Review on Immunotherapy-developmentof an alternative cancer treatment

G V Harini

St. Martin's Engineering College, Dhulapally(V), Kompally, Secunderabad, Telangana, India-500100

Abstract

Cancer immunotherapy involves the use of therapeutic modalities that determine a manipulation of the immune system by using immune agents such as cytokines, vaccines, cell therapies and humoral, transfection agents. Immunotherapy of cancer has to stimulate the host's anti-tumour response by increasing the effector cell number and the production of soluble mediators and decrease the host's suppressor mechanisms by inducing tumour killing environment and by modulating immune checkpoints. Immunotherapy seems to work better in more immunogenic tumours. Compared with previous standards of care (including chemotherapy, radiotherapy, and surgery), cancer immunotherapy has brought significant improvements for patients in terms of survival and quality of life. Immunotherapy has now firmly established itself as a novel pillar of cancer care. In this review we will see the evolution of immunotherapy.

Keywords: Cytokine, T cell, checkpoint inhibition, antitumour, antibodies

1. Introduction:

Immunotherapy is a type of cancer treatment that helps our immune system fight cancer. The immune system helps our body fight infections and other diseases. It is made up of white blood cells and organs and tissues of the lymph system.Immunotherapy is a type of biological therapy. Biological therapy is a type of treatment that uses substances made from living organisms to treat cancer.[3]

Most available immunotherapies, such as immune checkpoint inhibitors and chimeric antigen receptor (CAR) T-cell therapies, focus on immune cells called cytotoxic T cells, which are part of the adaptive, or specific, immune system. Cytotoxic T cells recognize and kill cancer cells that display specific molecules (antigens) on their surfaces. Once an innate immune response has been initiated, an adaptive immune response is stimulated, and both work together to eliminate infections or other threats to the body. Macrophages are innate immune cells that engulf and digest cancer cells, cell debris, bacteria, and other foreign substances. Normal cells are protected from being eaten by macrophages because they display a protein called CD47 on their surface. In effect, CD47 is a "don't eat me" signal to macrophages. Many cancer cells, however, also display CD47 on their surface, protecting them from macrophages.Natural killer (NK) cells are yet another type of innate immune cell that recently have been used to treat cancer. Metabolites produced by gut microbes appear to play an important role in antitumor immunity. In addition, new resources, including better cancer models, are needed to support additional basic research and preclinical drug development.

Technologies that enable analyses of single tumour and immune cells and advanced tumour imaging will drive progress in this emerging area of research. [4]

2. Evolution of cancer immunotherapy

Immunotherapy in cancer is a type of treatment discovered in the 1970s, with the onset of bladder cancer therapy with BCG [5] and IFN therapy in malignant melanoma. Various immune therapies such as IL 2 cytokine used in solid tumours like melanoma were discovered. A period of decline of these therapies followed, with powerful side effects and minor results. Along with studying the mechanisms of the immune response, there are cells involved in the immune response, mediators that cause stimulation or inhibition of the immune response, developing new therapies [2].

The field of immuno-oncology has been transformational in the care of cancer patients. William B. Coley, now widely accepted as the father of immunotherapy, first attempted to harness the power of the immune system for treating cancer in the late 19th century. Beginning in 1891, Coley injected more than a thousand patients with mixtures of live and inactivated bacteria such as Streptococcus pyogenes and Serratia marcescens with the hope of inducing sepsis and strong immune and antitumour responses. His cocktail of bacteria became widely known as "Coley's toxin" and represents the first documented active cancer immunotherapy intervention[1]. Coley achieved durable complete remissions in several types of malignancies, including sarcoma, lymphoma, and testicular carcinoma. However, the lack of a known mechanism of action for Coley's toxin and the risks of deliberately infecting cancer patients with pathogenic bacteria caused oncologists to adopt surgery and radiotherapy as alternative standard treatments early in the 20th century[9].

3. Types of immunotherapies

3.1.Cytokine Therapy

Cytokines are messenger molecules that are able to help controlling the growth and activity of immune system cells. Monoclonal antibodies are molecules generated in the laboratory that can target specific antigens on tumours. Combining them seems to be a good immunologic treatment. There is a fusion of the cytokine interleukin-2 (IL-2) and an antibody that recognizes peptides on the surface of the tumour cells that was studied in clinical trials. Treatment with IL-2 can enhance the activity of the immune system against tumour and, by linking IL-2 to the antibody, ALT-801 can target IL-2 to cancer cells[8]. Immune checkpoint inhibitor therapies are now widely indicated in numerous cancer types. Furthermore, numerous ongoing clinical trials are assessing the potential of other agonistic or inhibitory checkpoints to affect tumour-related outcomes. The checkpoints are not equal in their potential. For example, the agonistic OX40 antibody has modest clinical activity, but the CD28 antibody—even at very subtherapeutic doses—resulted in massive cytokine syndrome and the intensive-care hospitalization of the first 6 healthy volunteers treated. In that light, finding the right combination of ICI therapy to induce the optimal amount of immune activation remains an active area of clinical research[10].

3.2.Oncolytic virus therapy

Oncolytic virus therapy uses a modified virus that can make tumour cells self-destruct and release antigens therefore generating a greater immune response against the cancer. The best-

known oncolytic virus is an oncolytic adenovirus that also expresses the immune stimulating cytokine GM-CSF. This oncolytic adenovirus is administered intravesical and further enhances the anti-tumour immune response, being tested in a phase II/ III study in patients with carcinoma in situ (CIS) of the bladder or with non-muscle invasive bladder cancer plus CIS of the bladder and who have failed BCG therapy[13].

3.3.Checkpoint Inhibition

The knowledge of innate tumour suppression by a functioning immune system has paved the way for one of medicine's most profound discoveries: checkpoint inhibition. Through complex mechanisms, blocking the immune system's regulatory checks and balances using selective antibodies can provide antitumor activity with more tolerable toxicities [14]. This checkpoint, discovered by James Allison, led to the approval of ipilimumab for metastatic melanoma in 2011 as the first checkpoint inhibitor for cancer treatment. Ipilimumab is an anti-CTLA-4 monoclonal antibody and works by directly blocking CTLA-4, making way for downstream T cell activation, proliferation and eventual tumour destruction[15].

3.4.Antitumor Monoclonal Antibodies

The concept that cancer cells express certain potentially targetable antigens has paved the way for humanized antibodies as a treatment strategy for malignancy. Antibodies can target and destroy specific tumour antigens by interacting with immune cells through the antibody's fragment crystallizable (Fc) region. The Fc region on an antibody can bind to various Fc receptors (FcRs) that are found on natural killer cells, neutrophils, eosinophils, dendritic cells, or monocytes. Depending on the antibody class, this immune cell–antibody interaction can lead to tumour cell death in several ways, including complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP)[16]. This breakthrough has led to the development of many antitumor monoclonal antibodies (MABs), greatly influencing cancer treatment in the previous decades. The first therapeutic antibody in oncology is still widely used today: rituximab[17]. There are currently over 500 approved and investigational MABs engineered against solid and hematologic malignancies, as well as benign hematologic conditions, autoimmune and chronic diseases. Antibody–drug conjugates such as Kadcyla are providing promising options for many malignancies. Monoclonal antibodies remain one of the most exciting and evolving areas of cancer-directed therapy.

3.5.CAR-T Cell Therapy

Chimeric antigen receptor T (CAR-T) cell therapy has been at the forefront of the novel treatment of hematologic malignancies over the past few decades. In the early 1990s, Eshhar et al. sought to bypass the limitations of T cell silencing caused by the tumour microenvironment. In doing so, they developed the first chimeric antigen receptor, paving the way for an astounding new cancer treatment. In summary, a patient's T cells are collected, and, using a modified inactive virus, the T cells are essentially reprogrammed to produce 'special' receptors called chimeric antigen receptors, or CARs, on their surface. These reprogrammed chimeric T cells are then infused back into the patient. The CARs then

redirect T cell function and specifically allow the engineered T cells to latch onto cancer cells, propagating and facilitating their death[18]. Currently, CAR-T cells are FDA-approved for B cell lymphomas and ALL. CAR-T cells are revolutionizing the treatment of hematologic malignancies as they have shown remarkable response rates up to 94%.

4. Types of cancers where immunotherapy is effective:

Bladder cancer was the first indication for which an immunotherapy was used in 1970. Currently, there are a number of additional immune-based bladder cancer treatments under development. Most bladder cancers start in the transitional epithelial cells and are represented by urothelial carcinoma [6].Patients with moderate- to high-grade disease often receive intravesical immunotherapy with bacillus Calmette-Guérin (BCG). The standard treatment according to the guidelines for patients with muscle invasive bladder cancer includes cisplatin-based chemotherapy regimens, neoadjuvant administration followed by surgical removal of the bladder or radiation therapy and concomitant chemotherapy. Recurrent and metastatic bladder cancer is treated with chemotherapy regimens that include methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) or gemcitabine plus cisplatin (GC), two regimens with the same response rates[7].

Brain cancer is another cancer type that desperately needs new treatments with high response rates. New immune-based treatments are currently under development in brain cancer tumours treatment [11]. There are several types of brain cancer, classified according to the type of cell from which they originate. Gliomas, which originate in glial cells that support and protect neurons, account for more than 70% of the brain cancers. Astrocytomas have origins in astrocytes. Meningiomas are tumours that begin in the meninges of the brain and spinal cord. The mortality rate for brain cancer has remained increased for more than 30 years, although significant advances have been made in understanding the biology of brain cancers. Glioblastoma (GBM) is the most aggressive form of brain cancer. GBM patients typically have short life expectancies. Median progression free survival is of 6.9 months, and the median overall survival is of 14.6 months. In 2005, temozolomide was approved to treat GBM. In 2009, bevacizumab was granted accelerated approval for the treatment of GBM patients but there was no evidence of improvement in the overall survival. Current immunotherapies that are in study in brain cancer fall into six broad categories: cancer vaccines, checkpoint inhibitors, oncolytic virus therapy, adoptive cell therapy, and monoclonal antibodies[12].

Breast cancer is one of the major cancer types that affect the economy of all countries. Some new treatments have been developed and approved in the last years. New immune-based cancer treatments are currently under development.Promising clinical research in breast cancer is the use of immune checkpoint inhibitors that work by targeting molecules that serve as checks in the regulation of immune responses and block inhibitory molecules or activate stimulatory molecules. There are some phase I/ II studies that enrolled patients with breast cancer in different stages of the disease, for treatments with indoximod, an IDO inhibitor (IDO is expressed by a number of tumour types and correlates with poor prognosis), an anti-OX40 antibody (OX40 is a costimulatory molecule expressed after T cell activation that enhances T cell survival and anti-cancer effector function) and an anti-PD-L1 checkpoint inhibitor.

Monoclonal antibodies (mAbs) are generated in the lab and target specific antigens on tumours. Many antibodies are currently used in cancer treatment. New antibodies are tested in breast cancer: glembatumumabvedotin - an antibody-drug conjugate used in patients with advanced triple-negative breast cancer with cells that produce a protein called glycoprotein NMB, margetuximab, an anti-HER2 antibody used in patients with relapsed or refractory advanced breast cancer with cells that express HER2 at the 2+ level and lack HER2 gene amplification by FISH. Cancer vaccines elicit an immune response against tumour-specific or tumour-associated antigens. Several trials of vaccines, given alone or with other therapies, are currently enrolling breast cancer patients: NeuVax is under investigation to prevent breast cancer recurrence among patients with HER2 1+ and 2+ following surgery. GVAX, a therapeutic vaccine made from breast cancer cell lines irradiated and engineered to express the immune molecule GM-CSF[19].

Cervical cancer is another cancer type for which new immune-based cancer treatments are currently under development. Immunotherapy agents designed to treat these types of cancers are badly needed. Several checkpoint inhibitors that target multiple different checkpoints are currently under development. Ipilimumab, an anti-CTLA-4 antibody, is being tested in two clinical trials that enroll patients with cervical cancer; an OX40 immune modulator is being tested in combination with tremelimumab, an anti-CTLA-4 antibody; Urelumab-an anti-4-1BB/ CD137 antibody and nivolumab, an anti-PD-1 antibody; Lirilumab - an anti-KIR antibody, is being tested in combination with nivolumab; an anti-GITR antibody is also tested[20].

5. Conclusion:

In many ways, immunotherapy has forever changed the way we approach the practice of hematology and oncology and has emerged as a powerful tool in cancer care. The possibilities for further innovation involving these novel therapeutic agents will continue to shape the way we personalize cancer care, as more is discovered about how these agents both work and enhance traditional therapies, as well as how they provide new ways to approach malignancies that were previously difficult to treat. Through years of research and innovation, immunotherapy now has many sub-categories, including, but not limited to, checkpoint inhibition, monoclonal antibodies, CAR-T cells and oncolytic viruses.This research leaves the space wide open for innovation, with countless opportunities to both potentially incorporate these regimens into various permutations of standard of care and to enhance current practices. Further study on which patients will most benefit from certain agents, as well as the optimal sequencing of agents, will better allow the personalization of cancer care as more is understood on these therapeutic interventions. As the indications for currently approved agents continue to expand, and new agents are introduced and studied, the field of cancer immunotherapy continues to grow. These agents have changed the playing field, and as our knowledge of the pathophysiology and mechanism of action and interaction continues to evolve, so do the possibilities for the utilization and implementation of these novel agents. The progress made in oncology care as a direct result of the development and implementation of these immunotherapeutic agents has produced a watershed moment for cancer care that truly represents the power of studies that are founded in science and focused on clinical practice and outcomes.

1. A review of cancer immunotherapy: from the past, to the present, to the future
K. Esfahani, MD MSc,[*] L. Roudaia, MD,[*] N. Buhlaiga, MD,[*] S.V. Del Rincon, PhD,[†] N. Papneja, MD,[*] and W.H. Miller, Jr, MD PhD
2. Development of new immunotherapy treatments in different cancer types
DL Stanculeanu,[*,**] Zob Daniela,[*,**] A Lazescu,[**] R Bunghez,[**] and R Anghel[*]
3. Immunotherapy to Treat Cancerhttps://www.cancer.gov/about-cancer/treatment/types/immunotherapy
4. The Immune System and Microbiome - Opportunities in Cancer Research
https://www.cancer.gov/research/areas/treatment
5. Zdimerova H, Albert ML, Ingersoll MA. Harnessing the Host Immune Response to Infection - BCG ImmunoTherapy for Bladder Cancer, Infection and Cancer: Bi-Directorial Interactions. :340–387.
6. Sharma P. Bladder Cancer Immunotherapy review, Reviewed December 2014, Sources: ACS Facts and Figures 2014, National Cancer Institute Physician Data Query, National Cancer Institute Biological Therapies fact sheet, SEER Cancer Statistics Factsheets: Bladder Cancer, ClinicalTrials.gov, CRI documents
7. https://clinicaltrials.gov/show/NCT01928394 A Phase 1/ 2, Open-label Study of Nivolumab Monotherapy or Nivolumab Combined With Ipilimumab in Subjects With Advanced or Metastatic Solid Tumors, Bristol-Myers Squibb
8. Combination of IFNα and poly-I:C reprograms bladder cancer microenvironment for enhanced CTL attraction.
Muthuswamy R, Wang L, Pitteroff J, Gingrich JR, Kalinski P
J Immunother Cancer. 2015; 3():6.
9. Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited.Decker WK, Safdar ACytokine Growth Factor Rev. 2009 Aug; 20(4):271-81.
10. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412.
Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, Panoskaltsis N
N Engl J Med. 2006 Sep 7; 355(10):1018-28.
11. Reardon DA. Brain cancer immunotherapy review, Sources: National Cancer Institute; National Cancer Institute Physician Data Query (PDQ); American Cancer Society Cancer Facts & Figures 2015; Cedars Sinai Brain Tumors and Brain Cancer web page; GLOBOCAN 2012; CRI grantee progress reports and other CRI grantee documents, Last Updated April 2015
12. Wainwrighta DA, Nigama P, Thacia B, Deya M, Lesniak MS. Recent developments on immunotherapy for brain cancer. [Published online: 25 Apr 2012];Diabetes Care. 2012 :181–202.
13. Vasekar M, Degraff D, Joshi M. Immunotherapy in Bladder Cancer. Current Molecular Pharmacology. 2015 PMID:26177642.
14. Jiang, T.; Zhou, C.; Ren, S. Role of IL-2 in cancer immunotherapy. OncoImmunology 2016, 5, e1163462.
15. Tarhini, A.; Lo, E.; Minor, D.R. Releasing the Brake on the Immune System: Ipilimumab in Melanoma and Other Tumors. Cancer Biother. Radiopharm. 2010, 25, 601–613.

16. Zhao, J.; Chen, Y.; Ding, Z.-Y.; Liu, J.-Y. Safety and Efficacy of Therapeutic Cancer Vaccines Alone or in Combination with Immune Checkpoint Inhibitors in Cancer Treatment. Front. Pharmacol. 2019, 10.
17. Pierpont, T.M.; Limper, C.B.; Richards, K.L. Past, Present, and Future of Rituximab—The World's First Oncology Monoclonal Antibody Therapy. Front. Oncol. 2018, 8, 163.
18. Sermer, D.; Brentjens, R. CAR T-cell therapy: Full speed ahead. Hematol. Oncol. 2019, 37, 95–100.
19. Schechter AL, Hung MC, Vaidyanathan L, Weinberg RA, Yang-Feng TL, Francke U, Ullrich A, Coussens L Science. 1985 Sep 6; 229(4717):976-8.
20. Immunotherapy: an evolving paradigm in the treatment of advanced cervical cancer. Eskander RN, Tewari KS ClinTher. 2015 Jan 1; 37(1):20-38.