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REVIEW

# Immunotherapy as an Option for Cancer Treatment

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**Abstract** The progress in melanoma immunotherapy highlights the importance of immunotherapy for cancer treatment. Although the concept of immunotherapy emerged in the beginning of the twentieth century, the end of the century signaled the start of modern immunotherapy, which has recently allowed a staggering progress in the field of cancer immunotherapy. Currently, there is a wide variety of immunotherapeutic approaches and critical improvements are continually being made. Among different immunotherapeutic strategies, therapies based on the blockade of immune checkpoint molecules have shown unparalleled efficacy in late-stage cancer patients. Pre-clinical research using ex vivo and in vivo approaches demonstrates the promise of numerous novel strategies for the immunotherapy of cancer.

**Keywords** Immunotherapy · Immune editing · Cancer vaccine · Adoptive cell transfer · Monoclonal antibody · Adjuvants · Checkpoint inhibitors · Cytokines

**Abbreviations**

| | |
|---|---|
| ACT | Adoptive cell transfer |
| CARs | Chimeric antigen receptors |
| IL | Interleukin |
| Mab | Monoclonal antibodies |
| TILs | Tumor-infiltrating lymphocytes |

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## Introduction: Roots of Cancer Immunotherapy

The idea to use immunotherapy for the treatment of cancer refers to a variety of concepts intended to activate the immune system or restore the dampened anti-cancer immune response (Drake et al. 2014). Induction of recognition and targeted elimination of tumor cells and surrounding microenvironment via endogenous defense mechanisms can lead to stabilization and remission of the disease (Mellman and Steinman 2001). The concept of cancer immunotherapy essentially refers to the attempt of utilizing and boosting natural immune responses, to combine external therapy (chemo-/radiotherapy/surgery) with the internal defense and control machinery at hand, thereby maximizing treatment efficiency (Karakhanova et al. 2015).

The history of cancer immunotherapy goes all the way back to 1908, when Paul Ehrlich hypothesized the crucial role of the immune system in continuously surveilling early stages of transformed cancerous cells and eradicating them before clinical detection (Ehrlich 1909). William Coley, often referred to as "the father of cancer immunotherapy", conducted pioneering studies indicating the efficacy of the immune system in combating tumors (Levine 2008; McCarthy 2006). After several ineffective operations and repeated recurrences of the tumor, the extensive surgical wound would not heal, despite skin grafts, and eventually was infected with erysipelas (*Streptococcus pyogenes*). Under multiple attacks of high fever due to the infection, the tumor shrank and finally vanished completely, even the wound healed rapidly (Coley 1991). Unfortunately, subsequent

trials failed to reproduce Coley's impressive results (Tsung and Norton 2006) and, consequently, the treatment of cancerous tumors with his toxin mixture was not included in any modern therapeutic approach (Rosenberg et al. 2004). Nonetheless, the idea of immunotherapy as cancer treatment option was born and the interest was initiated for intensive development and research by several institutions and groups. Over the following decades, scientists began to better understand the connection of the immune system and the development of neoplastic diseases.

## Immune Surveillance

The idea of immune defense mechanisms acting as a guard against malignant processes was further developed by Frank M. Burnet and Lewis Thomas, who proposed the immune surveillance theory in 1957 (Burnet 1957; Dunn et al. 2002). As a result of malignant transformation, tumor cells start expressing specific epitopes (tumor-associated-antigens), which can be processed by dendritic cells (Boon et al. 1997; Mellman and Steinman 2001). After activation and migration to draining lymph nodes, mature dendritic cells will present the tumor-associated-antigens to T cells, thereby activating them with the ensuing T cell infiltration of the tumor and execution of their cytotoxic activity (Itano et al. 2003; Randolph 2001). Over the recent years, the theory of immune surveillance has evolved into a broader concept (Jimenez-Luna et al. 2016), as researchers learned that cancer cells are capable of evading the immune control and even utilizing immunosuppressive agents to downregulate cellular defense responses. This concept of cancer immune editing assumes that tumor formation is a dynamic process composed primarily of three sequential phases: "elimination, equilibrium and escape" (Disis 2014; Vesely and Schreiber 2013). Within the first phase of "elimination", immune surveillance identifies and destroys transformed cells via adaptive and innate responses, thereby inhibiting tumor development (Schreiber et al. 2011). The second phase of "equilibrium" constitutes a coexistence of a belligerent environment created by the adaptive immune system and constant proliferation of tumor cells (Teng et al. 2015).

This keeps the total expansion of the tumor in check, but eventually leads to the production of resistant cells with reduced immunogenicity (Swann and Smyth 2007). Therefore, further outgrowth is prevented, though the selective pressure of the immune system promotes the evolution of cells that are capable of evading immune surveillance (Dunn et al. 2004). Thus, the first two phases pave the way for the third stage of "escape" (Vesely et al. 2011). Cells with downregulated expression of MHC class I molecules, decreased levels of tumor-associated antigens and persistent expression of tolerogenic antigens will now proliferate uncontrollably (Kalbasi et al. 2013) and use their ability to evade destruction, to grow, invade surrounding tissues, and metastasize (Dunn et al. 2004).

## Immunotherapeutic Strategies

Based on the discoveries of William Coley, as well as other investigators, different strategies for cancer immunotherapy have been proposed, trying to combine boosting the immune response against tumors with shifting the balance of immune editing towards elimination, away from escape and equilibrium (Couzin-Frankel 2013; Kalbasi et al. 2013). These therapeutic approaches can be roughly divided into two groups: active and passive immunotherapy, based on how the patient's immune system is involved. Active immunotherapy is designed to stimulate the host's immune system, to generate endogenous defense response against cancer cells. Examples of the maim immunotherapeutic trials are listed in Table 1. The following approaches belong to active immunotherapy.

### Cancer Vaccines

Cancer vaccines can be defined as biological response modifiers, which in general stimulate or restore the immune system to fight cancer. Cancer vaccines are applied either in preventive or therapeutic settings (Baek et al. 2015; Lollini et al. 2006). The well-known examples for effective preventive vaccination are currently deployed human papilloma and hepatitis B virus vaccines designed to avert infections with carcinogenic pathogens (Malecki et al. 2016; Paavonen et al. 2009). Similar to Coley's first attempts, therapeutic cancer vaccines are intended to delay tumor growth or even induce shrinkage by stimulation of specific immune responses. To this end, antigens emulsified in incomplete Freund's adjuvant are injected subcutaneously, which triggers T cell activation and maturation of plasma cells, leading to production of tumor-specific antibodies and generation of antitumor effector T cells and, ultimately, long-lived T cell memory. The process of developing cancer vaccines with compelling effectiveness turned out to be very challenging, in comparison to the development of preventive cancer vaccines (Rosenberg et al. 2004). A long-awaited breakthrough in the field happened in April 2010 when the U.S. Food and Drug Administration (FDA) approved Sipuleucel-T as the treatment of metastatic castration-resistant prostate cancer (Small et al. 2006; Tsiatas et al. 2016).

### Adoptive Cell Transfer

Adoptive cell transfer (ACT), using tumor-infiltrating lymphocytes (TILs) or T cells with chimeric antigen receptors

**Table 1** Examples of the main immunotherapeutic trials

| | Target/immunotherapeutic | Tumor | Main outcomes | SAE | References |
|---|---|---|---|---|---|
| Cancer vaccine | HPV-16/18 AS04 | CIN | High efficacy against CIN2 associated with HPV-16/18 and non-vaccine oncogenic HPV types | ~24% | Paavonen et al. (2009) |
| | Prostatic acid phosphatase/Sipuleucel-T | Hormone refractory prostate cancer | Time to disease progression was not improved; high ratio of T cell stimulation | ~24% | Small et al. (2006) |
| | Prostatic acid phosphatase/Sipuleucel-T | Advanced prostate cancer | Survival benefit for patients treated with sipuleucel-T compared with those treated with placebo | ~24% | Higano et al. (2009) |
| Adoptive cell transfer | Autologous TILs, IL-2 | Malignant melanoma | Prolonged relapse-free survival in patients with only one metastatic lymph node | ~24% | Labarriere et al. (2002) |
| | Tumor-infiltrated DC | Glioblastoma multiforme | Tumor shrinkage; median survival 525 days; 5-year survival 18.8%; increased concentration of $CD8^+$ TILs | ~24% | Chang et al. (2011) |
| | Autologous cytokine-induced killer cells | Hepatocellular carcinoma | Recurrence-free survival 44.0 months after immunotherapy vs. 30.0 months in the control group | ~24% | Lee et al. (2015) |
| | Adjuvant immunotherapy with sentinel lymph node T lymphocytes | Colorectal cancer | 24-month survival rate 55.6 after immunotherapy vs. 17.5% in the control group; median overall survival of 28 months vs. 14 in control group | ~24% | Zhen et al. (2015) |
| | Activated marrow-infiltrating lymphocytes | Multiple myeloma | Progression-free survival 25.1 months after immunotherapy vs. 11.8 months | ~24% | Noonan et al. (2015) |
| | CAR-engineered T cells targeting IL-13 receptor α2 | Multifocal glioblastoma | Regression of all intracranial and spinal tumors | ~24% | Brown et al. (2016) |
| Monoclonal antibody | CD20/Rituximab | Lymphomas | Progression-free survival 74.9% in the rituximab group vs. 57·6% in the observation group | ~24% | Salles et al. (2011) |
| | CD30/Brentuximab | Hodgkin's lymphoma | Progression-free survival 42.9 months for patients in the brentuximab group vs. 24.1 months in the placebo group | ~7% | Moskowitz et al. (2015) |
| | EpCAM/Adecatumumab | Breast cancer | Probability for tumor progression was significantly lower in patients receiving high-dose adecatumumab and expressing high levels of EpCAM | ~9–13% | Schmidt et al. (2010) |
| Checkpoint inhibitors | PD-L1/Atezolizumab | Non-small cell lung cancer | Median overall survival 13.8 months after immunotherapy vs. 9.6 months in the docetaxel group (intention-to-treat) | ~15% | Rittmeyer et al. (2017) |

**Table 1** (continued)

| | Target/immunotherapeutic | Tumor | Main outcomes | SAE | References |
|---|---|---|---|---|---|
| Cytokines | IL-2 | RCC | Overall objective response rate 14%, 5% complete responses and 9% partial responses | Severe acute treatment-associated toxicities | Fyfe et al. (1995) |
| | IL-2 | Malignant melanoma | Overall objective response rate 16%, 6% complete and 10% partial | Severe acute treatment-associated toxicities | Atkins et al. (1999) |
| | IFN-α | Malignant melanoma | Four-year relapse-free survival 45.6% after immunotherapy vs. 38.9 in the observation group | ~ 31% | Okuyama et al. (2010) |

*SAE* serious adverse events, *HPV* human papillomavirus, *CIN* cervical intraepithelial neoplasia, *DC* dendritic cell

(CARs), is an approach for cancer immunotherapy that involves the extraction of certain cell populations from the resected tumor of an individual patient. TILs showing the highest affinity for the cancer cells of that patient are isolated and expanded in the laboratory (Legut et al. 2015; Restifo et al. 2012). Subsequently, they are re-injected into the patient, most commonly in combination with interleukin (IL)-2, and, due to the massive influx of activated TILs, tumor eradication and the overcoming of immune-suppressive signals can often be anticipated (Rosenberg et al. 2011). A number of clinical studies in patients with malignant melanoma and glioma, liver and colon cancers, as well as with multiple myeloma revealed therapeutic benefit of ACT in different types of malignancies (Chang et al. 2011; Labarriere et al. 2002; Lee et al. 2015; Noonan et al. 2015; Zhen et al. 2015). Another approach for ACT of cancer is the introduction of tumor-specific CARs into T cells collected from the patient's blood (Maus et al. 2014).

CARs are generated by the fusion of the antigen-binding region of a monoclonal antibody to receptors and co-stimulatory molecules expressed on the surface of the collected T cells, which will thus be targeted against and activated by selected antigens of the patient's tumor (Tsiatas et al. 2016). The most successful example of CAR-based ACT is regression of glioblastoma after therapy with CAR-engineered T cells targeting IL-13 receptor α2 in a patient with recurrent multifocal glioblastoma (Brown et al. 2016).

## Adjuvants

Adjuvants are compounds or macromolecular complexes that can help to modulate and enhance the potency and longevity of immune responses (Hubbell et al. 2009; Lim 2015). Within the concept of the active cancer immunotherapy, they are combined with vaccines or cellular approaches, as described above, to improve their efficacy and increase antigen-specific reactions. In addition, they are able to boost the functionality antitumor cells and responses to the actual tumor site by creating an inflammatory environment promoting the homing of effector lymphocytes (Rosenberg et al. 2004).

Passive immunotherapy can be subcategorized into specific and non-specific strategies. Non-specific passive immunotherapies create general defense responses whereas specific ones induce defined immune responses to a certain tumor antigen. In general, passive immunotherapy initiates immune responses of the host via externally produced components (e.g.: antibodies, cytokines, etc.) injected into the patient, to generate immediate protection and enhance pre-existing defense mechanisms (Waldmann 2003). In the case of passive immunotherapy, no immunological memory is usually generated and the anti-tumor effect is only transient.

Therefore, repeated administration of the therapeutic agents is necessary.

## Monoclonal Antibodies

Monoclonal antibodies (Mab) are deployed in passive cancer immunotherapy as specific binding molecules to tumor antigens overexpressed on the surface of cancer cells (van der Bruggen et al. 1991; Weiner et al. 2009). Mab stimulate the patient's immune system to activate the complement system and effector cells (natural killer cells, B and T cells), leading to inflammation by chemotactically attracting inflammatory cells (neutrophils, eosinophils, basophils, monocytes/macrophages, etc.) and, eventually, to the destruction of tumor cells (Ravetch and Bolland 2001). More than 45 monoclonal antibody products had market approval by the U.S. FDA in 2015 (Ecker et al. 2015) and 228 clinical trials at different stages are currently listed on clinicaltrial.gov for the search term: "monoclonal + antibodies + cancer + immunotherapy" (interventional studies only; access: 31.08.2016).

For hematologic neoplasia Mab against hematopoetic differentiation antigens, such as CD20 [Rituximab, (Herold et al. 2003; Salles et al. 2011)] and CD30 [Brentuximab, (Moskowitz et al. 2015)], as well as Mab against glucoproteins of solid tumors, e.g., EpCAM [Adecatumumab, (Schmidt et al. 2010)], Mab targeting tumor growth and differentiation regulating proteins as epidermal growth factor receptor (EGFR) [Cetuximab, (Modest et al. 2015)] or Erb-B2 receptor tyrosine kinase 2 (ERBB2) [Trastuzumab, (Piccart-Gebhart et al. 2016)] are used in clinical practice or are currently being evaluated in phase III clinical trials.

In addition, Mab can be targeted against the tumor microenvironment or even directly to immune cells (Weiner et al. 2010). For instance, Mab against the chemokine receptor type 4 (CCR4) which is overexpressed on the surface of regulatory T cells can deplete these immunosuppressive cells from the tumor microenvironment, therefore, diminishing immunosuppression and restoring anti-tumor immune response (Lee et al. 2005). These features make the Mab against CCR4 an attractive anti-cancer drug (Tanaka et al. 2016). Besides, a variety of other strategies are being deployed in antibody therapy, ranging from "naked" antibodies to radioactively conjugated ones (radioimmunotherapy), as well as antibodies linked to a drug-activating enzyme (antibody-directed enzyme prodrug therapy) (Goldenberg et al. 2006). This creates an opportunity of systemic administration of a non-toxic agent, being guided to the tumor site and converted by the antibody into a cytotoxic drug.

## Checkpoint Inhibitors

Under physiological conditions, immune checkpoints are essential for the prevention of autoimmunity and the maintenance of self-tolerance (Pardoll 2012). They keep the balance of immune responses by promoting or inhibiting T cell activation (Borst et al. 2005). Malignant cells have the ability to develop mechanisms to dysregulate the expression of immune checkpoint proteins to obtain immune resistance (Topalian et al. 2016). For example, up-regulated programmed death-ligand 1 (PD-L1) receptor transmits inhibitory signals that lead to reduced $CD8^+$ T cell proliferation (Topalian et al. 2012) and even drives antigen-specific T cells into apoptosis (Chemnitz et al. 2004; Eggermont et al. 2015; Larkin et al. 2015; Weber et al. 2015).

Atezolizumab, the Mab-based inhibitor of the PD-L1 signaling was approved by the FDA for the treatment of urothelial carcinoma in May of 2016 and has just recently been granted fast track status for locally advanced or metastatic non-small cell lung cancer, overexpressing PD-L1 (Rittmeyer et al. 2017). Combined PD-1 and CTLA-4 pathway inhibition approaches showed significantly increased survival and objective response rates in patients with advanced melanoma, renal cell carcinoma (RCC) and non-small cell lung carcinoma (Callahan et al. 2014; Wolchok et al. 2013). Fueled by such promising results, pre-clinical research on checkpoint inhibitors became a rapidly developing field, and a wide variety of new checkpoint protein targets (TIM-3, LAG-3, IDO1, B7-H3, B7-H4, ICOS, OX40, 4-1BB, etc.) are under investigation.

## Cytokines

Cytokines are immunomodulating agents secreted by immune cells as well as endothelial cells, fibroblasts, and diverse stromal cells and can mediate paracrine, endocrine or autocrine signaling (Dinarello 2007). They represent a vast and promptly responding network, allowing the cells of the immune cells to communicate with one another, to orchestrate a coordinated, efficient and rapid response to a target antigen (Lee and Margolin 2011). The ability of cytokines to stimulate immune effector cells and enhance tumor cell recognition and activation of cytotoxic cells at the tumor site makes them promising agents for cancer therapy (Wolf et al. 2000). Several cytokines are currently investigated in a clinical setting (GM-CSF, IFN-α, IFN-γ, IL-2, IL-8, IL-12, IL-15, IL-18 and others) due to their broad anti-tumor activity (Vacchelli et al. 2016). Besides immune-stimulating agents, pre-clinical research is also invested into the neutralization of immune-suppressive cytokines, such as transforming growth factor β and IL-10 (Stewart et al. 2013). The FDA has approved two cytokines for therapeutic anti-cancer use in the United States: high-dose IL-2 (Aldesleukin) treatment for metastatic melanoma and RCC in 1992 (Atkins et al. 1999; Fyfe et al. 1995) and adjuvant use of interferon (IFN)-α in patients with stage III melanoma in 1995 (Okuyama et al. 2010). However, high toxicity of both

interleukins leads to the necessity of a careful selection of patients for immunotherapy with IL-2 and IFN-α (Amin and White 2013). Based on the long-time experience as well as durable response and survival of patients with RCC and melanoma treated with the cytokines this therapy could be recognized as an immunotherapeutic option for particular cancers especially in context of a combination with other therapies. For example, a study by Schwartzentruber et al. (2011) described the results of treatment of patients with malignant melanoma with gp100 peptide vaccine and IL-2. The trials showed a significant improvement of overall clinical response, progression-free and median overall survivals of patients treated with the combined immunotherapy. Thus, cytokine-based immunotherapy can still be recognized as a valuable option for cancer treatment.

## Delivery of Immunotherapeutic Agents

Apart from all the benefits of immunotherapy, we should also recognize the side effects of such treatments. Since, the high-dose IL-2 therapy in malignant melanoma and RCC has a long history, we are aware of even long-time side effects (Atkins et al. 1999). In particular, high-dose IL-2 therapy can lead to a massive cytokine release and IL-2-dependent inflammation as well as to the vascular leak syndrome (Alwan et al. 2014). On the other hand, even the most successful immunotherapeutic strategies, such as targeting of checkpoint molecules, induce so-called immune-related adverse events in 60–75% of patients (Hodi et al. 2010). Therefore, optimization of immunotherapeutic approaches towards reduction of side effects is urgently needed. One possibility would be the improvement of delivery strategies of immunotherapeutic drugs.

As the easiest way of such approaches we can recognize the local administration of the drugs, alone or in combination with systemic applications. One study has been recently published describing local intra-tumoral injection of the oncolytic Newcastle disease virus in combination with systemic CTLA-4 blockade (Zamarin et al. 2014). That pre-clinical approach led to regression or eradication of established tumors. A related approach is to create an intra-tumoral drug depot. A study of Hanes et al. (2001) described delivery of IL-2 using a polymeric system from gelatin and chondroitin-6-sulfate for the experimental immunotherapy of brain and liver tumors. This approach showed a therapeutic benefit for the tumor-bearing animals in the pre-clinical model used in the study (Hanes et al. 2001).

Nanocarriers can improve anti-cancer effects of immune checkpoint receptor targeting, as well as that of cancer vaccines. For anti-PD-L1 therapy, Roeven et al. (2015) demonstrated an improvement of anti-cancer effects by siRNA delivered by cationic lipoid and polymeric nanoparticles. Nanoparticle formulation of anti-cancer vaccines enhances lymphoid tissue draining, leading to improved antigen presentation as well as T cell activation, which was demonstrated in a number of experimental studies in tumor-bearing animals (for review see Fan and Moon 2015). Another interesting approach to deliver anti-cancer vaccines represents the use of cancer-derived exosomes. For instance, Ristorcelli et al. (2009) demonstrated reduced tumor growth in a pancreatic cancer mouse model using exosomes derived from the pancreatic cancer cell lines.

Hence, new approaches for the delivery of immunotherapeutics to their specific targets can diminish side effects of immunotherapy. Therefore, novel pre-clinical strategies showing the promising effects of new delivery strategies deserve to be tested in clinical trials.

## Concluding Remarks

The progress in melanoma immunotherapy highlights the importance of further investigations in the field of cancer immunotherapy. Development of new efficient immunotherapies for different types of cancer requires a much deeper understanding of the basic interactions between the tumor and the immune system. In this context, we lay a particular stress on the importance of pre-clinical research using in vivo tumor models, with the overarching of translating pre-clinical findings into clinical research. There is no doubt that more translational research is needed to optimize existing immunotherapeutic protocols and to develop new approaches in this field. However, we believe that the future of tumor therapy belongs to immunotherapy.

**Compliance with Ethical Standards**

**Conflict of interest** The authors declare no conflict of interest.

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