Effective Cancer Immunotherapy – Are We There Yet?

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LEARNING OBJECTIVES
1. State the goal of cancer immunotherapy.
2. List and describe the different categories of cancer immunotherapy.
3. Discuss advantages and disadvantages of each category of cancer immunotherapy.
4. Explain the rationale of bispecific antibodies in cancer immunotherapy.
5. Describe the molecules involved in inhibitory checkpoints of T cell activation.

ABSTRACT
The possibility of harnessing a patient’s own immune system to fight cancer has intrigued clinicians for decades. Exciting new advances in the field of immunology have increased the likelihood that this may become a reality. While the development of cancer vaccines continues to be of interest, to date only one cancer vaccine has received FDA approval. However, humoral (monoclonal antibodies) and cellular (adoptive cell transfer) immune applications show significant promise. Advances in the ability to engineer a patient’s own immune system cells to redirect the activity to the tumor appear to have moved the field of cancer immunotherapy to the brink of realistic and effective cancer treatment options.

INDEX TERMS: Cancer immunotherapy, monoclonal antibodies, adoptive cell therapy, bispecific T-cell engagers, chimeric antigen receptors


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INTRODUCTION
The December 20, 2013 issue of the journal Science named Cancer Immunotherapy its “Breakthrough of the Year”. While acknowledging that the long-range impact of an immunotherapeutic approach to cancer treatment is still to be determined, the journal felt that recent clinical trials had confirmed its potential, thus warranting its selection for this recognition.1

The classic cancer treatment approaches for the past
100 years have been surgery, radiation, and chemotherapy, also known as “slash”, “burn”, and “poison”. All are associated with risks and/or adverse side effects, and some cancers are resistant to these approaches. Thus, morbidity and mortality for cancer patients remain high.

Immunotherapy is an approach in which the body’s own immune system is directed against the cancer and has become accepted as a promising fourth component of medicine’s armamentarium in the war against cancer. Multiple approaches have been used in an attempt to harness the immune system including activation of both the innate and adaptive immune responses.

The host can clearly initiate an immune response against cancer cells. Many tumors are infiltrated by cells of both innate and adaptive immunity. Spontaneous antibody responses have been identified for more than 100 tumor-associated antigens (TAA) and spontaneous regression of melanoma lesions has been observed with clonal expansion of T cells. These observations support that the immune system is capable of recognizing antigens associated with tumors. However, for the majority of patients, tumor progression indicates that the tumor often is able to elude the immune defenses mounted by the body. The goal of immunotherapy is to enhance the immune system’s ability to identify and destroy tumors. Two broad approaches that have been explored include enhancing the immunogenicity of the tumor itself, and promoting the anti-tumor effector responses of the immune system.

Cancer Vaccines
There has been long-standing interest in the idea of actively immunizing cancer patients against their disease with attempts to develop therapeutic cancer vaccines reported as early as the 18th century. However, objective, durable responses have seldom been documented.

A successful cancer vaccine requires the identification of an appropriate TAA, and the induction of a potent immune response. Because TAAs often closely resemble or are identical to self-antigens, it is important to develop a vaccine that maximizes a therapeutic response while minimizing a pathological autoimmune response.

The initial step in activating an immune response requires the capturing and processing of antigens derived from the tumor by dendritic cells (DC), and suitable activation (maturation) of the DC. Vaccines commonly include adjuvants to increase immunogenicity, which likely play a role in recruitment and activation of DCs. Once activated, the tumor-antigen-loaded DC must present the antigen in a complex with an appropriate major histocompatibility complex (MHC) protein to be able to generate protective T-cell responses. Although the production of cytotoxic CD8+ effector T cells is recognized as an important component of this response, DC may also activate natural killer (NK) cells, natural killer T (NKT) cells, and trigger antibody production. Often cytokines are co-administered (interleukin [IL]-2 or granulocyte-monocyte colony stimulating factor [GM-CSF]) to enhance the immune response.

A consideration regarding the effectiveness (or lack thereof) of a cancer vaccine is the immunosuppressive effects generated by many tumors, which oppose effective T cell function. Intra-tumor hypoxia triggers release of vascular endothelial cell growth factor (VEGF) that inhibits T cell diapedesis from the vasculature and entry into the tumor environment. Tumor cells produce a variety of immunosuppressive molecules, including ligands for the receptor programmed death 1, prostaglandin E2, arginase, and indoleamine 2,3-dioxygenase which suppress T cell activation and/or function. Tumor cells can also escape T cell recognition by down-regulating expression of MHC molecules or the target tumor antigens. The outcome may be the generation of T cells that are progressively impaired in terms of their proliferative and functional abilities, which has been suggested to be a primary reason for the relative ineffectiveness of the majority of cancer vaccines.

In spite of the above difficulties, the first human antigen-targeted cancer vaccine was approved by the Food and Drug Administration (FDA) in 2010. Provenge (sipuleucel-T) is a cell-based vaccine used for advanced prostate cancer.

Antibody-Based Therapeutics
In addition to the active immunity induced by vaccines, passive immune approaches, including the infusion of antibodies or immune cells, provide an alternative
approach for cancer immunotherapy by circumventing the requirement to activate the patient’s immune system. The finding of spontaneous antibody production against a wide variety of TAAs and sporadic reports of spontaneous tumor regression in the absence of exogenous treatment led to the speculation that humoral immunity may be an effective anticancer approach.

**Monoclonal Antibodies**

The technique for producing monoclonal antibodies (mAb) enabled for the first time the production of therapeutic quantities of antibodies specific for a target antigen. A major problem with attempting to use these early mAb as therapeutic agents was that they were mouse proteins, and thus were highly immunogenic when injected into humans. A variety of techniques were developed to “humanize” these agents, to minimize the immunogenicity of the mouse-derived peptides. A chimeric mAb is one in which the Fc region of the original mouse antibody has been replaced by a human Fc fragment. The term humanized mAb is usually used to refer to a mAb in which major portions of the Fab region have also been replaced by human sequences, leaving only the hypervariable regions (complementarity determining regions) of mouse sequences remaining. While several of the mAbs approved for clinical use are either chimeric or humanized mAbs, the majority of antibodies currently in various phases of development have fully human peptide sequences.

Monoclonal antibodies are thought to function in several ways. MAb directed against cell surface targets (e.g. epidermal growth factor receptor [EGFR], receptor activator of nuclear factor-kB ligand [RANKL], vascular endothelial growth factor [VEGF]) can cause receptor blockade, inhibition of signaling pathways, and induction of apoptosis. Once bound to their target tumor antigen, mAb may induce phagocytosis by Fc receptor-bearing monocytes, macrophages and dendritic cells, or initiate antibody-dependent cellular cytotoxicity (ADCC) by NK cells. The antibody-coated cell may activate complement, resulting in complement-mediated cytolysis. The first mAb approved as an anti-cancer treatment was rituximab (anti-CD20) in 1997. Most of the mAbs approved for clinical use are fairly well-tolerated and may induce significant clinical results, though none appear to be able to cure cancer as single agents. Antibody conjugates have also been tested in which a mAb is coupled with radionuclides or other toxic compounds, to deliver the treatment modality directly to the tumor cells and enhance treatment efficacy.

**Monoclonal Antibodies Against T Cell Activation Checkpoints**

An additional application of monoclonal antibody technology in cancer immunotherapy is to block inhibitory checkpoints of T cell activation. T-cell activation is modulated by co-stimulatory and co-inhibitory signaling pathways. It requires T cell receptor (TCR) recognition of its target antigen which is presented by an antigen-presenting cell (APC) in association with an appropriate MHC protein (MHC class I proteins present peptides to cytotoxic CD8+ T cells, while MHC class II molecules present peptides to CD4+ T cells). Recognition of and binding to its cognate antigen and MHC class molecule is not sufficient for T cell activation; a second co-stimulatory signal is required such as CD28 on CD4+ and CD8+ T cells, and one of its ligands (B7-1 [CD80] or B7-2 [CD86]) on the APC. In the absence of a co-stimulatory signal, T cell activation does not occur.

Co-inhibitory receptors on T-cells exist as well (immune checkpoints). Cytotoxic T lymphocyte antigen 4 (CTLA4; CD152) is an inhibitory receptor that also binds B7-1 and B7-2 on APCs. CD28 is constitutively expressed on T cells and provides the required co-stimulatory signal for T cell activation upon ligation by B7-1 and B7-2. With T-cell activation, CTLA4 is induced, which suppresses T cell responses by co-opting B7-1 and B7-2 binding and inducing CD28 down regulation. Clearly, multiple co-stimulatory and co-inhibitory receptor-ligand pairs collectively determine T-cell activation (or inactivation) and fate.

CTLA4 was the first immune inhibitory checkpoint receptor to be targeted, clinically. Ipilimumab is an anti-CTLA4 mAb designed to block this inhibitory checkpoint molecule and restore T-cell activation, proliferation and cytotoxicity, and has been approved by the FDA to treat metastatic melanoma. There are numerous other co-inhibitory molecules that are potential targets for immunotherapy.

Program death protein 1 (PD1; CD279) is another...
inhibitory receptor found on activated T cells, which primarily limits T-cell activity at the site of an inflammatory response (i.e., in the tumor microenvironment). When bound by one of its ligands (PD1 ligand-1 [PDL-1; CD274] or PD1 ligand-2 [PDL-2; CD273]), PD1 suppresses T cell function. PD1 is also found on B cells and NK cells; thus PD1 blockade may also contribute to immunomodulation by enhancing antibody production and NK cell activity. PD1 ligands are upregulated on the surface of many different types of tumors, implying a role in immune suppression by those cancer cells. Both anti-PD1 and anti-PDL-1 and -2 mAbs are being investigated as therapeutic agents to enhance T-cell immune responses by blockade of this immune inhibitory checkpoint.

**Bispecific Antibodies**

An alternative approach to simple mAbs was to create antibodies with dual specificity, or bispecific antibodies (bsAbs). Bispecific antibodies are created by joining two “half” mAbs (one heavy chain and one light chain), each of which recognizes a different antigen; thus bsAbs are capable of binding to two different antigen targets simultaneously; one antigen-binding site recognizes the tumor target, while the other recognizes an immune system cell (Figure 1). BsAbs have been shown to inhibit growing tumors in vivo.

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**Figure 1.** A. Structure of an immunoglobulin molecule. Immunoglobulin (Ig) G molecule consisting of two heavy chains (solid) and two light chains (striped). Each chain consists of a variable region (darker solid \[V_H\] and stripe \[V_L\]) and a constant region (lighter solid \[C_H\] and stripe \[C_L\]). B. Structure of a Bispecific Antibody derived from two distinct monoclonal antibodies (mAb), consisting of one heavy chain and one light chain for one antigen (e.g., anti-CD3), and the other heavy chain and light chain specific for a second antigen (e.g., anti-tumor-associated antigen [TAA]). C. Bispecific T-cell engager (BiTE) - consisting of the \[V_H\] and \[V_L\] fragments from two different mAbs, linked. BiTEs are capable of forming an immunologic synapse between a T cell and a tumor target cell, activating the T cell to induce tumor cell lysis in absence of antigen:MHC presentation to T cell receptor.
BsAb constructed to engage Fcγ receptors (FcγRI, CD64) on macrophages, facilitating phagocytosis of the tumor cell, failed to demonstrate sufficient efficacy, and development appears to have been halted. Other bsAbs have been engineered to recognize a component of the TCR complex (usually a component of the CD3 co-receptor signaling complex), thereby recruiting T cells to the tumor site and inducing a cytotoxic immune response. Cytotoxic T cells are the most potent killer cells of the immune system, are efficiently activated and induced to proliferate, and are capable of killing multiple times. BsAbs that recruit T cells are able to recruit and activate any cytotoxic T cells, without regard to TCR antigen specificity, need for costimulation, or peptide presentation by appropriate MHC molecules. The bsAb can establish an immune synapse between the T cell and the tumor cell without needing the TCR to recognize and bind an antigen-MHC complex.

The first bsAb approved for clinical use was catumaxomab, which targets the protein epithelial cell adhesion molecule (EpCAM, CD326). EpCAM is found on nearly all human adenocarcinomas, most epithelial cell carcinomas, and hepatocellular carcinoma. Catumaxomab is an anti-EpCAM/anti-CD3 bsAb capable of binding target tumor cells and T cells. However, it is a full-size antibody, and was shown to also be capable of binding to FcγR, inducing NK-dependent ADCC, and phagocytosis by macrophages. It is thus described as a triomab, a monoclonal, bispecific, trifunctional antibody (Figure 2).

Figure 2. Trifunctional bispecific monoclonal antibody. Antibody forms tricellular complex between tumor target cell, T cell, and Fc receptor+ cell (monocyte, macrophage, dendritic cell, natural killer cell [NK]). Figure depicts catumaxomab, the first bispecific antibody approved for clinical use, which targets EpCAM (epithelial cell adhesion molecule) via its anti-EpCAM arm, and T cell CD3 via its anti-CD3 arm. Antibody recruits Fcγ-receptor-bearing cells of the innate immune system via its Fc portion.
Bispecific T-cell Engaging Antibodies
Initially, the majority of bsAbs that were developed as possible therapeutic agents were full-size antibodies, which often have poor penetration into solid tumors. Subsequently, stable, smaller sized molecules have been developed with better penetration into tissues or better access to active sites of protein targets. These include bispecific T-cell engaging (BiTE) antibodies that are created from the minimal binding domains of two different mAbs (both the heavy and light chains attached by a linker sequence) resulting in a single-chain variable region (scFv; Figure 1). BiTEs have been shown to induce a cytolitic immunologic synapse in the absence of MHC-antigen engagement that can overcome tumor cell escape by MHC down-regulation.

Blinatumomab was the first BiTE therapeutic agent developed, and is the most advanced in clinical trials. It is an anti-CD19 (B cell antigen)/anti-CD3 antibody, designed to target cytotoxic T cells to B cell malignancies. In an early Phase 2 clinical trial of adults with B-precursor cell acute lymphoblastic leukemia (B-ALL) with minimal residual disease (MRD) in their bone marrow, 81% of patients (13/16) became MRD negative. In July 2014, the FDA awarded blinatumomab Breakthrough Therapy Designation, which is intended to expedite development and review of new drugs for serious and life-threatening diseases.

Cell-Based Therapies
The concept of “tolerance” is an important component of the immune system and refers to the lack of an immune response to “self” antigens that regulates and prevents immune destruction of self-tissues. However, since most tumor-associated antigens are closely related to or identical to self-antigens, many tumors are not very immunogenic and the body fails to mount an effective anti-tumor response. In addition, many if not most tumors blunt the endogenous immune response of the patient. Thus an intriguing approach to cancer immunotherapy is the transferring of potent effector cells into patients to mediate an anti-tumor response. Several different approaches to cell-based therapies have been used over the past several decades, including both allogeneic and endogenous (autologous) cells.

Adoptive Cell Transfer: Lymphokine Activated Killer Cells
Attempts to use alloreactive T cells capable of recognizing and destroying the patient’s cancer cells had minimal success. Availability of suitable donors, as well as graft-versus-host toxicities limited the effectiveness of this approach. An alternative to allogeneic cell therapies is adoptive cell transfer or therapy (ACT), which involves the infusion of autologous lymphocytes into patients that have been removed from the patient, expanded and activated ex vivo, and re-infused into the blood. Sources of endogenous lymphocytes include both the peripheral blood and the tumors themselves.

Early attempts to implement ACT used bulk (unselected) T-cell populations obtained from the patient’s peripheral blood. Bulk populations of T cells include two types of effector cells, CD8+ cytotoxic T cells (CTL) and NK cells, both of which are capable of cytotoxic targeting. They also include CD4+ helper T cells, which may play an essential role in effective CTL activation. In addition to using bulk peripheral blood cells, selected subpopulations of peripheral blood leukocytes have been explored. NK cells have been isolated and evaluated in ACT, but showed only modest activity as solo effector cells.

Classic ACT appears to be primarily effected through CD3+CD8+ CTL, and their anti-tumor responses are MHC-restricted. The approach has been to isolate and expand/activate peripheral blood T cells ex vivo using high doses of IL-2. The resulting activated cells, termed lymphokine activated killer cells (LAKs), were then reinfused into the patient. IL-2 infusion directly into patients, with or without autologous T cells, has also been used to stimulate the patient’s immune system. Although some clinical success was reported, there was substantial toxicity associated with high doses of IL-2, and often, insufficient expansion of effector T cells for a significant anti-tumor response. One of the challenges for effective ACT is recruiting the therapeutic T cells to specific tumor sites. To date, identification of target proteins and T cell interaction with tumor cells have been more efficient and effective in hematologic malignancies as compared with solid tumors.

Adoptive Cell Transfer: Tumor Infiltrating Lymphocytes
CTL naturally infiltrate some tumors (tumor-infiltrating lymphocytes [TILs]), and their presence is associated with increased survival. Use of TILs as therapy requires that T cells are obtained from
surgically resected solid tumors, expanded and activated ex vivo with IL-2, and reinfused into the patient. Early studies in mice reported that TILs produced a 50-100X more effective anti-tumor response than LAK cells and have shown promising results in patients with metastatic melanoma, with overall response rates of ~50% and complete response rates of ~20% reported. 95% of complete responses are ongoing, some with up to 5 years follow-up. However, serious, potentially life-threatening toxicities have also been observed. Lymphodepletion by pre-conditioning patients with chemotherapy and total body irradiation (which is thought to reduce suppressive T regulatory cells [Tregs]) improved the antitumor activity and resulted in overall response rates of 72% and complete response rates of 40%, but with a corresponding increase in adverse toxicities.

While TIL-therapy can induce long-lasting, complete elimination of disease in a subset of patients with metastatic melanoma, TIL-based therapy is not an option for many cancer patients and many types of cancers. TIL therapy may be limited because particular tumors are not resectable, do not contain TILs, or an insufficient quantity of TILs can be expanded and activated ex vivo to be clinically effective. Also, this procedure is labor intensive, time consuming and expensive.

Adoptive Cell Transfer: Cytokine-induced Killer Cells
Cytokine-induced killer (CIK) cells are CD8+ T cells with diverse TCR specificities that have potent non-MHC restricted cytotoxic activity. Peripheral blood T cells are harvested, expanded ex vivo and activated with IL-2 and agonistic mAbs against CD3. The resulting cells are a heterogeneous population of effector cells with potent cytolytic activity and in vivo anti-tumor effects.

Adoptive Cell Transfer: Genetically Retargeted T cells
During T cell development in the thymus, precursor cells that express a TCR with high affinity for self-antigens are eliminated in the process of negative selection. Thus, while endogenous T cells that express tumor-reactive/self TCRs exist in many cancer patients, most have relatively weak affinity for antigen. An alternative approach to traditional adoptive cell therapy is to use genetically engineered T cells that express unique TAA-targeting receptors. Two types of genetically-engineered receptors have been explored: TCR gene transfer, and chimeric antigen receptors.

Naturally occurring T cells can be genetically engineered to express a second, high-affinity tumor-reactive TCR through TCR gene transfer, and have potent anti-tumor activity in vivo. The “substrate” cell chosen to be transduced with the TAA-specific TCR is often a virus-specific (usually Epstein-Barr virus [EBV]) cell. The substrate cell can still respond to viral antigens through its endogenous TCR and thus in vivo survival and functioning of the cells may be prolonged by recurrent stimulation/signaling through the endogenous TCR. Only a small number of patients have been treated with this approach, but results are promising. However on-target (recognition of antigen), off-tissue (i.e. off-tumor) toxicities have been reported, resulting in T-cell mediated autoimmunity that can be fatal. Potential limitations of TCR gene transfer include the facts that tumor targeting with this procedure is still MHC-restricted, and the transduced TCR is restricted to one HLA type, as well as limited to only protein tumor antigens.

The second type of engineered receptors is a chimeric antigen receptor or CAR. The unique CARs combine the antigen-recognition property of monoclonal antitumor antibodies with the cellular cytolytic capacity and self-renewal of T cells. CARs consist of an antigen-recognizing extracellular domain generated by joining the variable regions of the heavy and light chain of a mAb linked in a single-chain fragment (scFv), and joined to an intracellular signaling domain capable of activating the cell in the absence of TCR-antigen-MHC interaction (Figure 3). Various immune cells can be redirected in terms of immune reactivity by CARs, including T cell subsets, T progenitor cells, and NK cells. CARs have been designed that target many different malignancies, and because their antigen recognition and cellular activation are MHC-independent, they can be used to treat all patients that express the target molecule.

First generation CARs linked the scFv domain to the cytoplasmic activation domain of the TCR signaling co-receptor CD3 (usually the zeta chain of CD3). Although these CARs induced some antitumor response, it was not sustained in most patients. Second
Figure 3. Chimeric antigen receptor (CAR). A single-chain fragment (scFv) produced by linking variable segments from heavy and light chains (VH and VL) of a monoclonal antibody specific for a tumor-associated antigen. This scFv is then linked via a transmembrane region (TM) to a signaling cytoplasmic domain (e.g. signaling domain of CD3 zeta chain), and inserted into a T cell membrane. The result is a unique receptor capable of binding to tumor target cell and inducing cytotoxic activity of T cell, bypassing requirement for antigen recognition by the T cell receptor. Second generation CARs insert an additional signaling domain from a T-cell co-stimulator (e.g. CD28), while third generation CARs insert a second co-stimulatory molecule (e.g. CD137). The additional co-stimulatory domains result in enhanced T cell activation (increased proliferation, cytokine secretion, cytotoxicity and in vivo persistence) of the engineered T cell.

As with genetically-engineered TCR-T cells, lymphodepletion in the recipient prior to infusion of the CAR+ T cells (CARTs) improves survival of the infused T cells as does selection of T cell subsets of which to insert the CAR receptor. T-cell subsets with endogenous TCR-specificity for a known viral antigen (e.g. EBV) can result in enhanced T-cell proliferation and survival as the bispecific T cells are stimulated by both tumor antigen (transduced CAR) and viral antigen (endogenous TCR). Importantly, CART cells can establish immunologic memory.

CAR activation does not require that the TA be presented in association with a self-MHC molecule, and bypasses many of the immune-escape mechanisms of tumor cells. Also, the scFv antigen-recognition domain is not limited to protein targets, but can also recognize lipid and carbohydrate antigens. However, they
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generally are not able to recognize internal antigens, only surface-associated TAAs. As was reported with engineered high affinity TCRs, there is the potential for serious cytotoxicity with CARs. The most promising results using CAR-engineered T cells have been with CARs targeting CD19+ B cells in a variety of B-cell malignancies. In an early study, this approach resulted in complete response in 14 of 16 patients (88%) with relapsed or refractory B-ALL. Clinical trials are being conducted on patients with B-cell lymphoma, chronic lymphocytic leukemia (CLL) and adult and pediatric B-ALL.

CONCLUSIONS

Despite somewhat erratic progress over the past 100 years, immunotherapy as an effective treatment in the war against cancer seems to be approaching success. The immune system’s ability to identify and destroy cancer cells can be effectively harnessed, at least for some types of tumors. It has been suggested that immunotherapies will be used for 60% of people with advanced cancer within the next 10 years.

Recent developments including immunotherapeutic agents that target immune regulatory checkpoints show great promise, as they work to enhance the patient’s immune system in general, rather than requiring identification of specific tumor antigens. Genetically engineered T cells with high affinity TCRs or CARs are able to localize to sites of antigen expression and destroy target tissues (unfortunately both tumor and normal cells). While immunotherapy has been shown to produce some dramatic (and sometimes durable) clinical responses, it also has been associated with potentially serious toxicities.

As was found to be true with chemotherapy, using combination approaches targeting multiple immune system pathways (i.e. CART cells plus anti-CTLA4) is likely to be the most efficacious approach. Combining immunotherapy with radiotherapy, chemotherapy or targeted agents may also result in enhanced responses. Most available clinical data suggest that immunotherapeutic agents likely produce the greatest clinical benefit if used early in the treatment protocol.  

Most of the novel immunotherapies discussed in this article are still in clinical trials and not yet available to the general public. However the increasing availability and success of some of these immunotherapies have prompted some researchers to suggest that in the future, cancer may become a controllable chronic disease in a significant proportion of patients.

REFERENCES

15. Ascieto PA, Marincola FM. What have we learned from cancer immunotherapy in the last 3 years? J Transl Med. 2014;12:141-51.
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