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Cancer immunotherapy – is it really a “game-changer”?

Did you know?

1,375

All trials involving cancer immunotherapy on clinicaltrials.gov¹

Introduction

Traditionally, cancer is treated by surgery, chemotherapy or radiotherapy. However, some of the most exciting breakthroughs are now being made using another type of treatment called immunotherapy. This treatment is well established in other medical conditions such as rheumatoid arthritis and allergic asthma. Numerous sources now declare immunotherapy to be a “game-changer”^{2,3} in cancer treatment and we will discuss that here.

¹ See [https://clinicaltrials.gov/ct2/results?term=cancer+immunotherapy](https://clinicaltrials.gov/ct2/results?term=cancer+immunotherapy;); accessed 25 July 2017

² See BBC health; 9 October 2016; ‘Immunotherapy cancer drug hailed as ‘game changer’; <http://www.bbc.com/news/health-37588541>

³ See Ravulapati S, MD, et al.; ‘Immunotherapy in Squamous Cell Skin Carcinoma: A Game Changer?’; © 2017 Elsevier; [http://www.amjmed.com/article/S0002-9343\(17\)30011-6/fulltext](http://www.amjmed.com/article/S0002-9343(17)30011-6/fulltext)

Immunotherapy is not just one type of treatment, but a variety of treatments that harness the power of the immune system to fight diseases. Cancer is a clever disease and can evade, or even use, the immune system to grow and spread. Immunotherapy can trigger the immune system to treat cancer like a bacteria or virus, and attack the disease.

History

Cancer immunotherapy has been explored as a treatment option as far back as the 19th century, when William B. Coley was injecting live and inactivated bacteria (Coley’s toxins) into tumours to trigger an immune system response and attack the cancer cells. Unfortunately, the mechanism of action of Coley’s toxins was not well understood and a number of patients died as a result of the effects of the treatment. Interest in Coley’s toxins declined, with surgery, radiotherapy and eventually chemotherapy becoming the standard for cancer treatment.

Fast forward to the 20th century, T cells (part of the immune system) were noted to directly attack cancer cells and cells infected with bacteria or viruses. In the 1970s, Interleukin-2 was found to enhance T-cell production. This showed some efficacy in the treatment of established metastatic cancer.⁴ It wasn’t until 1997 that the first monoclonal antibody was

⁴ See Rosenberg SA, et al. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. *N Engl J Med.* 1985;313(23):1485-1492

approved by the FDA for the treatment of a cancer, Non-Hodgkin's Lymphoma.⁵

The last decade has seen significant progress in understanding the function of molecular pathways and the genetic signals that operate along them. This in turn has led to the development of a number of new immunotherapies with increasing effectiveness against numerous types of cancer.

Types of cancer immunotherapy

Monoclonal antibodies

These man-made antibodies are made up of multiple copies of one type of antibody and can work in a number of different ways⁶:

1. **Attaching:** They have the ability to attach to specific cancer cells, aiding the immune system in identifying and attacking the cancer cells.
2. **Blocking:** A functioning immune system uses checkpoint molecules to stop over-activity and damage to healthy cells. Some cancer cells are able to make high levels of these molecule receptors, causing the immune system's cancer-attacking T cells to turn off. Monoclonal antibodies can block checkpoint molecule receptors, including PD-1, PD-L1 and CTLA-4. They can also block growth factor receptor molecules which are used by cancer cells to survive and divide.
3. **Carrying:** They can carry specific cancer-killing drugs or radiation directly to cancer cells.

Cancer vaccines⁷

Vaccines are traditionally thought of as something that protects a person from developing a disease, and it is true to say that there are vaccines commonly available that help prevent cancer developing from specific viruses.⁸ However, there are also immunotherapeutic vaccines available that can boost the immune system's response to cancer after it has been diagnosed. When these vaccines are injected into the body, the antigens they contain can either lead to

T cells being activated or antibodies being produced that can target the cancer.

Oncolytic virus therapy⁹

This type of therapy involves injecting a genetically modified virus into the tumour. Once inside the cancer cells, the virus makes copies of itself which leads to cells bursting and dying. At this point antigens are released, thereby triggering an immune system reaction. Any cancer cell with the same antigens throughout the body will be targeted and healthy cells are left alone.

Other, non-specific immunotherapies¹⁰

Non-specific immunotherapies do not specifically target cancer cells, but can be given on their own or in addition to another treatment to help enhance the immune system's response to fighting cancer.

Companion diagnostics

Treatment is only part of the overall care for the patient. Companion diagnostic devices (in vitro devices or imaging tools) are now being used by medical professionals and provide information that enables them to use therapeutic treatments, such as immunotherapy, safely and effectively and avoid any potential risks or side effects. These devices and tools can be used at all stages of cancer management by identifying those that will likely benefit or be harmed by the treatment and to monitor the response so that any adjustments can be made to try to improve the outcome.¹¹

Reasons for optimism

There have been reported successes where people with seemingly incurable cancer have gone into complete remission.¹² A number of immunotherapy treatments have now been approved or are being evaluated for multiple cancer types.^{13,14} Such is the excitement around immunotherapy that the American Society of Clinical Oncology (ASCO)

⁵ See Targeted Oncology; 21 August 2014; 'A Brief History of Immunotherapy'; <http://www.targetedonc.com/publications/special-reports/2014/immunotherapy-issue3/a-brief-history-of-immunotherapy>

⁶ See Cancer Research UK; Last review 27 November 2014; 'Monoclonal Antibodies'; <http://about-cancer.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/biological-therapy/types/monoclonal-antibodies>

⁷ Cancer.net; Approved April 2017; 'Understanding Immunotherapy' <http://www.cancer.net/navigating-cancer-care/how-cancer-treated/immunotherapy-and-vaccines/understanding-immunotherapy>

⁸ See American Cancer Society; Last revision 8 August 2016; 'Cancer Vaccines'; <https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/cancer-vaccines.html>

⁹ See footnote 7

¹⁰ See footnote 7

¹¹ See US Food and Drug Administration; last update 10 October 2016; <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407297.htm>

¹² See Bosely S; 4 February 2016; 'The closest thing yet to a cure for terminal cancer?'; <https://www.theguardian.com/science/2016/feb/04/revolutionary-drug-immune-system-advanced-cancer>

¹³ See Grady D; 12 July 2017; 'F.D.A. Panel Recommends Approval for Gene-Altering Leukemia Treatment'; <https://www.nytimes.com/2017/07/12/health/fda-novartis-leukemia-gene-medicine.html>

¹⁴ See National Cancer Institute; 30 May 2017; 'FDA Approves Immunotherapy Drugs for Patients with Bladder Cancer'; <https://www.cancer.gov/news-events/cancer-currents-blog/2017/approvals-fda-checkpoint-bladder>

named it the “advance of the year” in 2016.¹⁵ Researchers are also studying whether using immunotherapy combined with surgery or radiation therapy can cure more people with early-stage disease.¹⁶

One of the more established uses of immunotherapy in cancer treatment is to treat malignant melanoma. Melanoma is the most lethal skin cancer and incidence has been steadily increasing over the last 30–40 years. The standard of care for over 3 decades has been dacarbazine, although this treatment has not shown any significant improvement in overall survival.¹⁷ Ipilimumab was approved for treating advanced melanoma by the FDA in 2011 and a number of other immunotherapies have subsequently been approved. This includes 3 checkpoint inhibitors, an oncolytic virus, 3 cytokine therapies and a combination therapy.¹⁸ However, there is still a significant mortality risk due to the aggressive nature of malignant melanoma. There is benefit from immunotherapy, but added survival is measured in months rather than years, with a 2 year survival rate commonly less than 30%.¹⁹

Risks

Although immunotherapy has fewer side effects than chemotherapy or radiotherapy, significant problems can still manifest with this treatment. Most side-effects are low-risk, simple skin reactions similar to an allergic reaction. However, there are other issues that require prompt medical attention, such as inflammation of the gut and lungs or problems with the endocrine system. There have been reports of a number of patient deaths, leading to trials being put on hold.²⁰

Some critics believe too many trials are ongoing and not enough care is being taken, with drug makers using a somewhat scattergun approach in the hope of finding the magic bullet to treat cancer.

A potential barrier to the success of combination immunotherapy is the cost to healthcare systems, with a single immunotherapy treatment costing over USD 100,000 per patient per annum.²¹ Forecasters predict sales of checkpoint inhibitors will reach USD 30 billion by 2022.²²

Impact on insurance

Insurers will need to keep up with developments in cancer treatment and react accordingly. Some markets already have products that assist with the high cost of treatment and other associated costs including inpatient/outpatient treatment, day-to-day living expenses and income replacement.

If new vaccines are developed for other cancers and given prophylactically, overall cancer incidence may decrease and as a result some insurance products could become cheaper for the customer. Also, with likely improvement in cancer survival, there could be a considerable increase in people with a history of treated advanced cancer becoming insurable. Regular studies should be carried out to ensure that product offerings are relevant and pricing reflects actual mortality and morbidity risk.

Conclusions

At the beginning of this article, the question was asked about cancer immunotherapy being a “game-changer”. At this point cancer immunotherapy is in its relative infancy but has a large amount of potential. Some remarkable successes have been noted, but significant benefits still appear limited to a relatively small proportion of people diagnosed with specific cancers and side-effects remain an issue. Giving immunotherapy in combination with other treatments and making use of companion diagnostics will likely be key to improving cancer survival in the future.

¹⁵ See Vose, J.M, Clinical Cancer Advances 2016: Annual Report on Progress Against Cancer © 2016, American Society of Clinical Oncology; <http://ascopubs.org/doi/full/10.1200/jco.2015.65.8427>

¹⁶ See Patel, J, MD; 8 November 2016; ‘9 Things to Know About Immunotherapy and Lung Cancer’; <http://www.cancer.net/blog/2016-11/9-things-know-about-immunotherapy-and-lung-cancer>

¹⁷ See Bhatia, S. MD, et al.; Treatment of Metastatic Melanoma: An Overview; ©2009 Oncology Journal; <http://www.cancernetwork.com/melanoma/treatment-metastatic-melanoma-overview/page/0/1>

¹⁸ See Wolchok, J, M.D., Ph.D; ‘What Makes Immunotherapy a Promising Treatment for Melanoma?’; <https://www.cancerresearch.org/cancer-immunotherapy/impacting-all-cancers/melanoma>

¹⁹ See Robert C, et al.; ‘Ipilimumab plus dacarbazine for previously untreated metastatic melanoma’; ©2011 N Engl J Med 2011; 364:2517-2526; <http://www.nejm.org/doi/full/10.1056/NEJMoa1104621>

²⁰ See Kenilworth, N.J.; July 5 2017; ‘Merck Provides Further Update on Three Multiple Myeloma Studies Evaluating KEYTRUDA® (pembrolizumab) in Combination with Pomalidomide or Lenalidomide’; <http://www.businesswire.com/news/home/20170705006004/en/>

²¹ See Pietrangelo, A; 12 October 2016; ‘The Value and Cost of Immunotherapy Cancer Treatments’; <http://www.healthline.com/health-news/value-and-cost-of-immunotherapy#1>

²² See Herper M; May 11 2017; Has Merck Lucked Into A \$10 Billion Drug?; <https://www.forbes.com/sites/matthewherper/2017/05/11/has-merck-lucked-into-a-10-billion-drug/#861f15288c8c>

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