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An Overview of Promising Immunotherapeutic Strategies in Oncology

Abstract

In the last two-and-half decades the field of cancer immunotherapy has made remarkable progress, largely due to the clinical development of novel agents including, cytokines, monoclonal antibodies, vaccines, immune checkpoint blockade inhibitors and genetically engineered chimeric antigen receptor (CAR) T cells. Vaccine therapy is specifically designed to stimulate the body's immune system to recognize and target specific antigen(s) on tumor cells. By comparison, the goal of immune checkpoint therapy is not to activate the immune system to attack particular tumor-associated targets, but rather to disable inhibitory pathways that might block effective antitumor T cell responses. Adoptive cell therapy, involves the administration of autologous immune cells with antitumor activity that have been generated and manipulated ex-vivo. The current article will review the clinical development of these promising immunotherapeutic strategies, and briefly discuss their feasibility, utility and affordability in clinical practice.

Keywords: Immunotherapy; Vaccines; Immune Checkpoint Therapy; Adoptive Cell Therapy; Immunotherapeutic Strategies; CAR T Cells; Sipuleucel-T; Ipilimumab, Nivolumab; Pembrolizumab

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Abbreviations: CAR: Chimeric Antigen Receptor; FDA: Food Drug Administration; OS: Overall Survival; AEs: Adverse Events; CTLA-4: Cytotoxic T Lymphocyte Antigen-4; PD-1: Programmed Cell Death-1; mAb: Monoclonal Antibody; ACT: Adoptive Cell Therapy; TCR: T Cell Receptors; TILs: Tumor Infiltrating Lymphocytes

Introduction

The idea that patients could be immunized to induce antigen specific T cells capable of destroying tumor cells became a reality, with the identification of distinguishing tumor antigens [1-4]. Vaccine-based therapies promote the induction of immune responses with exquisite specificity for targeted antigens. Over the years, several vaccination strategies including immunization with whole tumor cells, tumor lysates, peptides, proteins, recombinant viruses, DNA/mRNA encoding tumor antigens, or *ex vivo* generated dendritic cells pulsed with antigens have been explored in clinical trials for various cancers [5-9]. Although, many trials have been associated with robust immune responses, observed clinical effects have been modest and seen only in a subset of patients [10-12]. This is because, most clinical trials have enrolled late stage patients with large tumor burdens who are likely immunosuppressed. The field of cancer immunotherapy reached an important milestone in 2010, when Sipuleucel-T was approved for the treatment of men with metastatic castrate-resistant prostate cancer by the US Food Drug Administration (FDA). Sipuleucel-T is an autologous cell-based vaccine which was designed to elicit host immunity against tumor cells that express prostate acid phosphatase. In a pivotal phase III, placebo-controlled study, designated IMPACT, the vaccine achieved significant survival benefits in men with advanced metastatic prostate cancer [13]. Sipuleucel-T demonstrated an overall survival of 4.1 months compared to placebo and to date, remains the only FDA approved therapeutic cancer vaccine. The vaccine is generally well tolerated with limited adverse events (AEs) including chills, pyrexia, headache, asthenia, dyspnoea, vomiting and tremor. The adverse events associated with the vaccine have been primarily grade 1 and 2, with durations of 1 to 2 days.

In recent year's immune checkpoint therapy, involving Ipilimumab, Pembrolizumab and Nivolumab have achieved remarkable and durable clinical responses in some patients, including long--term remissions with no clinical signs of cancer [14-18]. JP Allison and coworkers first demonstrated that cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) a molecule which is expressed on activated T cells and T regulatory cells, down regulates anti-tumor T cell responses, and *in vivo* administration of anti CTLA-4 monoclonal antibody (mAb) resulted in the rejection of tumors, including pre-established tumors [19]. Similarly, programmed cell death-1 (PD-1) was identified as another immune checkpoint molecule that limits the response of activated T cells by engagement of specific ligands expressed by activated T cells. CTLA-4 and PD-1 negatively regulate T cell activation via distinct pathways [20]. Ipilimumab (anti CTLA-4) is a humanized mAb and became the first immune checkpoint therapy to be approved by the FDA for the treatment of advanced melanoma in 2011. Pembrolizumab and Nivolumab, are two distinct mAbs against PD-1, and were approved by the FDA in 2014 for treatment of advanced melanoma. In March 2015, Nivolumab received FDA approval for the treatment of advanced or metastatic non-small cell lung cancer.

Interruption of immune checkpoints with mAbs is commonly associated with auto-immune sequelae and inflammatory damage to normal parenchyma. The most common AEs related to Ipilimumab, include rash/pruritus, enterocolitis, uveitis, pancreatitis, hypophysisitis and leucopenia. With vigilance and early intervention with corticosteroids and/or anti-TNF therapy, colitis symptoms have been readily treatable and only rarely associated with life-threatening complications. Nivolumab and Pembrolizumab

were associated with a lower rate of grade 3 or 4 AEs compared with Ipilimumab.

Adoptive cell therapy (ACT), is another promising immunotherapeutic strategy which involves the administration of expanded host cells, called tumor infiltrating lymphocytes (TILs) or genetically engineered chimeric antigen receptor (CAR) T cells or T cell receptors (TCR) with antitumor T cell responses [21]. In the 1980's and 1990's, pioneering work by SA Rosenberg and co-workers, first demonstrated that IL-2, a T cell growth factor when administered to host cells can induce activation, proliferation and survival of antitumor effector T cells and result in tumor regression [22]. Present day, ACT technology, relies on the *ex vivo* generation of large numbers ($1x10^{11}$) of antitumor lymphocytes that have been selected for high-avidity recognition of tumor, as well as for proliferation *in vivo* which is necessary for effective cancer regression. A substantial increase in cell persistence and the incidence and duration of clinical responses was seen when patients received a lympho depleting preparative regimen before cell infusion. Currently, there are several investigational agents, including TILs, CARs and TCRs that are being explored in adoptive cell therapy trials, for melanomas, sarcomas, leukemia and lymphomas with emerging results [21].

Discussion

After decades of rigorous pre-clinical and clinical development, it is safe to say that immunotherapy has joined the ranks of surgery, radiation and chemotherapy as an important modality for cancer treatment. In a milestone phase III trial of advanced melanoma, Ipilimumab administered with or without gp100 peptide vaccine was compared with gp 100 alone. The trial demonstrated that Ipilimumab use was associated with an increase in OS to 10 months compared to 6.4 months in the gp 100 only arm and 60% of these patients benefitted from long-term responses lasting greater than 2 years [14]. In two large clinical trials, nivolumab induced durable tumor regression (objective response rate of 6 to 17%) and prolonged stabilization of disease (rates of 12 to 41% at 24 weeks) in patients with advanced cancers, including non--small-cell lung cancer, melanoma, and renal-cell cancer [17,18].

ACT and other specialized methods of cancer immunotherapy associated with complex manufacturing procedures, are technically challenging and pose barriers to widespread adoption into clinical practice. The requirements for the development of personalized treatments involves considerable production and manufacturing costs which ultimately results in high per patient costs that are not economically feasible. For example, the only FDA approved therapeutic vaccine Sipuleucel-T costs ~$100,000 for one course of treatment. The prohibitive costs of the drug prompted the sponsoring company to file for Chapter 11 in November 2014. By contrast, other immunotherapy techniques, such as, lyophilized peptide-based vaccines have potential advantages in terms of production costs and logistical ease of distribution and application. Peptide vaccines also permit targeted immune response to be precisely monitored, quantified, and correlated with clinical outcome, i.e., they provide quantifiable biomarkers that might serve as predictors of clinical efficacy.

CTLA-4 and PD-1 negatively regulate T cell activation via distinct pathways. In preclinical models, combined blockade of PD-1 and CTLA-4 achieved more pronounced antitumor activity than blockade of either pathway alone [23,24]. These results have recently been validated in a randomized, double-blind, phase III study of Nivolumab alone or Nivolumab plus Ipilimumab and was compared with Ipilimumab alone in patients with previously untreated stage III or IV melanoma [25]. The data indicated that Nivolumab alone or when combined with Ipilimumab demonstrated significantly longer progression-free survival than Ipilimumab alone. Importantly, in patients with PD-L1 negative tumors, the combination of PD-1 and CTLA-4 blockade was more effective than either agent alone. Other combination therapies, involving immune checkpoint inhibitors with vaccine or ACT and cytokine cocktails are currently in clinical development.

Conclusion

In recent years immunotherapy has emerged as one of the most promising strategies for the treatment of cancer. The key to the continued success of immunotherapy would be to utilize a multifaceted combinatorial approach, by harnessing the full potential of novel immunotherapeutic regimens, to elicit sustained and durable antitumor immune responses.

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