

Cancer Immunotherapy

December 2016

The British Society for Immunology (BSI) is the largest immunology society in Europe. We represent the interests of over 3000 immunologists working in academia, clinical medicine, and industry. Our main objective is to promote and support excellence in research, scholarship and clinical practice in immunology for the benefit of human and animal health. We are also a founding member of the International Union of Immunological Societies (IUIS), a member of the European Federation of Immunological Societies (EFIS), and work to develop close links with our partners in North America and Australia.

Key points:

- Approximately 14 million people across the world are diagnosed with cancer every year and about 8 million people die from this disease annually.
- The immune system protects us from infections and also has the ability to detect and destroy cancer cells. However, cancers have evolved to evade immune destruction in order to progress.
- A new class of cancer therapies, collectively termed immunotherapies, work by enhancing or modifying the immune system to re-establish a targeted elimination of cancer cells. Because these treatments work by harnessing a patient's own immune system, they have the potential to achieve long-lasting remission with fewer side-effects compared with traditional cancer treatments.
- In addition to those already approved for use in the UK, there are many ongoing research efforts and clinical trials, generating promising results for treating a wide range of cancer types.
- Overall, by manipulating the behaviour of individual immune systems, these medicines can potentially treat and even cure some of humankind's greatest medical challenges, including cancer.
- Continued and increased support of immunotherapy research, from basic science through to clinical trials, is critical to identify the best cancer targets, mechanisms and methods of treatment.

Introduction

Cancer is a global issue and one of the leading causes of death in the developed world. Every year, there are some 14 million new cases of cancer diagnosed worldwide with 350 000 of said cases occurring in the UK¹. Approximately half of these cases result in death to the patient before reaching 10 years post-diagnosis¹. Still, cancer survival has almost doubled in the last 40 years¹ as a result of research efforts in prevention, early diagnosis, and treatment options.

The immune system is well known for protecting us against numerous infections but is now known to be important in detecting and destroying cancers. Early work, from over a century ago, suggested that activation of the immune system might help to combat cancer; we now know with certainty that the immune system plays an important role in detecting and killing cancer cells. However, as cancers develop they become resistant to the immune system – cancer is said to evade immunity. Bypassing this evasion has become a main focus of research into novel cancer therapies.

Traditional cancer treatments include chemotherapy, radiotherapy, and surgery. There have been significant advancements in cancer management and treatment, which have reduced cancer morbidity and mortality substantially. However, these are commonly associated with unpleasant side-effects, such as nausea, fatigue, and hair loss. New research is constantly looking for novel and more refined ways of treating or managing cancer. Cancer immunotherapy is designed to reactivate the body's immune response to the cancer and is showing exciting promise, with clear benefit now demonstrated in some cancers such as melanoma, lung, kidney, head and neck and Hodgkin's lymphoma.

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The immune system and cancer

Cancer is a disease of uncontrolled cellular proliferation and growth. In fact, cancer cells develop several characteristic features that contribute to the initiation and progression of the disease. These defining factors are termed 'the Hallmarks of Cancer', one of which is to avoid immune destruction.

The immune system is constantly scanning for mutations and malfunctions in cells that could lead to cancer, a process known as immunosurveillance. Where immunosurveillance fails, cancer can develop. The changes that transform a normal cell to a cancerous one involve the generation of new forms of host molecules known as cancer antigens or tumour associated antigens (TAAs). These distinguish cancer cells from normal, healthy cells and allow the immune system to recognise cancerous tissue.

However, cancer cells are genetically unstable and as they grow randomly produce variants with properties that can enable the cell to hide from the immune system, for example by preventing the expression of TAAs or by secreting immunosuppressive molecules. Immune cells will kill most of the tumour cells, but leave the variants that have been able to hide from or suppress the immune system. Eventually, these resistant tumour cells will develop into a clinically apparent tumour.

What is cancer immunotherapy?

The aim of cancer immunotherapy is to reawaken or "reboot" the immune system, enabling it to once again attack the tumour. This can be done in several ways.

Generally, the main types of cancer immunotherapies are:

Monoclonal antibodies – Some cancers, such as breast cancer and lymphomas, display certain molecules on their surface at very high levels; these can be attacked by monoclonal antibodies (laboratory-generated immune proteins that target these highly expressed molecules). For example, Herceptin (also known as Trastuzumab), detects a molecule known as HER2 on breast cancer cells; it interrupts the function of the molecule and recruits immune cells that destroy the antibody coated

breast cancer cells. Identifying patients that express the HER2 molecule at high levels allows them to be selected for this type of therapy.

Adoptive T cell therapy – As well as targeting the tumour cells, immunotherapies also target the immune cells directly. For example, a patient's T cells can be removed and those that will attack the tumour can be expanded in the lab and reintroduced into the patient. Similarly, T cells can be genetically modified so that they more readily recognise the tumour. This approach includes Chimeric Antigen Receptor (CAR) T cells. No CAR T cell therapies are currently licensed for clinical use but this approach has shown promise in clinical trials, particularly in leukaemia.

Immune checkpoint inhibitors – The immune system has built in stop signals, or brakes. In healthy individuals these serve to end an immune response and prevent the immune system damaging healthy tissue. Many cancers exploit these stop signals (so called immune checkpoints) and prematurely stop the immune response; checkpoint inhibitors are currently the most promising type of immunotherapy; blocking immune checkpoints allows the immune system to attack the tumour. This type of immunotherapy has recently been approved for use first in melanoma (the aggressive type of skin cancer), under the brand names Keytruda and Yervoy, and is being tested in many other cancer types.

Oncolytic virus therapy – Some viruses are being used to boost immune activity in cancer. These oncolytic (cancer-bursting) viruses act in two ways; they kill some cancer cells directly and activate the immune system to mop up others. A herpes virus called T-VEC has recently been approved for use in melanoma and many other viruses are being tried in laboratory and clinical studies.

Cancer vaccines – There are two types of cancer vaccines; prophylactic (preventative) and therapeutic vaccines (treatment). As well as treating cancer, some viruses are known to cause cancer. For example, infection with certain types of human papillomavirus (HPV) is linked to greater than 70% of cervical carcinoma cases and several other types of cancer including, head and neck cancer². Prophylactic vaccines that prevent infection with the virus (e.g. Gardasil for HPV associated cervical carcinoma) are given to prevent infection-associated cancer, and

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other virus vaccines under development will hopefully impact on other cancer types in the future. Therapeutic cancer vaccines act differently. They are designed to treat an existing cancer by enhancing the immune response against particular TAAs. An example of a therapeutic vaccine is Provenge for treating prostate cancer.

Advantages over traditional cancer therapies

The immune system is excellent at protecting us against infection because it is very selective and attacks only those cells it needs to. Cancer immunotherapy has a similar advantage, it is highly selective for the cancer cells and can potentially be tailored to the patient's individual cancer, a form of personalised medicine.

Advantages of immunotherapy include:

- Results in fewer side effects than traditional therapies in some cases. Chemotherapy and radiotherapy are non-specific treatments that cause damage to non-cancerous cells and are commonly associated with unpleasant side effects (e.g. hair loss, nausea etc). Immunotherapies are not without side effects but, as treatments develop, these are becoming more manageable.
- Offers possibility for long-term cancer remission and decreases risk of recurrence by stimulating a long lasting immune guard against the cancer.
- May be an effective way of treating many different cancer types – as far as we know, the immune system is capable of eliminating all cancer types under the right conditions. The challenge is to design treatments that allow the immune system to operate.

Challenges

Cancer immunotherapy is portrayed in the media as providing hope for the long sought after "cure for cancer". However, this is an emerging field and there are a number of challenges yet to be overcome before the full potential of cancer immunotherapy can be realised. Cancer immunotherapy is not a "one size fits all" treatment. That is, where one treatment may work for a particular patient, it may not work for another patient. It is likely that the future of cancer therapy will actually involve several individual immunotherapies, probably used in combination with conventional treatments, with potential for long-term or even life-time use.

The main challenges at present include:

- Labour intensive and high cost, especially for treatments involving the engineering of a patient's individual immune cells.
- Requires stratification of patients into very specific subsets defined by the molecular/immune characterisation of their cancer; this is an area that is currently very poorly understood.
- At this time, the long-term effects and effectiveness is unknown.

¹Cancer Research UK (2012). Cancer statistics

²NHS choices (2014). HPV vaccine.