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Cancer Immunotherapy

ABSTRACT

Cancer immunotherapy employs the immune system of the human body to fight and kill cancerous cells. This review article explores the translational research in immunotherapy that is revolutionising cancer treatment, including the use of cancer vaccines, checkpoint inhibitors, chimeric antigen receptor T-cells, cytokines and monoclonal antibodies.

INTRODUCTION

The immune system rests on two pillars: the innate, general immune system and the adaptive, specialised immune system. Both systems work together but carry out different tasks.The main aim of the innate immune response is to instantly prevent the spread of foreign pathogens, or germs, throughout the body. If the innate immune system is ineffective in destroying these pathogens, the adaptive immune response sets in – this is specific to the pathogen presented.

Many tumours are recognised as foreign by the adaptive immune system. However, this response can be inhibited by immunosuppressive mechanisms within the tumour, which is why patients do not always achieve long-term responses to existing immunotherapies. Cancer immunotherapy, also known as immuno-oncology, is a type of cancer treatment that uses the immune system to prevent, control and eliminate cancer. It can be used in combination with chemotherapy, radiation, surgery or targeted therapies to increase their efficiency. Cancer immunotherapy comes in many forms, including cancer vaccines, checkpoint inhibitors, chimeric antigen receptor T-cell therapy, cytokines and monoclonal antibodies.[1]

TYPES OF CANCER IMMUNOTHERAPY

Cancer Vaccines

Over the years, researchers have been looking at vaccines as a potential treatment for cancer. Similar to how vaccines work against other diseases, cancer vaccines are designed to recognise proteins on specific cancer cells. In turn, this helps the immune system to recognise and attack those cancer cells. Currently, there are four vaccines approved by the U.S. Food and Drug Administration (FDA) that can help prevent cancer, as well as two others for the treatment of cancer.

Preventive Cancer Vaccines

It is established that viral infections are to blame for the development of many cancers, and in fact, preventive vaccines have been found to play a significant role in reducing the risk. For example, cervical and head and neck cancers can be caused by the human papilloma virus (HPV), whereas liver cancer can be triggered by the hepatitis B virus (HBV). In light of this, numerous vaccines have been developed that can prevent HBV and HPV infection and, consequently, protect against HBV- and HPV-related cancers.

Cervarix®, for instance, is an FDA-approved vaccine used in preventing infection by the two strains of HPV that cause the most cervical cancers: HPV types 16 and 18.[2] Similarly, the Gardasil® vaccine prevents infection by HPV types 6, 11, 16, and 18, whereas Gardasil-9® prevents infection by HPV types 16, 18, 31, 33, 45, 52, and 58, and also prevents genital warts caused by HPV types 6 or 11.[3,4] Overall, all 3 vaccines can help prevent the development of HPV-related anal, cervical, head and neck, penile, vaginal, and vulvar cancers. In regard to the hepatitis B virus, HEPLISAV-B® is a vaccine that protects against infection by HBV and so helps in the prevention of HBV-related liver cancer.[5]

Therapeutic Cancer Vaccines

Nowadays, it is possible to identify targets on apatient's tumour that can help distinguish cancer cells from normal cells. Often, these targets are normal proteins produced at abnormal levels by cancer cells, such as prostatic acid phosphatase for example, which is often overexpressed by prostate cancer cells. By using this information, researchers have been able to develop vaccines such

as the FDA-approved Sipuleucel-T (Provenge®) vaccine which is used for the treatment of patients with advanced prostate cancer.[6] The European Medicine Agency have also approved in 2016 a vaccine (PDX-Survivac) that targets survivin, which is a protein that is over-expressed on ovarian cancer cells preventing their death.[7]

PDX-Survivac is also in a phase 2 clinical trial (ClinicalTrials.gov Identifier: NCT03836352) where subjects with advanced and recurrent solid tumours have been enrolled. The tumours include ovarian cancer, hepatocellular carcinoma, non-small cell lung cancer, and bladder cancer.

Along similar lines, Ambler et al.[8], at the Francis Crick Institute, London, UK, have designed a KRAS neoantigen peptide vaccine. KRAS is a gene that when it mutates makes cells to become cancerous. This mutation is present in many types of lung, bowel and pancreatic cancers. Promising results on mice speared clinical trials of this vaccine (ClinicalTrials.gov Identifier: NCT04117087).

The Bacillus Calmette-Guérin (or BCG) vaccine is another therapeutic cancer vaccine, used to treat early-stage bladder cancer. Specifically, it is a tuberculosis vaccine that uses weakened bacteria to fuel the immune system. In 1990, it became the first immunotherapy to be approved by the FDA.[9] Thirty years later, the search continues, and in fact, other cancer vaccine targets are currently being evaluated in clinical trials, including 5T4-, p53- and telomerase-based cancer immunotherapy.[10,11,12] Oncolytic viruses are also being designed and used for cancer immunotherapy. In fact the first oncolytic virus (OV) to treat metastatic melanoma have been approved.[13] Specifically, in the field of cancer virotherapy, OV can be armed with transgenes to increase their ability to kill cancer cells and leave normal cells unharmed.

Checkpoint Inhibitors

Immune checkpoints are proteins on immune cells that need to be activated or inactivated to elicit an immune response. Sometimes, cancer cells use these checkpoints to avoid attack by the immune system. Checkpoint inhibitor drugs are used to target these checkpoints, which therefore makes them a promising new avenue for cancer treatment. Two types of checkpoint inhibitor drugs are those that target the checkpoint proteins PD-1 or PD-L1 (programmed death ligand 1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) on T-cells.[14]

Examples of FDA-approved antibody drugs that target PD-1 include Cemiplimab (Libtayo®), Nivolumab (Opdivo®) and Pembrolizumab (Keytruda®). Examples of drugs that target PD-L1 include Atezolizumab (Tecentriq®), Avelumab (Bavencio®) and Durvalumab (Imfinzi®). Overall, these drugs have been significant in treating different types of cancer, from advanced cutaneous squamous-cell carcinoma[15] to non-small-cell lung cancer.[16] Also, Ipilimumab (Yervoy®), which targets CTLA-4, is used to treat melanoma of the skin and continues to be tested for other cancers as well.[17]

Chimeric Antigen Receptor T-Cell Therapy

Adoptive cell transfer (ACT) is an immunotherapy approach where a patient's own immune cells are collected and used to treat their cancer. Several types of ACT exist, but, CAR T-cell therapy is the most advanced in terms of clinical development. In CAR T-cell therapy, T-cells are taken from a patient's blood and then engineered so as to attack cancer cells. Specifically, the gene for a chimeric antigen receptor that binds to a protein on the patient's cancer cells is added. In the end, large quantities of the CAR T-cells are grown in the lab and given to the patient by infusion.

The use of CAR T-cell therapy has, until recently, been limited to small clinical trials. However, in 2017, two CAR T-cell therapies were approved by the FDA: Tisagenlecleucel (Kymriah®) for the treatment of acute lymphoblastic leukaemia[18] and Axicabtagene ciloleucel (Yescarta®) for advanced lymphomas.[19]

Cytokines

Cytokines such as interferon and interleukin are a group of proteins that play a central role in boosting the immune system. Over the years, researchers have created man-made versions of these to treat cancer. For example, interferon is used for different types of cancer including kidney cancer, melanoma, multiple myeloma and a few types of leukaemia. Similarly, interleukin is used to treat kidney cancer, although it is also in clinical trials for other types of cancer.[20]

Monoclonal Antibodies

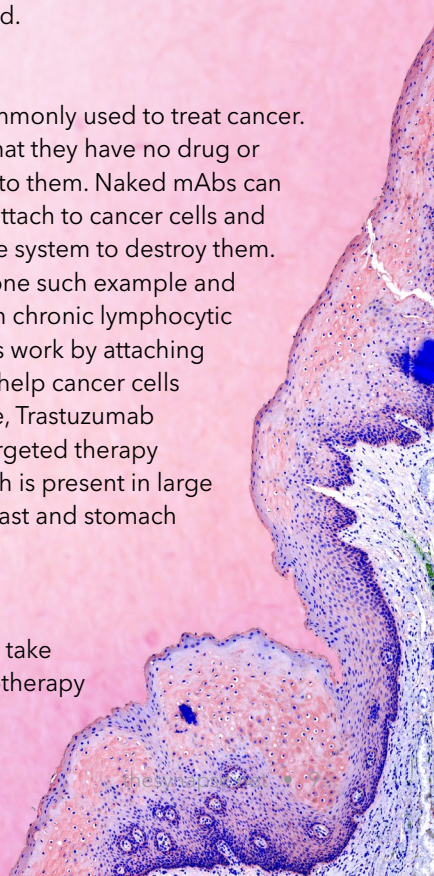
Monoclonal antibodies (mAbs) are artificial versions of immune system proteins. Since they can be designed to attack definite parts of a cancer cell, mAbs can be useful in treating cancer. mAbs used to treat cancer can be bispecific, conjugated or naked.

Naked mAbs

Naked mAbs are the most commonly used to treat cancer. They work by themselves, in that they have no drug or radioactive particles attached to them. Naked mAbs can work in different ways. Some attach to cancer cells and act as a marker for the immune system to destroy them. Alemtuzumab (Campath®) is one such example and is used to treat individuals with chronic lymphocytic leukemia.[21] Other naked mAbs work by attaching to and blocking antigens that help cancer cells grow and spread. For example, Trastuzumab (Herceptin®) is an antibody-targeted therapy against the HER2 protein which is present in large amounts on the surface of breast and stomach cancer cells.[22]

Conjugated mAbs

Conjugated mAbs are used to take radioactive particles or chemotherapy drugs directly to cancer cells.



Specifically, these mAbs circulate around the body until they find and hook onto the target antigen. As such, the toxic substance is delivered where it is needed the most, which decreases the damage to normal cells in other parts. An example of a radiolabelled mAb is Yttrium-90-Ibritumomab Tiuxetan (Zevalin®) which is used in patients with relapsed follicular non-Hodgkin lymphoma.[23] Similarly, the chemolabelled mAb Brentuximab vedotin (Adcetris®) has shown remarkable efficacy in CD30-positive lymphomas, such as Hodgkin's lymphoma and systemic anaplastic large-cell lymphoma.[24]

Bispecific mAbs

Bispecific mAbs are composed of parts of two different mAbs, that is, they can attach to two different proteins at the same time. An example is Blinatumomab (Blincyto®), used to treat some types of leukemia, where one part attaches to the CD19 protein found on some leukemia and lymphoma cells, and the other part attaches to the CD3 protein found on T- cells. By binding to both CD3 and CD19 proteins, Blinatumomab is able to bring both the cancer cells and immune cells together, which is meant to elicit the immune system to attack the cancer cells.[25]

SIDE EFFECTS OF IMMUNOTHERAPY

In general, the side effects of immunotherapy are different from those seen with conventional treatments. This is because they result from a misdirected or overstimulated immune response rather than the effects of chemical or radiological therapy. Overall, the side effects of immunotherapy vary depending on the treatment type, as well as the location, type of cancer and the patient's overall health. In principle, immune-related side effects can have an effect on any tissue or organ, and can range from mild and moderate to severe becoming life-threatening under particular circumstances.[26,27] In most cases, however, immunotherapy-related side effects can be managed with immunosuppressive drugs such as steroids as long as they are addressed early.

CONCLUSION

In the last few decades, immunotherapy has become central in treating different types of cancer, so much so that new ways of working with the immune system are constantly being discovered. Epigenetic research, for instance, is showing that there is the potential to combine epigenetic drugs with immunotherapeutic agents.[28] Similarly, it has been found that the role of the microbiome in controlling the immune response is essential and therefore also significant in cancer immunotherapy. Indeed, research is already ongoing to find out how to modulate the microbiome and enhance the immunotherapeutic effect when treating cancer.[29] Translational research in cancer immunotherapy is in hyper drive and will provide other possibilities in the fight against cancer.

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