Journal of Advanced Zoology
ISSN: 0253-7214
*Volume **45** Issue **1** Year **2024** Page **504:507***

Immunotherapy: A New Generation Treatment For Cancer

Ritika Roy[1], Bidisha Ghosh[2], Suranjana Sarkar[3], Subhasis Sarkar[4], Semanti Ghosh[5*]

[1,2,5]Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore, Kolkata -700121*
[3,4]Department of Microbiology, Swami Vivekananda University, Barrackpore, Kolkata -700121

***Corresponding Author:** Semanti Ghosh*
***Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Barrackpore, Kolkata -700121. Email: semantig@svu.ac.in*

Abstract

Cancer related deaths are increasing nowadays. The use of radiotherapy and chemotherapy are effective but can be limited for their toxicities. Immunotherapy is a less toxic form of cancer treatment that boosts our immunity to fight cancer. Spontaneous reduction of uncontrolled cancerous tumors is now recognized as a rare phenomenon, and immunosuppression is linked to an increased risk of cancer. The immunotherapy of cancer has played a notable role in the few years. It made a lot of cutting-edge and promising new cancer treatments that control the immune system possible. Monoclonal antibodies, cellular immunotherapy, cytokines therapy, immune checkpoint and vaccines become successful therapies for treating hematological cancers in preclinical models, clinical trials and practice. Immune responses to tumors have been shown to be boosted by toll-like receptor agonists. Additionally, T cells, NK cells, and dendritic cells are used in cell-based immunotherapies, which have been developed to treat cancer and tumors. Oncolytic immunotherapy is promoting novel components of cancer immunotherapy. This article reviews recent developments in cancer immunotherapy, as well as novel approaches, ongoing clinical trials, and prospective directions. We also highlight how cancer vaccines, autoimmunity, the tumor micro-environment and metabolomics is aiming to solve those challenges.

Keywords: Immunotherapy, Immune checkpoint inhibitors, Cellular immunotherapy, Monoclonal antibodies, Cytokines, Oncolytic immunotherapy.

INTRODUCTION:

Cancer is a condition in which the body's cells grow in uncontrolled way and spread to other parts or organs of the body. It has an impact on general health. In 2020, cancer will claim the lives of roughly 10 million individuals worldwide (Sung et al., 2021). According to the American Cancer Society's forecast for 2021, experts predict that almost 1.9 million individuals will receive a cancer diagnosis and about 608,570 people will pass away from the disease (Siegel et al., 2021). It is projected that by 2030, there would be 21 million deaths worldwide from cancer. A number of well-known cancer therapies, including radiation,

chemotherapy, and surgery, have significant drawbacks, including severe toxicity and drug resistance. According to clinical practice, for patients with advanced solid tumors, they frequently fall short of providing benefits for long-term survival. An immunosuppressive tumor microenvironment (TME) is discovered by scientists in conjunction with immunological research, cellular biology, and molecular methods. According to research, immunosuppression is substantially associated with cancer growth and metastasis (Giannone et al., 2020). Numerous clinical researches have shown that cancer immunotherapy is developing into a potent new technique to improve selectivity of cancer treatment with decreased adverse effects. Immunotherapy still has certain safety and efficacy issues when used in clinical settings. The various forms of cancer immunotherapies are overviewed in this review along with their clinical status, benefits, and drawbacks.

Immune checkpoint blockade therapy

It is necessary for immune resistance and tissue protection when the immune system is responding to pathogenic infection. However, the elevated expression of checkpoints during tumor formation and activity might promote tumor immune evasion by impairing immune cell function (Xu et al., 2021). Immune checkpoint inhibitors, can stop immunosuppressive signals from spreading, strengthening or regaining the body's antitumor defenses. Immune checkpoints include CTLA-4 (cytotoxic T lymphocyte antigen 4), PD-1 (programmed cell death protein 1) and PD-L1 (programmed cell death ligand 1). On functional $CD8^+$ and $CD4^+$ T lymphocytes, CTLA-4 is present. When early T cell activation occurs, CTLA-4 and the co-stimulatory receptor CD28 compete with one another for binding to the ligands B7-1 and B7-2 synthesized on antigen-presenting cells (APCs). Then by triggering downstream negative immune response regulation, T cell proliferation and IL-2 secretion are suppressed (Willsmore et al., 2021; Chikuma et al., 2017). It eventually prevents an appropriate immune response to tumor cells. PD-1 is an additional integral membrane protein that T cells express. T cells, APCs, and tumor cells can all express PD-L1. T cell reaction to TCR triggering signals is inhibited by PD-1's binding to PD-L1 by activating the PI3K-AKT and JAK-STAT signaling pathways (Barclay et al., 2018; Jiang et al., 2019). The FDA in the United States has approved the use of three anti-PD-1 antibodies (pembrolizumab, nivolumab, and cemiplimab), one anti-CTLA-4 antibody (ipilimumab), and three anti-PD-L1 antibodies (atezolizumab, avelumab, and durvalumab) for the treatment of different cancers (Barclay et al., 2018). In 2011, the FDA approved ipilimumab, a monoclonal antibody that targets CTLA-4, for use in patients suffering from metastatic melanoma (Robert et al., 2011). It is the first immune system that has been clinically tested and authorized. The initial clinically recognized immunological checkpoint blocker. Using ipilimumab as a treatment 20% of individuals with advanced melanoma survived longer than 4 years, and just a small number of patients lived more than 10 years (Schadendorf et al., 2015). Ipilimumab is also frequently employed to treat cancers including lung, kidney, and prostate cancer (Grünwald, 2015). However, it is less effective than metastatic carcinoma. Efficiencies less than 10% are typically considered to be subpar. In general, PD-1/PD-L1 blockers have a higher anticancer therapeutic efficacy than CTLA-4 blockers. In patients with advanced melanoma, pembrolizumab was found to be more effective than ipilimumab in prolonging both progression-free survival and overall survival (Robert et al., 2015). Nivolumab has a therapeutic response rate of more than 80% in individuals with classic Hodgkin's lymphoma (Ansell et al., 2015). Additionally, for a number of cancer patients, PD-1/PD-L1 blocking antibody has a greater than 10% healing effect. There was a strong association observed between the expression of PD-L1 within the tumour and the overall response rate (ORR) of PD-1/PD-L1 inhibitors. Scientists report that the ORR for the PD-L1 beneficial group was 34.1%, and the ORR for the PD-L1 unfavorable group was 19.9% (Carbognin et al., 2015). These biomarkers will be useful in determining which cancer patients would well-being from immune checkpoint inhibitor treatment. When the predictive value of biomarkers is validated in a larger group population, immunological checkpoint blockade therapy and precision medicine will progress.

Adoptive cell therapy

Adoptive cell therapy (ACT) involves removing immune-competent cells from cancer patients, genetically modifying those cells in vitro to boost immunological activity, and then injecting those cells back into the patients to bolster their immune systems' capacity to combat cancer. T cell receptor modified T (TCR-T) cells, chimeric antigen receptor modified natural killer cells (CAR-NK), lymphokine activated killer cells (LAK), cytokine activation killing (CIK) cells, and tumor-infiltrating lymphocytes (TILs) are examples of immune-competent cells. TILs, TCR-T cells, and CAR-T cells are the most researched of all ACT treatments. In ACT therapy, TIL cells are isolated from tissues close to the tumor via ACT with TILs, expanded in vitro to a large scale, and then reintroduced into the patient. When ACT with TCR or CAR is reinfused into the

patient, it can selectively identify and attack tumor cells because it removes T cells from the patient's peripheral blood and genetically modifies them to express TCR or CAR (Yang et al., 2022).

Cytokines

Cytokines are glycoproteins secreted by immune cells. Important proteins called cytokines aid in controlling the activity of immune cells as well as the development of tumors. Interleukins-2 (IL-2) is one kind of cytokine produced in a lab. IL-2 has been licensed for the treatment of renal cell carcinoma and melanomas, and is especially helpful when a tumour is resistant to conventional therapy. To increase effectiveness, it can be given either alone or in combination with interferon-alpha. Fever, chills, lethargy, gastrointestinal problems, weight gain, and a rare but significant cardiovascular toxicity are some of the negative effects of IL-2. Other example of cytokines therapy is Interferon alpha (IFN-alpha) which contains 150 amino acids. It binds to immune cells receptor and create an immune reaction towards malignant cells. IFN-alpha is recommended for a number of malignancies, including hairy cell leukemia, follicular non-Hodgkin's lymphoma, kidney cancer, Kaposi's sarcoma associated with AIDS, and melanoma. GM-CSF is another cytokine therapy which uses as a supportive treatment after chemotherapy. This treatment is typically used in conjunction with bone marrow or stem cell transplants to replenish the myeloid series (Che and Rahman, 2017).

Cancer Vaccines

Tumor-associated antigens (TAAs) and tumor-specific antigens (TSAs) are used in cancer vaccines to elicit an immune response from the body, notably a potent and enduring one from $CD8^+$ T cells that stops tumor cells from proliferating, spreading, and coming back. There are numerous cancer vaccines, including preparations based on cells, DNA, RNA, and proteins/peptides. Cancer vaccines are classified into two types based on their clinical application: preventative and therapeutic. The aim of the therapeutic cancer vaccines is to induce or enhance tumor-specific immune responses, which in turn kill tumor cells, whilst the preventive cancer vaccines attempt to prevent tumor development by eliciting immune response. Cervical cancer vaccinations that target human papillomavirus (HPV) are now the most successful preventative cancer vaccines. It can prevent the HPV virus. However, they are generally useless if you have cancer or a persistent HPV infection. As a result, not only preventative but also therapeutic cancer vaccinations are required. Several studies have demonstrated that some advanced cancer patients have positive outcomes even after being vaccinated against cancer (Che and Rahman, 2017).

Oncolytic Immunotherapy

Oncolytic viruses (OVs) are the foundation of oncolytic immunotherapy. By multiplying in cancer cells without harming healthy cells, OVs have the ability to activate both the innate and adaptive immune systems and cause tumor cells to lyse. One kinds of cancer immunotherapy treatments where oncolytic viruses can selectively target, proliferate inside, and kill tumors. Oncolytic immunotherapy is thought to be a means for the immune system to detect tumor cells and produce long-lasting antitumor response by causing virus-induced tumor cell death, also known as immunogenic cancer cell death (ICD). ICD and immunological responses to the virus work together to provide effective antitumor effects. FDA licensed talimogene laherparepvec (T-VEC), a genetically engineered oncolytic herpes simplex virus (HSV), for the treatment of metastatic melanoma in 2015 (Yang et al., 2022).

CONCLUSION:

Immune-based cancer therapies have been discovered by a better knowledge of the immune system. The development of immunotherapy against cancer cells has been based on enlisting and modifying the human immune system. Over the years, lots of immunotherapies have been accepted for use on years, the market, including cytokines, immunological adjuvants, preventive and therapeutic tumor vaccines, and monoclonal antibodies. Numerous clinical trials have proven that immunotherapy is beneficial in the treatment of cancer. Immunotherapy decreases cancer recurrence and raises the patient's overall survival rate. Immunotherapy is preferable to traditional treatment because it is more target-specific, has fewer side effects, is more tolerable by patients, and is more economical over the long run. Future research will likely confirm the major biological and clinical role of immunotherapy in cancer treatment.

ACKNOWLEDGEMENT

We would like to thank School of Life Sciences, Swami Vivekananda University for their support to carry out this study.

REFERENCES

1. Ansell, S. M., Lesokhin, A. M., Borrello, I., Halwani, A., Scott, E. C., Gutierrez, M., ... & Armand, P. (2015). PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. New England Journal of Medicine, 372(4), 311-319.
2. Barclay, J., Creswell, J., & León, J. (2018). Cancer immunotherapy and the PD-1/PD-L1 Cckpoint pathway. Archivos espanoles de urologia, 71(4), 393-399.
3. Carbognin, L., Pilotto, S., Milella, M., Vaccaro, V., Brunelli, M., Caliò, A., ... & Tortora, G. (2015). Differential activity of nivolumab, pembrolizumab and MPDL3280A according to the tumor expression of programmed death-ligand-1 (PD-L1): sensitivity analysis of trials in melanoma, lung and genitourinary cancers. PloS one, 10(6), e0130142.
4. Che I. C. N., Rahman M. S. 2017. Immunotherapy for Treatment of Cancer, Borneo journal of medical sciences, 11: 3-12.
5. Chikuma, S. (2017). CTLA-4, an essential immune-checkpoint for T-cell activation. Emerging Concepts Targeting Immune Checkpoints in Cancer and Autoimmunity, 99-126.
6. Giannone, G., Ghisoni, E., Genta, S., Scotto, G., Tuninetti, V., Turinetto, M., & Valabrega, G. (2020). Immuno-metabolism and microenvironment in cancer: key players for immunotherapy. International journal of molecular sciences, 21(12), 4414.
7. Grünwald, V. (2015). T-cell checkpoint inhibitors in metastatic renal cell carcinoma. Current Opinion in Urology, 25(5), 411-415.
8. Jiang, X., Wang, J., Deng, X., Xiong, F., Ge, J., Xiang, B., ... & Zeng, Z. (2019). Role of the tumor microenvironment in PD-L1/PD-1-mediated tumor immune escape. Molecular cancer, 18(1), 1-17.
9. Robert, C., Schachter, J., Long, G. V., Arance, A., Grob, J. J., Mortier, L., ... & Ribas, A. (2015). Pembrolizumab versus ipilimumab in advanced melanoma. New England Journal of Medicine, 372(26), 2521-2532.
10. Robert, C., Thomas, L., Bondarenko, I., O'Day, S., Weber, J., Garbe, C., ... & Wolchok, J. D. (2011). Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. New England Journal of Medicine, 364(26), 2517-2526.
11. Schadendorf, D., Hodi, F. S., Robert, C., Weber, J. S., Margolin, K., Hamid, O., ... & Wolchok, J. D. (2015). Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. Journal of clinical oncology, 33(17), 1889.
12. Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2021). Cancer statistics, 2021. Ca Cancer J Clin, 71(1), 7-33.
13. Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 71(3), 209-249.
14. Willsmore, Z. N., Coumbe, B. G., Crescioli, S., Reci, S., Gupta, A., Harris, R. J., ... & Karagiannis, S. N. (2021). Combined anti-PD-1 and anti-CTLA-4 checkpoint blockade: Treatment of melanoma and immune mechanisms of action. European Journal of Immunology, 51(3), 544-556.
15. Xu, Y., Gao, Z., Hu, R., Wang, Y., Wang, Y., Su, Z., ... & Zhou, X. (2021). PD-L2 glycosylation promotes immune evasion and predicts anti-EGFR efficacy. Journal for Immunotherapy of Cancer, 9(10).
16. Yang, L., Ning, Q., & Tang, S. S. (2022). Recent advances and next breakthrough in immunotherapy for cancer treatment. Journal of Immunology Research, 2022.