Journal of Integrative Oncology
ISSN: 2329-6771

Chawla and Chawla, J Integr Oncol 2014, 3:2
DOI: 10.4172/2329-6771.1000124

Mini Review Open Access

The Promise of Oncoimmunology: Integrating Immunotherapy with Conventional Cancer Treatments

Cheena Chawla P[1*] **and Anil Chawla**[2]

[1]*Founder-President & CEO, World Healthal Trust, 57-A (Basement), Sant Nagar, East of Kailash, New Delhi, India*

[2]*Chairman, Chimera Gentec Pvt. Ltd., 34, Knowledge Park-1, Greater Noida, U.P, India*

[*]**Corresponding Author:** Cheena Chawla P, Founder-President & CEO, World Healthal Trust, 57-A (Basement), Sant Nagar, East of Kailash, New Delhi, India, Tel: 91-11-9818921035; E-mail: pcheena@gmail.com

Received date: October 22, 2014; **Accepted date:** November 17, 2014**; Published date:** November 24, 2014

Abstract

The goal of immunotherapy is to eliminate cancer cells through the transfer of ex vivo expanded and activated immune cells. Immune cells such as Dendritic Cells (DCs), Natural Killer (NK) cells, Cytotoxic T-cells, and Cytokine Induced Killer (CIK) cells have been investigated for active immunotherapy against cancer. Besides, the passive transfer of Monoclonal Antibodies has been an effective treatment for some cancers. However, for immunotherapy to become the mainstay of treating various cancers, it is pertinent that encouraging data on the clinical trials are available that clearly demonstrate the importance of immunotherapy in enhancing patient survival rate for different cancers and improving their quality of life. Promising trials evaluating the safety and efficacy of immunotherapy for prostate cancer, renal cell carcinoma, gastric and colorectal cancers has opened the door to research in oncoimmunology for integrating immunotherapy with conventional cancer treatments.

Keywords: Immunotherapy; Dendritic cells; Tumour antigens; Survival rate; Cytokines; Monoclonal antibodies; CAR T-cells; Micrometastases

Introduction

The standard clinical care for cancer patients begins with surgical removal of the solid tumour followed by chemotherapy and radiotherapy. These conventional treatments, however, do not always achieve complete destruction of small groups of metastatic cells or micro metastases that are too small to be detected by imaging and, therefore, pose the risk of developing into lethal metastases. In this light, immunotherapy holds great promise as this treatment can effectively 'educate' the immune cells of cancer patients to specifically recognize and destroy autologous tumour cells. Moving to the forefront of cancer therapy, immunotherapy offers not only effective destruction of micro metastases, but also restores the physical function of cells damaged by conventional therapies.

Cancer cells differ from healthy ones due to the presence of faulty proteins that are formed as result of genetic alterations/mutations in tumour cells, and these defective proteins are termed as Tumour Associated Antigens (TAA). Stimulating the immune system to recognize the micrometastases carrying the TAA, thus destroying the autologous tumour cells is the hallmark of immunotherapy. The ideal tumour antigens are those that are expressed in a significant proportion of patients affected by a particular cancer type and are not expressed in normal tissues, besides being vital to the growth and survival of cancer cells.

Cancer immuonotherapy comprises a variety of treatment approaches such as administration of cytokines, anti-tumour monoclonal antibodies and cancer vaccines. With recent advances in molecular biology, the application of cytokines has emerged to be a promising integrative strategy for cancer treatment. Cytokine immunotherapy has many advantages compared with traditional therapeutic methods such as chemotherapy and radiotherapy. It not only has fewer side effects, but also can avoid tumours developing resistance to treatment and specific immune tolerance to tumour antigens. Monoclonal antibodies have actually had a major impact on clinical oncology as some popular cancer drugs like trastuzumab and rituximab are monoclonal antibodies. Similarly, the clinical value of therapeutic cancer vaccines has been realized with several successes of these vaccines.

Cancer Immunotherapy attempts to harness the power and specificity of the immune system to treat tumours. It is a safe, effective, painless and highly personalized treatment for cancer. Instead of killing tumour cells with chemotherapy and radiation therapy, which leads to reduced immunity, immunotherapy uses the body's natural immune system or defence machinery to fight cancer. Also called biologic therapy or biotherapy, it effectively cleans up tiny tumours and metastatic cancer cells, and prevents the recurrence of malignant tumours without harming healthy cells. Combination of immunotherapy with chemotherapy and radiotherapy can effectively combat cancer, reducing the risk of recurrence of cancer and improving the patient's quality of life.

Basically, Dendritic cells (DCs) are professional antigen-presenting cells (APCs) that play a central role in the immune system [1,2]. These cells initiate an antigen-specific cytotoxic T lymphocyte response, whereby tumour antigens are recognized resulting in killing of those tumour cells [3]. Cytokine induced killer (CIK) cells are a unique population of cytotoxic T lymphocytes (CTL) that are generated by incubation of peripheral blood lymphocytes with anti-CD3 monoclonal antibody, IL-2, IL-1 and interferon gamma (IFN-γ). CIK cells show strong anti-tumour cytotoxicity under both in vitro and in vivo conditions. These cells have higher proliferative and cytolytic activities in comparison with the lymphokine activated killer

(LAK) cells that are essentially activated natural killer (NK) cells. CIK cells have shown promising anti-tumour effects against various cancers, such as hepatoma, leukemia, liver, renal, and gastric cancer, in preclinical and clinical studies.

The three basic steps of immunotherapy are: a) Blood is drawn and peripheral blood mononuclear cells (PBMCs) are collected from the cancer patient; b) Special antigen presenting cells called Dendritic cells (DC) and Cytokine Induced Killer (CIK) cells are isolated, cultured and pulsed in vitro with tumour-lysate of the patient, within a GMP certified laboratory; c) Cancer-sensitive cells are replicated to normally counts >5 billion cells and are injected back to the same patient through intravenous infusion. These cells hunt and kill cancer cells present anywhere in the body [4]. There are no side effects of this treatment, although some patients may experience fever and chills that subside within 2-8 hours.

Emphasis on Clinical Studies

In order to extend the benefit of immunotherapy to cancer patients, it is pertinent to conduct clinical trials on specific cancers to assess and evaluate the efficacy of this therapy over the conventional lines of treatment. Several research groups in USA, China, Korea, Australia, Denmark and the Netherland are conducting clinical trials to evaluate the efficacy of immunotherapies developed by them for different cancers. Some such trials have shown the effectiveness of immunotherapy for renal cell carcinoma, prostate cancer, colorectal cancer, gall bladder cancer, lymphoma and melanoma.

In a study by Higano et al., the safety and efficacy of active cellular immunotherapy with Sipuleucel-T was evaluated in advanced hormone-resistant prostate cancer by randomized, double-blind, placebo-controlled, Phase III trials [5,6]. The patients randomized to Sipuleucel-T demonstrated a 33% reduction in the risk of death and thus demonstrated a survival benefit compared with those treated with placebo. Sipuleucel-T is a patient-specific vaccine produced by transiently incubating the patient's own peripheral blood mononuclear cells with a fusion protein consisting of prostatic acid phosphatase (prostate cancer-specific antigen) linked to the dendritic cell growth and differentiation factor called 'granulocyte macrophage colony-stimulating factor (GM-CSF). The US Food & Drug Administration approved the use of first therapeutic cancer vaccine 'Provenge' (Sipuleucel-T) in 2010 because of its unique survival benefit to prostate cancer patients.

Similarly, Kantoff et al. have demonstrated the survival benefit of a Poxviral-based PSA-targeted immunotherapy in metastatic castration-resistant prostate cancer [7,8]. For this, PROSTVAC-VF treatment comprising two recombinant viral vectors, each encoding transgenes for PSA and three immune costimulatory molecules (B7.1, ICAM-1, and LFA-3) was evaluated for safety and for prolongation of progression-free survival (PFS) and overall survival (OS) in a randomized, controlled, and blinded Phase II study. Not only did the PROSTVAC-VF immunotherapy was well tolerated but it was associated with a 44% reduction in the death rate.

Renal cell carcinoma (RCC) comprises approximately 2% of all malignancies and the localized disease is treated by surgery followed by standard management by surveillance [9]. As this disease is highly resistant to chemotherapy with response rates of <10%, with a short duration of response, immunotherapy using interleukin-2 (IL-2) or interferon-alpha (IFN-α) has become an accepted standard treatment for patients with RCC after radical nephrectomy. It is an excellent model to explore immunotherapeutic approaches because its pathophysiological characteristics indicate a strong immune response to tumour antigens.

A study by Zhan Hai-lun et al. has shown the feasibility, safety and efficacy of immunotherapy using autologous tumour lysate (TL)-pulsed dendritic cells (DCs) and cytokine-induced killer (CIK) cells in patients with localized or locally advanced RCC after surgical resection [10,11]. An increase of the CD4+/CD8+ ratio and a decrease of CD4+CD25 high cells were observed after TL-pulsed DC-CIK cells or IFN-α immunotherapy. All patients tolerated the TL-pulsed DC-CIK cells immunotherapy very well, and side effects in the DC-CIK group were less than in the IFN-α group. The metastasis and recurrence rates were significantly decreased after TL-pulsed DC-CIK cells or IFN-α immunotherapy compared with the control group ($P<0.01$).

Gastric and colorectal cancers (GC and CRC)—the major malignant diseases of alimentary tract)—also have poor prognosis and are resistant to chemo- and/or radiotherapy. The prophylactic effects of dendritic cell (DC) vaccination have been evaluated by Daiqing Gao et al. on disease progression and clinical benefits in a group of 54 GC and CRC patients treated with DC immunotherapy combined with cytokine-induced killer (CIK) cells after surgery with or without chemo-radiotherapy. DCs were prepared from the mononuclear cells isolated from patients using IL-2/GM-CSF and loaded with tumour antigens [12]. CIK cells were prepared by incubating peripheral blood lymphocytes with IL-2, IFN-γ, and CD3 antibodies [13]. DC/CIK therapy reduced the risk of post-operative disease progression ($p<0.01$).

Clinical studies have also been conducted to assess the patient response to a yet another approach to immunotherapy that involves the engineering of patient's own immune cells to recognize and attack their tumours. Called Adoptive Cell Transfer (ACT), this therapy has shown promising results in patients with advanced acute lymphoblastic leukemia and those with lymphoma. Basically, the patient's T-cells are genetically engineered to produce special receptors on their surface called Chimeric Antigen Receptors (CAR) that are proteins which recognize specific tumour antigens. To deliver the genetic material needed to produce the T-cell receptors, viral vectors are used that are disabled to cause disease but have the capacity to integrate into cells' DNA. These engineered CAR T-cells are grown in a laboratory under sterile conditions and are infused back into the patient. The unique structure of CAR T-cells endows them with tumour specific cytotoxicity and resistance to immunosuppressive microenvironment in cancers [14].

Brian G Till et al. have shown the safety, feasibility and potential anti-tumour activity of adoptive T-cell therapy in a proof-of-concept clinical trial that involved patients with relapsed or refractory indolent B-cell lymphoma or mantle cell lymphoma. These patients were treated with autologous T-cells genetically modified by electroporation with a vector plasmid encoding a CD-20-specific chimeric T-cell receptor and neomycin resistance gene [15].

It is well understood that the immune response is responsible for controlling nascent cancer through immunosurveillance. However, if tumours escape this control, they can develop into clinical cancer. Although surgery and chemo- or radiotherapy have improved survival rates significantly, treating cancer by enhancing the function of T cells —the key immune cells— can improve tumour targeting [16-18]. The results of some clinical trials using these cells are quite promising, although the challenges involved in generating effective anti-tumour

responses are numerous and remain to be tackled for different cancers [19,20].

Discussion

The excitement for immunotherapy is steadily growing for this unique therapy harnesses the power of a patient's immune system to combat cancer. There is a complex interplay between cancer cells and the host immune response. Developments in cancer immunotherapies are based on exploring the use of cytokine induced killer cells, tumour-specific monoclonal antibodies and cancer vaccines. The first FDA-approved therapeutic cancer vaccine Provenge (Sipuleucel-T) today provides significant benefits to patients with castrate-resistant prostate cancer. With several clinical studies been done, it is all too clear that immunotherapy is safe, feasible and has the remarkable potential to promote clinically significant tumour regressions. The clinical trials now underway are being designed to test new hypotheses based on the lessons learned from the earlier, proof-of-principle studies.

Several immunological deficiencies have been linked with enhanced tumour development. Persistence inflammation associated with chronic infections may also encourage new tumour formation, as some cancers namely, colorectal, hepatocellular, cervical and gastric carcinomas are strongly associated with underlying chronic inflammatory responses [21]. Interestingly, vaccines that aim to control inflammation induced by chronic infections happen to serve as effective tumour prevention measures [22]. For example, hepatitis B vaccination has successfully reduced the incidence of liver cancer [23,24]. Similarly vaccines against oncogenic human papilloma virus (HPV) have achieved success in preventing cervical cancer [25,26].

Today rapid progress is being made in the field of immunotherapy, employing a well-defined and data-driven approach, for designing the next generation of optimized therapies coupled with standardized immune monitoring assessments.

Conclusion

The immune system can be sufficiently induced to respond against cancer as evident from several immunotherapeutic approaches recognized by the scientific community as potent tools for combating certain cancers. While the potential of oncoimmunology is being understood widely, new research and clinical studies for a multitude of therapeutic applications based on immunotherapy are underway. With greater understanding of the factors that influence tumour microenvironment, effective personalized strategies for cancer management are poised to be developed in future.

References

1. Banchereau J, Steinman RM (1998) Dendritic cells and the control of immunity. Nature 392: 245-252.
2. Romani N, Gruner S, Brang D, Kämpgen E, Lenz A, et al. (1994) Proliferating dendritic cell progenitors in human blood. J Exp Med 180: 83-93.
3. Parmiani G, Pilla L, Castelli C, Rivoltini L (2003) Vaccination of patients with solid tumours. Ann Oncol 14: 817-824.
4. den Brok MH, Nierkens S, Figdor CG, Ruers TJ, Adema GJ (2005) Dendritic cells: tools and targets for antitumor vaccination. Expert Rev Vaccines 4: 699-710.
5. Higano CS, Schellhammer PF, Small EJ, Burch PA, Nemunaitis J, et al. (2009) Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. Cancer 115: 3670–3679.
6. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, et al. (2010) Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 363: 411–422.
7. Higano CS, Small E, Schellhammer P, Yasothan U, Gubernick S, et al. (2010) Sipuleucel-T. Nat Rev Drug Discov 9: 513-514.
8. Wang K, Gao X, Pang J, Liu X, Cai Y, et al. Dendritic cells transduced with a PSMA-encoding adenovirus and cocultured with autologous cytokine-induced lymphocytes induce a specific and strong immune response against prostate cancer cells. Urol Oncol 2009; 27: 26-32.
9. Thurnher M, Radmayr C, Ramoner R, Ebner S, Bock G, et al. (1996) Human renal-cell carcinoma tissue contains dendritic cells. Int J Cancer 68: 1-7.
10. Zhan HL, Gao X, Qiu JG, Cai YB, Situ J, et al. (2006) Effects of dendritic cells co-cultured with CIK cells on renal carcinoma cells. Chin J Pathophysiol 22: 1993-1998.
11. Zhan Hai-lun GAO Xin, PU Xiao-yong, LI Wei, LI Zhi-jian, Zhou Xiang-fu, et al.(2012) A randomized controlled trial of postoperative tumour lysate-pulsed dendritic cells and cytokine-induced killer cells immunotherapy in patients with localized and locally advanced renal cell carcinoma. Chinese Medical Journal 125:3771-3777.
12. Frankenberger B, Schendel DJ (2012) Third generation dendritic cell vaccines for tumor immunotherapy. Eur J Cell Biol 91: 53-58.
13. Steinman RM, Banchereau J (2007) Taking dendritic cells into medicine. Nature 449: 419-426.
14. Han EQ, Li XL, Wang CR, Li TF, Han SY (2013) Chimeric antigen receptor-engineered T cells for cancer immunotherapy: progress and challenges. J Hematol Oncol 6: 47.
15. Mesiano G, Todorovic M, Gammaitoni L, Leuci V, Giraudo Diego L, et al. (2012) Cytokine-induced killer (CIK) cells as feasible and effective adoptive immunotherapy for the treatment of solid tumors. Expert Opin Biol Ther 12: 673-684.
16. Hontscha C, Borck Y, Zhou H, Messmer D, Schmidt-Wolf IG (2011) Clinical trials on CIK cells: first report of the international registry on CIK cells (IRCC). J Cancer Res Clin Oncol 137: 305-310.
17. Till BG, Jensen MC, Wang J, Chen EY, Wood BL, et al. (2008) Adoptive immunotherapy for indolent non-Hodgkin lymphoma and mantle cell lymphoma using genetically modified autologous CD20-specific T cells. Blood 112: 2261-2271.
18. Moiseyenko V, Imyanitov E, Danilova A, Danilov A, Baldueva I (2007) Cell technologies in immunotherapy of cancer. Adv Exp Med Biol 601: 387-393.
19. Schlom J (2012) Recent advances in therapeutic cancer vaccines. Cancer Biother Radiopharm 27: 2-5.
20. Marr LA, Gilham DE, Campbell JDM, Fraser AR (2012) Immunology in clinic review series; focus on cancer: double trouble for tumours: bifunctional redirected T cells as effective cancer immunotherapies. Clinical and Experimental Immunology, 67:216-225.
21. Chow MT, Moller A, Smyth MJ (2012) Inflammation and immune surveillance in cancer. Semin Cancer Biol 22: 23-32.
22. Aggarwal BB, Shishodia S, Sandur SK, Pandey MK, Sethi G (2006) Inflammation and cancer: how hot is the link? Biochem Pharmacol 72: 1605-1621.
23. Asia-Pacific Working Party on Prevention of Hepatocellular Carcinoma (2010) Prevention of hepatocellular carcinoma in the Asia-Pacific region: consensus statements. J Gastroenterol Hepatol 25: 657-663.
24. Chang MH (2011) Hepatitis B virus and cancer prevention. Recent Results Cancer Res 188: 75-84.
25. Kane MA (2010) Global implementation of human papilloma virus vaccine: lessons from hepatitis B vaccine. Gynecologic Oncology 117:532-535.
26. Roden R, Monie A, Wu TC (2006) The impact of preventive HPV vaccination. Discov Med 6: 175-181.