Principles of cancer treatment by immunotherapy

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Abstract

The concept of immunotherapy as a modality to treat cancer was recognized more than a hundred years ago. High-dose interleukin-2 (IL-2) was one of the first agents to demonstrate that the host's immune system can be harnessed to treat even advanced malignancy, as was shown in a subset of patients with renal cancer and melanoma. Many tumours are immunogenic and provoke a host immune response, but this is normally not sufficient to overcome host tolerance. For decades now, researchers have tried various methods to enhance host immunological responses, such as the use of non-specific immunotherapeutic cytokines, tumour vaccines, adoptive immunotherapy and the use of monoclonal antibodies against a wide variety of molecules. This review discusses the principles of the various types of immune therapy and focuses on some of the recent developments and successes in treatment. The article concentrates on the applications of immunotherapy in solid tumours, though it has immense value in haematological cancers.

Keywords CD8 cytotoxic T lymphocyte; cytokine; interleukin-2 (IL-2); ipilimumab; PD1 blockade

Introduction

The cytotoxic T lymphocyte has a critical role in an immunological cascade that ultimately results in the lysis of tumour cells in an antigen specific manner. Activation begins when T cells recognize and bind to antigens or peptide fragments expressed on the surface of antigen presenting cells that are bound to type 1 major histocompatibility complex (MHC) molecules. The activation also requires the presence of co-stimulatory molecules. Once T cells are activated, there is recruitment of T helper cells that secrete cytokines such as interleukin-2 (IL-2) and granulocyte-macrophage colony-stimulating factor (GM-CSF), which further enhances T cell activation and proliferation (Figure 1). Despite these immunological responses to the presence of cancer cells, effective immunity does not develop against the vast majority of cancers because of impaired tumour recognition by immune cells, poor tumour immunogenicity and the presence of an immunosuppressive milieu in the tumour micro-environment.

Immune therapy is aimed at mediating the rejection of metastatic cancer in humans and has developed considerably over recent years. Several strategies exist that will be discussed in more detail below. These include non-specific therapies which do not depend on particular antigens, but are aimed at harnessing the innate immune system, such as with the cytokine IL-2. More specific therapies target tumour antigen with antitumour vaccines or with tumour infiltrating lymphocytes from the patient's own tumour, cultured and re-infused back into the patient. A large area of ongoing growth and success lies with monoclonal antibodies to various antigens, including to inhibitory receptors on T cells themselves.

Glossary of terms

- MHC: major histocompatibility complex: a crucial cell surface molecule expressed on cells which can present antigenic peptides. T lymphocytes can only recognize antigens when they are presented with MHC.
- Cytotoxic T lymphocyte, also called CD8+ T cell, or killer T cell: a type of white blood cell that has a major role in the destruction of infected somatic and tumour cells, also virally infected cells.
- T-regulatory cells: a specialized sub-population of T cells that suppresses the immune system and maintains tolerance to self antigens.
- Dendritic cells: the major antigen presenting cells, they capture, process and present antigens to T cells.
- Cytokines: The term used to refer to immunomodulating agents such as interferons and interleukins.

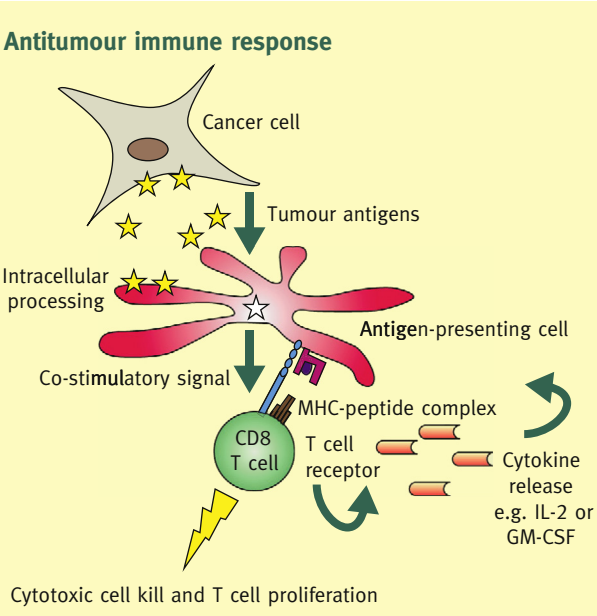

Figure 1 Dendritic cells capture antigens released by cancer cells. After intracellular processing, antigenic peptides are loaded onto major histocompatibility complex (MHC) molecules on the surface of the dendritic cell. Specific T cells encounter these MHC-peptide complexes in conjunction with a co-stimulatory signal. The activated T cells proliferate and secrete cytokines, resulting in the production of a cascade of immune effector cells (IL-2, interleukin 2; GM-CSF, granulocyte-macrophage colony stimulating factor). Not shown but also of importance are B lymphocytes, CD4+ T helper cells and cells of the innate immune system such as natural killer cells and macrophages. (Reproduced with permission BMJ 323 (1289)).

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Antigen independent immune responses and non specific therapies

Interleukin 2 (IL-2) and interferon alpha (IFNα) are antigen independent non-specific cytokine therapies that serve to enhance innate immune mechanisms. Receptor binding of IL-2 leads to recruitment of kinases, which in turn leads to production of secondary cytokines and reduced tumour proliferation. IL-2 has been used in renal cancer and melanoma where it has led to complete and durable remissions in approximately 6% of treated patients.[1] It has, however, not gained widespread acceptance because of significant toxicity.

In 2011 Schwartzentruber et al. showed that the response rate, progression-free survival and overall survival are improved when interleukin is used along with a peptide vaccine in metastatic melanoma. Overall survival was 17.8 months in the vaccine IL-2 combination group compared to 11.1 months in the IL-2 group alone.[2] This study was proof of concept that the therapeutic efficacy of immunization was enhanced by the administration of IL-2.

IFNα has been used in a range of haematological malignancies, renal cancer and advanced melanoma. In addition to its direct anti proliferative effects, it activates natural killer (NK) cells and macrophages, and augments the expression of class 1 MHC. Its use results in a 10–15% response rate in metastatic renal cancer and melanoma. It has also demonstrated activity in Kaposi's sarcoma, various lymphomas and hairy cell leukaemia.[3] It has a license to be used as an adjuvant therapy following resection of high risk stage 2 and 3 melanoma, where it has consistently been shown to reduce recurrence rates but without showing similarly consistent improvements in overall survival. Owing to a lack of convincing evidence in improving survival and its significant side effects, it is not widely used in Europe.

Cancer vaccines

Much work has been done to identify cancer antigens with the expectation that vaccinating with them would stimulate the immune system to inhibit the growth of established cancers. This approach has largely shown little efficacy but continues to be further developed. There has been some recent success in prostate cancer with a dendritic cell-based vaccine. The dendritic cell has been shown to be a pivotal cell in cancer induced immune response. It has versatile immunological functions in antigen capture and processing and can be used to deliver prostate cancer antigens for effective T cell activation.

Use of Sipileucel-T (Provenge), an FDA approved agent for the treatment of castrate-resistant minimally symptomatic prostate cancer, has been shown to result in an improvement of overall survival in this group of patients (Figure 2). This is a personalized antigen-based immunotherapy where patient's dendritic cells are harvested by leukapheresis and expanded ex vivo by incubating with a fusion protein. The fusion protein contains a prostatic antigen (prostatic acid phosphatase) that is fused with an immune-cell activator, granulocyte-macrophage colony-stimulating factor. After 2 days of culture, the antigen-loaded dendritic cells and T cells are re-infused into the patient (Figure 3). Although it rarely induced tumour regression, three phase 3 trials have shown an improvement in overall survival, the largest of which was the IMPACT study that was powered to detect an

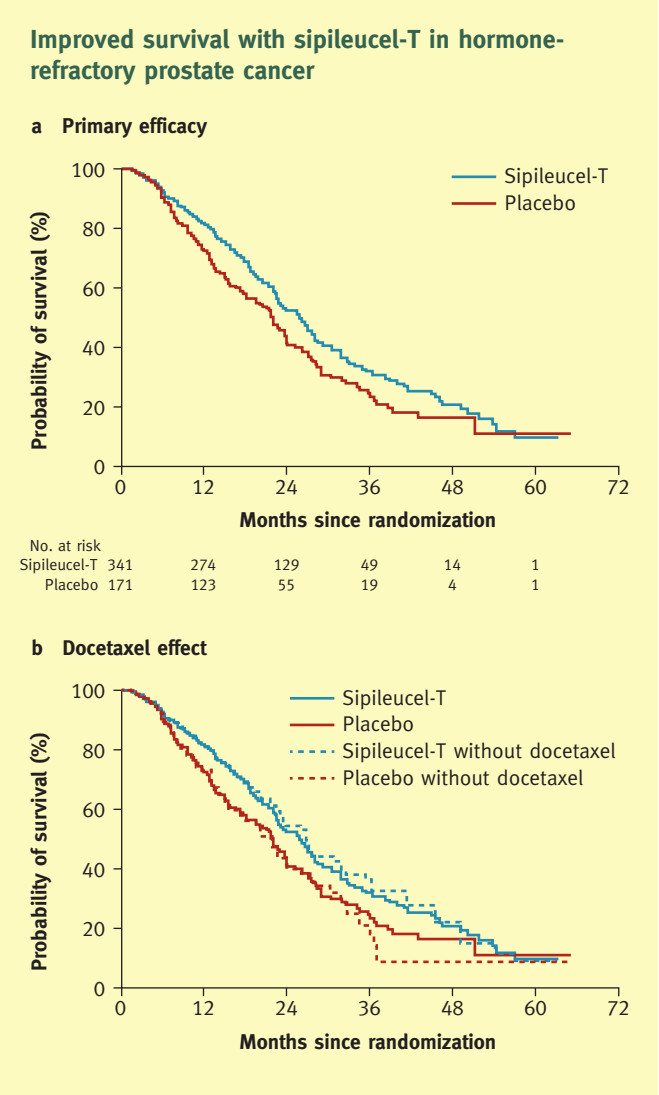

Figure 2 (From Philip W. Kantoff, M.D. et al. Sipileucel-T Immunotherapy for Castration-Resistant Prostate Cancer. *New Engl Med J* 2010: **363;** 5. Reproduced with kind permission. Copyright of the Massachusetts Medical Society).

improvement in overall survival. This study replicated the 4.1 month improvement in overall survival of prior studies and was granted FDA approval in April 2010.[4] The results of a UK trial are awaited, but NICE have recently said that: 'based on the evidence presented so far, it (Sipileucel-T) costs too much for the benefit it provides'.[5]

Prostvac-VF is a further prostate cancer vaccine in development. It is a fowlpox virus that has been genetically engineered to contain a copy of the human PSA gene. It is given combined with immune adjuvants and has shown encouraging results in early studies.[6] Results from a large phase 3 trial are awaited.

As noted before, cancer vaccines in combination with an immune activator such as IL-2 have been shown to enhance clinical efficacy in metastatic melanoma.[2] On the whole, however, cancer vaccines have had limited impact on clinical outcomes and it is thought that perhaps it is in the adjuvant setting of minimal residual disease, that their clinical impact will be the greatest.

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