e.g. mesenchymal stem cells and tumor vascular cells) that suppress effector T cell activities.

These are in short some of the steps in cancer immunotherapy, that have proven challenging to researchers. Despite these roadblocks, some significant successes have been seen with ongoing research efforts. Some of these are described in the next sections.

MONOCLONAL ANTIBODIES THERAPY

Monoclonal antibodies have been employed in cancer immunotherapy in one of the following ways (7):

a)They can be designed to target **specific tumor antigens**. Tumors produce antigens that when recognized by the antibodies, will be targeted for elimination. Clinically relevant tumor antigens are being identified by researchers at a rapid pace. Among many such tumor antigens it is crucial to recognize and prioritize the important ones based on their possible roles in oncogenesis, their specificity, and frequency in different cancers (8).

b) Monoclonal antibodies could be designed to target **growth factors** that support the growth of specific tumors.

c) Finally, monoclonal antibodies could be **linked to anticancer drugs**, radioisotopes, or other toxins, so that when they specifically bind to the tumor cells, these agents exert anti-cancer effects.

Various mechanisms of action exist by which monoclonal antibodies exert therapeutic actions (9). Upon binding to the specific antigen on tumor cell, they could exert apoptosis. They could block growth factor receptors, thus preventing tumor cell growth. In cells that express antibodies, monoclonal antibodies can exert anti-idiotype antibody formation. Furthermore, monoclonal antibodies may indirectly kill tumor cells, through the recruitment of monocytes, macrophages and natural killer cells, and this type of action is called antibody-dependent cell mediated cytotoxicity (ADCC). Alternatively, monoclonal antibodies could bind to the complement cells and enable tumor killing, a process known as complement dependent cytotoxicity (CDC).

Significant limitations to using monoclonal antibodies in cancer therapy exist as tumors tend to express antigens in a heterogeneous fashion, and at different densities throughout the tumor tissue. Also tumor blood flow may be so constricted that monoclonal antibodies cannot reach to the site of action. Since monoclonal antibodies for therapy are derived from non-human cell-lines, there is always the possibility of immune attack against them. Half-lives of

monoclonal antibodies need to be considered for effective therapy. Also, specificity of tumor antigen has to be chosen so that cross reactivity does not occur against normal tissues.

Several monoclonal antibody therapies have been developed to target B cell malignancies. Of them **Rituximab** developed against the antigen CD20 was first approved by the Food and Drug Administration (FDA). Rituximab has been indicated for treatment of low-grade lymphomas refractory to conventional chemotherapy (10). It has also been studied as a first-line of treatment in low-grade non-Hodgkin lymphoma with some success, and as a combination therapy along with conventional chemotherapy in intermediate grade or diffuse large cell non-Hodgkin lymphomas (11) (12) (13) (14). Due to the high expression of CD20 in B cell malignancies several other monoclonal antibody therapies have been developed. **Tositumomab** (15) and **Ibritumomab** (16) are two of these, which have additionally been labeled with radioisotopes for tumor cytotoxic effects. **Ofatumumab** is yet another monoclonal antibody against CD20 antigen that has been approved for use in chronic lymphocytic leukemia (17).

For other forms of cancer, there now exists approved monoclonal antibody therapies. Briefly, these are **Trastuzumab** against HER2 antigen indicated for breast cancer (18), **Alemtuzumab** against CD52 for chronic lymphocytic leukemia (19), **Cetuximab** and **Panitumumab** against EGFR for colorectal cancer (20) (21), **Bevacizumab** against VEGFA for colorectal, breast and lung cancers (22) (23) (24), and **Gemtuzumab ozogamicin** against CD33 for acute myelogenous leukemia (25). Finally, only recently the monoclonal antibody, **Ipilimumab**, which blocks cytotoxic T-lymphocyte associated antigen 4, has shown positive survival results in clinical trial for metastatic melanoma (26).

Thus, monoclonal antibody therapy has shown considerable successes in the clinic. With further advances in the identification of specific tumor targets, low toxicity considerations, and enhancement of antibody structures that amplify antitumor effects, major breakthroughs can be expected in this area.

CYTOKINES

Cytokines are approved and used in cancer therapy for their immunostimulatory effects (27). Cytokines are proteins or glycoproteins that work in autocrine or paracrine fashions, and they regulate the functions of natural killer cells (NK cells), macrophages, neutrophils, as well as B and T cells. Interferon alfa 2b (INF α-2b) and interleukin-2 (IL-2) have been approved by the FDA for treatment of cancer.

Interferon alfa (INF-α) plays many roles in the immune system. For instance, it upregulates MHC class I, tumor antigens, Fc receptors, and adhesion molecules genes. It has an anti-angiogenic agent. In addition, it stimulates B and T cell activities, and those of macrophages, and dendritic cells. Treatment with INF-α has shown considerable successes in chronic myeloid leukemia (28) (29), melanoma (30), hairy cell leukemia (31), renal cell carcinoma (32), and Kaposi's sarcoma (33).

Interleukin-2 (IL-2) is a T cell growth factor. As a high dose regimen, IL-2 has been given in renal cell carcinoma (34) and metastatic melanoma (35) to obtain enhanced patient survivals. IL-2 has been administered with peptide vaccines for metastatic melanoma, generating the peptide-reactive T cells in most of the patients (36). When used in combination with adoptive cell transfer, IL-2 therapy proved superior in metastatic melanomas (37).

Granulocyte-monocyte colony stimulating factor (GM-CSF) is a cytokine that can reconstitute myeloid lineages, and its use has been approved for stem cell and bone marrow transplantations. It has been shown to reduce neutropenia following chemotherapy, thus enabling the usage of higher doses of chemotherapy (38). In addition, for non small cell lung carcinoma

(NSCL), tumor cells engineered to secrete GM-CSF have induced the formation of reactive T cells in patients (39).

Interleukin-12 (IL-12) is a cytokine that promotes NK and T cell activities, and it is a growth factor for B cells. In use along with peptide vaccine for melanoma, IL-12 has led to increased reactive T cell activity (40). Moreover, promising anti-cancer activities have been demonstrated for a few cutaneous T cell lymphoma patients treated with IL-12 (41).

VACCINES

Vaccine therapy for cancer is aimed at producing active immunologic response, and specific activity against particular tumor antigens. Various forms of vaccines have been developed for this purpose and tried in clinical trials. These strategies include the application of whole tumor cells, gene-modified tumor cells, naked plasmid DNA, peptides and proteins, viral gene transfer vectors, and antigen modified dendritic cells (DC) (42) (43).

Vaccines with viral, bacterial, or yeast vectors have been developed to contain recombinant genes such as tumor antigens, cytokines, immunostimulatory agents. In the body they will be delivered to antigen presenting cells (APC) to generate an immunologic reaction against the vector proteins. Of these vectors, the poxviral vectors have been thoroughly investigated. Examples of viral based vectors in clinical trials include **PSA-TRICOM** (44) for prostate cancer, and **PANVAC-VF** (45) for pancreatic cancer. Limitations with the approach of viral vaccines involve the dominance of viral antigens over tumor antigens, risk of toxicity with live viral agents, and weak antitumor effects.

Vaccines with peptides or proteins have yielded some success in the clinical setting. The peptide or protein used could be a single agent or a combination of proteins, such as, heat-shock proteins, anti-idiotype antibodies, agonist peptides, or fusion proteins. These are easy to produce, and elicit immunologic reaction against the specific epitope of tumor antigen different from the wild-type protein. This approach generally necessitates the delivery of an adjuvant to stimulate immunogenicity. Disadvantages include weak immunologic response, tumor easily escaping immune detection through mutation of their antigen, and the poor ability to activate a balancedCD4 and CD8 subsets for prolonged effects. **Provenge** in Phase III clinical trials for prostate cancer is a vaccine developed to stimulate T cell immunity against prostatic acid phosphatase(PAP) (46) (47). **Oncophage** is an autologous tumor-derived HSP gp96 peptide complex that has been used as vaccine therapy for melanoma as well as renal cell carcinoma (48) (49). **gp100:209-217(210M)** is a synthetic peptide from the gp100 melanoma-associated antigen that has shown promise in melanoma (50). **Stimuvax**, a cancer vaccine against the extracellular core peptide of MUC1, a type I membrane glycoprotein, has been studied in lung cancer with significant improvement over the best supportive care (BSC) arm (51).

Tumor cell vaccines can employ either autologous or allogenic tumor cells for vaccine therapy. In autologous scenario, tumor cells are extracted by surgery. Otherwise allogenic cell lines have been developed (especially for melanoma) that express various common tumor antigens. In addition, these tumor cells could be treated with viral vectors such that they express immunostimulatory agents such as IL-2, GM-CSF, or other co-stimulatory molecules. Another approach is to irradiate the tumor cells, so that they lose their proliferative property, and then to deliver these cells into the patient. The goal is that these tumor cells will stimulate an inflammatory process, or will be processed and recognized by dendritic cells to stimulate anti-tumor immunity. **OncoVax** is autologous irradiated tumor cells, with or without Bacille Calmette-Guerin (BCG) as adjuvant has shown significant activity in colon cancer (52) (53) (54). **Reniale** is the lysate of autologous tumor cells,

preincubated with IFN-γ (to increase immunogenicity) and tocopherol acetate (that protects cell membranes during the incubation process), has shown significant improvements in renal cell carcinoma therapy (55) (56).

DNA and RNA vaccines are recent developments in this field and they include the delivery of either DNA or mRNA vectors in an appropriate delivery system (such as cationic liposomes) with or without cytokines (IL-2 or GM-CSF) and separate plasmids harboring other non-self antigens. These vectors are designed to express specific tumor antigens, and are generally easy to produce and stable. This strategy has proven to be particularly viable to induce strong immunogenicity towards weak tumor antigens. Among others, one promising clinical trial has shown success in prostatic cancer patients, through the transfection of dendritic cells with mRNAs from three allogeneic prostate cancer cell-lines (57).

Dendritic cells vaccines have been greatly investigated from many years now. They involve the delivery of clinical grade DCs that have been loaded with antigens, such as, peptides, whole proteins, tumor lysates, mRNA, or viral vectors. These are costly to produce, labor-intensive, and require ex-vivo cell culture. Moreover the possibility of tolerization by immature DCs remains a risk. Clinical trials using dendritic cell vaccines have yielded inconsistent results at best, and our understanding has to be further honed in this field to achieve desired results (58).

FUTURE ENDEAVORS

There are some critical areas where our knowledge of cancer immunotherapy can be honed for further successes. For example, better diagnostics need to be developed to access the potential effectiveness of different immunotherapies in patients. The identification and differentiation of therapeutic responses versus pathological autoimmune responses, is one area where additional improvement has to occur. Additionally, diagnostics could also be geared to identify patients for whom certain immunotherapies would harbor greater chances of success. Moreover, in the future the combination of one or more immunotherapy strategies together, or along with conventional chemotherapies might prove more successful for the eradication of cancer and the prevention of relapse.

In conclusion, targeting the immune system for cancer therapy, is an exciting as well as challenging approach in the fight against cancer.

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