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Advanced Combinatorial Radioimmunogenetic Therapy for Cancer

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Abstract

Cancer is one of the important challenges in the world of biological sciences today. The disease is a major threat next to the climate change. The current therapeutic technologies like chemotherapy, radiotherapy not only destroy the normal cells and even are outdated and ineffective. More selective, targeted methods and recent advancement in delivery system is the need of the hour. A more rationale targeted methods collectively called as radioimmunogenetic therapy which is a revolutionary approach towards complete eradication of the malignancies.

Keywords: Cancer; Radiation; Immunogenic; Gene therapy; Dendritic cells; CRISPR; SmaRT; Immunotherapy

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Introduction

Cancer, a genetic disease is a silent tsunami and is even more threatening than the terrorist. Cancer is estimated to cause one in seven deaths worldwide according to American Cancer Society in 2016. The disease is characterised by the unregulated cell growth, invasion and the spread of cells from site primary site (origin) to the other sites in the body (Lauren Pecorino). Trademarks of cancer cells are distinguishable from the normal cells. Growth signal autonomy, evasion of growth inhibitory signals, evasion of apoptosis, unlimited replicative potential, angiogenesis, invasions and the metastasis are some major hallmarks of cancer cells.

The intention of cancer therapy is to root out cancerous tissues without disturbing normal healthy cells and without harmful side effects. Traditional approach like chemotherapy and radiotherapy destroy the normal healthy cells. Cancer cells have the ability to hide; is termed as Rogue cancer cells and survive treatment after the rest of the tumour is destroyed. Professor Adam Mead of Oxford University's Radcliff Department of medicine said, "It is increasingly recognised that tumour contains variety of different cell types, including the so-called cancer stem cells that drive the growth and relapse of patient's cancer." these cells are very rare and extremely difficult to find after treatment as they become hidden within the normal tissues. Chemotherapy is treatment process where chemo rays are used to treat patient. It is normally provided to cancer affected patient. The rays really strong and sometimes patient which cannot sustain the pressure are immunologically down and weak. Cytotoxic medicine is the medicine they provide when talk about chemotherapy. Chemotherapy can be performed along with other therapies like radiotherapy in order to effectively shut down the cancer cells. Radiation helps to destroy the other remaining cells even after the treatment of chemotherapy. Chemotherapy affects the normal bio physiological behaviour of the patient. The eradication of the risk of emerging o cancer cells back is the prejudice of chemotherapy.

Combinatorial therapy, a treatment that combines two or more therapeutic agents, is a comer stone of cancer therapy by Mohitkari et al. Combine of gene and radiation therapy is modernistic approach in the munitions against cancer. Combinatorial radio/gene therapy led the foundation of new technologies towards cancer treatment. The combine radio/gene therapy has now entered the clinical phase in prostate cancer [1,2]. Our novel approach is to add gene therapy to the standard of care therapy (radio therapy). The combinatorial effect of this therapy carries a promising approach in oncology.

Literature Review

Background of the field

Gene therapy is the use of genes (cDNA) expressing a protein

in the cell to treat the disease. Compensating the faulty genes with normal healthy gene and establishing the lost gene function is the substance of gene therapy. It is universally accepted that cancer has genetic origin. With the understanding of molecular basis of cancer, the advent of new approach of treatment evolves with the use of gene transfer method. Cancer may be due to DNA damage, mutation, carcinogenic agents, radiations, infectious pathogens. These mutated genes are good target for gene therapy. The radioimmunogenetic therapy is one of the most advance therapeutic technologies.

There are different approaches for treatment in oncolytic studies. Unlike chemo and radiotherapy, methods like MDR gene approach, genomic approach, suicide gene technology, p53 tumour suppressor gene approach, immunologic approach like adoptive immune therapy, vector based therapy etc are on the carts.

Recombinant antibodies based therapy shows tremendous advanced in gene therapy for cancer but combinatorial therapy is more selective and targeted. The combine radio/gene therapy, Radioimmunogenetic and immunogenetic therapy are some phenomenal approach.

Immunotherapy or immune targeted gene therapy

Our immune system is the home for most anticancer immune regulatory cells. Both humoral and cellular mediated shows immune response towards tumour cells. Antibody mediated (recombinant antibodies) are effective anti tumour reagent. They show potent response when the conformational tumour antigen or antigenic fragments are expressed at the cell surface of the tumour. Recombinant antibodies or monoclonal antibodies are widely used in immunotherapy. Localisation of tumour after tagging with markers like radioisotope or fluorescent probe is a prevalent technology. After coupling with toxic agents like toxin or radioisotope attempting to deliver a 'lethal hit' to bombard with targeted tumour cells. Humanised antibodies (monoclonal antibody) like herceptin specific for Her2/neu on breast cancer cell and rituximal coded for cd20 on Hodgkin's lymphoma were approved clinically [3].

CD4+ and CD8+ T lymphocytes response to tumour antigen presented with MHC

MHC are antigen presenting cells. T cells recognised target cells via TcR of antigen. TcR is associated with CD3 complex. TcR shows high specificity for antigen. TcR/CD3 complex counteracts with antigen bounded with MHC encoded molecule. Activation of both CD4+ and CD8+ T lymphocyte shows effective antitumour immunity. Components of CD4+ T cells Th1 or Th2 secrete cytokines IL2 and IFN gamma (Th1); Th2 secrete IL4, IL10, IL13. Th1 and Th2 codes cytokine help to CD8+ T cells and B lymphocytes respectively. Immunologists believe that CD4+ Th1 lymphocytes facilitate CD8+ T cell mediated tumour immunity (**Figure 1**).

Dendritic cell based immunotherapy

Dendritic cell is integral part of lymphohaemopoetic system. DCs are professional APC and induce immune response. They are major effectors of innate immunity towards tumour cells. Phagocytes, NK cells, complementation, interferon characterised the ability to recognise pathogens and also have the ability to send danger signal [4,5] to the cells of adaptive immune system. Adaptive immunity is thought to have diverse immunoglobulin genes and immunological memory. These danger signal triggers the activation of DCs migration and maturation inducing immunological response towards pathogen elimination. Inducing effective antitumor immunity is an elusive goal and should be inducing autoimmunity. Tumour related autoimmune exist rarely and is reported in case of paraneoplastic neurologic disorder. Dendritic cell plays crucial role in immunological approach therapy either in as vector based or targeted approach. An 'intelligent missile' generic cancer vaccine equipped within tumour antigen, chaperones, DC activation and with specific ligand will be promising.

Ribozyme mediated knock out of cancer cell

Ribozyme are catalytic RNA and having motifs such as hammerhaead, hairpin, axhead, group1 intron and RNAse P. Ribozyme cleaved the target in trans and haults the oncogenic gene expression of H ras, p210 bcr-abl, c-fos, viral oncogene etc. Hammerhead ribozyme knock out the c- fos oncogene expression.

Particle mediated gene transfer foster immunotherapy

Immunotherapy is supported by PMGT. PMGT codes for intracellular delivery of biologically active molecule. A gold coated with DNA containing the gene of interest accelerating by the motive force that helps to penetrate the target tumour cell. Reduce restriction on the size of DNA vector is one advantage of PMGT. Genomic DNA, plasmid DNA, reporter gene cloned in lambda phage can all be effectively delivered to mammalian cells by PMGT [6-8]. Based on the hypothesis that selective activation of immunologic recognition mechanism, downstream from the immune recognition event might provide preferential destruction of melanoma cells in vivo. Identifying the selective biomarkers of successful immune response following PMGT will be essential for more approach towards vaccine development.

Radiation therapy

Radiation treatment is considered as standard therapy in oncology. From technology to radiobiology and radio physics,

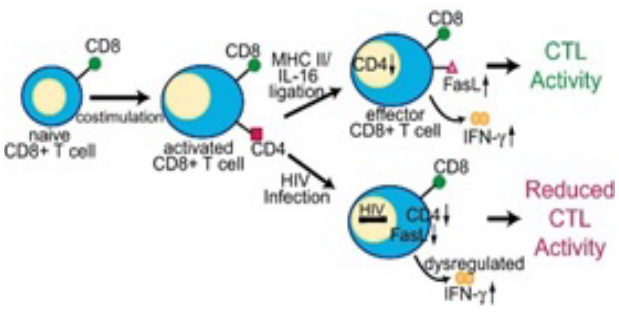

Figure 1 CD4+ and CD8+ T lymphocytes response to tumour antigen presented with MHC.

significant advancement in the field of oncology erupts. Radiation dose play crucial role in controlling the tumour and probability damage of normal cell. Radio therapeutic technology improves the therapeutic index of global cancer treatment. Normal tissue damage is a concern in radiation treatment. High dose of radiation induces treatment related toxicity [9,10]. High radiation may cause rectal damage. Rectal shield is usually employed for tolerance to rectal damage. Despite enormous contribution in global cancer disparities with the advent of radiation oncology, always shows irregular outcomes in terms of proximity of normal tissue damage.

Our approach is the rise of the combinatorial therapy where combination of radio/chemo with the immune system ability to knock out the malignancies called as radio immunotherapy with the machinery of gene transfer method. Combine impact of radiation and immune cells with tools of gene therapy may show greater efficiencies in global cancer dispute.

Combinatorial Therapy

Despite huge progress in treating malignancies, new technology and methodology need to be developed. Our immunity's suitable modulation will provide effective therapeutic alternative during critical cancer progressions. Both viral and non-viral vector gene transfer method were used to deliver the gene product such as cytokines, xenogenic tumour associated antigen, monoclonal antibodies, specific ligand, co stimulatory molecule, CRISPR cas9 and proapoptotic regulatory factor to the target cell after radiation treatment. Radiation may halt the progression of tumour growth and with the implementation of immune trojans fight for the throne. Successful combination of radio/chemo therapy with drug at suitable dose and active participation of immune cells will be a novel approach reversing the tumour cell resistance to chemo/radio therapy. Immune cells like cytokines with co stimulatory effect hunt down the hidden tumour cell which are undetected. Various sensitizing agent in combination with immune drugs target the cancer cell effectively. Radiation alone cannot kill the tumour cell because tumours are resistant to ionisation. Tumour growth of the mice treated with radiation plus CpG+ ova-liposome was greatly inhibited and approximately 60% of mice treated were completely cure by Chamato et al. [11]. Moreover, the combine therapy with radiation and CpG+ OVA liposome allowing the induction of OVA tetramer+ LCC-OVA specific cytotoxic T lymphocyte (CTL) in tumour inducing mice eradicate 80% to 90% of the intractable carcinoma. In another case reported by Meredith et.al. that significantly effective when human recombinant alpha interferon INF of unit 3 ×10 (6) U on alternate days beginning 5 days before RIT administered with taxol having radio sensitizing effect and antitumor activity not only increase the expression of tumour associated antigen (TAG-72) but also shows expected reversible hematologic toxicity. Interferon increased the effective whole-body radiation dose [12].

SNAG and Clinical Hindrance of Radio Immunogenetic Therapy

Despite hallmark in the evolution of cancer therapeutics, several complications are counteracted by the patients. Administering a genetically modified virus into human carries numerous therapeutic concerns including toxic viremia, viral effects on the body organ such as liver, kidney etc. Bacteraemia and viremia were general clinical issues. Addition of radiation therapy worsens such complications. Hepatic and renal toxicity symptoms are explored by the cancer patients upon treatment. Alcohol intake and flutamide use contributed the rise in ALT [13]. Toxicity is observed after radiation therapy process. Adenovirus mediated HSV-TK pro drug gene therapy is associated with the abnormality in liver function and cytopenia [14]. Hemato and hepato abnormalities were related to the association of pro drug and can be resolved spontaneously. GU and GI are common radiation related side effects [15-21].

Discussion

Future directions

Novel live savings therapeutic approach took time to establish as a well deserve routine treatment. Gene therapy for cancer is improving slowly. This technology has already shown promising impact in the world of oncology [22-32]. New powerful technology like TALENS, CRISPR/cas9 system paves the way in successful delivery to the targeted tumour cell. SmaRT technology still be put to test in clinical trials. Combinatorial therapy radio immunotherapy, monoclonal antibodies based therapy, prodrug activation strategies, E1A cancer gene therapy, VEGF- targeted antiangiogenic gene therapy, oncolytic viral replication selective therapy, suicide gene, ribozyme, tumour suppressor mediated gene therapy are still prospering in the field of oncology. Liposome driven targeted gene delivery shows 90% efficiency in successfully targeting the cancer cells [33-37]. Refinement of various clinical complications regarding radio/immune/gene therapy approach towards cancer is a major concern in future. Achieving the best radio sensitization, maximal cytotoxicity and exploring the combination of radiation with different genetic and immunogenic approach using stylist technology like monoclonal antibodies, CRISPR, TALENS, SmaRT will be highly appreciated [38-41].

Conclusion

Results of clinical cancer gene therapies are currently very preliminary and clinical trials have been initiated. The attempt to stimulate the immune system to eliminate cancer cell is significantly a new window to science of oncology. Gene therapy would be viable options for patients with cancer in future. Gene therapy is one of the promising tools and having its different version of strategies employed collectively with the advanced gene transfer tool, stylist new editing tools like TALENS, CRISPR and SmaRT will foster the healthier environment of modern medicine. Combinatorial therapy shows more effective than the traditional therapy like chemotherapy. To make gene therapy or combinatorial therapy a viable option for cancer some barrier needs to overcome so that it could become a healthier alternative of traditional therapy and new promising revolution in the science of oncology will evolve.

References

1 Mulherkar R (2001) Gene therapy for cancer. Curr Sci 81: 5.

2 Maria TV, Chaki V, Laura K, Aguilar (2000) Brian case study of combine gene and radiation therapy as an approach in the treatment of cancer. BINS 2: 1.

3 Weiner L (1979) Monoclonal Ab therapy for cancer. Semin Oncol 26: 43-51.

4 Shwin M, Lu L, Kalinski P, Akers S, Lotze M (1999) Th1/Th2 balance in cancer, transplantation and pregnancy. Springer Semin Immunopathol 21: 399-359.

5 Matzinger P (1998) An innate sense of danger. Semin Immunol 10: 399-415.

6 Rakhmilevich A, Yang N (2000) *In vivo* particle mediated gene transfer for cancer therapy in methods in molecular medicine. In: Gene therapy: Methods and protocol, Walther W, Stein U (eds), Humana press, Totowa. New Jersey, USA.

7 Weiner L (1999) Antibody therapy of Cancer. Semin Oncol 26: 43-51.

8 Welts SA (1997) Antibody based immunological therapies. Curr Opin Immunol 9: 717-722.

9 Lindsay N, Su C (2016) Gene therapy: A toolkit for targeting cancer. J Young Invest 30: 4.

10 Wilkinson R, Wiedenheft B (2014) A CRISPR method for genome engineering. F1000prime Reports 6: 3.

11 Chamoto K, Takeshima T, Wakita D, Okhuri T, Ashino S, et al. (2009) Combination immunotherapy with radiation and CpG based tumour vaccination for eradication of radio and immune resistant lung carcinoma cells. Cancer Sci 100: 934-949.

12 Meredith RF, Alvarez RD, Patridge EE, Khazadi MB, Lin CY, et al. (2001) Intraperitoneal radioimmunotherapy of ovarian cancer: A phase 1 study Cancer. Biother Radiopharm 1: 305-315.

13 Herman JR, Alder HL, Cordova AE, Martinez RA, Woo S, et al. (1999) Dr. Peter Scardino's Prostate Book: The complete guide to overcoming prostate cancer, prostatitis and BPH. Hum Gene Ther 10: 1239-1249.

14 Hasenburg A, Tong XW, Martinez RA, Hoffman MC, Kieback CC, et al. (2000) Thymidine kinase gene therapy with concomitant topotecan chemotherapy for recurrent ovarian cancer. Cancer Gene Ther 7: 839-844.

15 Teh BS, Woo SY, Butter EB (1999) Intensity modulated radiation therapy (IMRT): A new frontier in radiation oncology. Oncologist 4: 433-442.

16 Mov LRN, Arpe AH, Uestone JA, Mov Kyr MB (1999) Host B7-1 and B7-2 costimulatory molecules contribute to the eradication of B7-1-transfected P815 tumor cells via a CD8 +s T cell-dependent mechanism. J Immunol 162: 4817-4823.

17 Nsley PS, Dbetter JA (1993) The role of the CD28 receptor during T cell responses to antigen. Annu Rev Immunol 11: 191-212.

18 Mitsuma S, Shizawa YH, Ito K, Riyama MH, Ayashi WM, et al. (1994) Adoptive immunotherapy mediated by anti-TCR/IL-2-activated tumour-draining lymph node cells. Immunol 3: 45-51.

19 Miyao H, Chou T, Ito K, Riyama MH, Mitsuma S, et al. (1994) Treatment of advanced primary lung cancer associated with malignant pleural effusion by the combination of immunotherapy and chemotherapy. Oncology 51: 87-94.

20 Ohno K, Shizawa YH, Ukada TH, Takeda T, Hi YY, et al. (1996) Adoptive immunotherapy with tumor-specific T lymphocytes generated from cytokine gene- -modified tumor-primed lymph node cells. J Immunol 156: 3875-3881.

21 Rgador PA, Tzehoval E, Katz A, Vadai E, Revel M, et al. (1992) Interleukin 6 gene transfection into Lewis lung carcinoma tumor cells suppresses the malignant phenotype and confers immunotherapeutic competence against parental metastatic cells. Cancer Res 52: 3679-3686.

22 Ashshi AM, El-Shemi AG, Dmitriev IP, Kashentseva EA, Curiel DT, et al. Combinatorial strategies based on CRAd-IL24 and CRAd- ING4 virotherapy with anti-angiogenesis treatment for ovarian cancer. J Ovarian Res 9: 38.

23 Rashid MAMB, Toh TB, Silva A, Nurrul Abdullah L, Ho CM, et al. (2014) Identification and optimization of combinatorial glucose metabolism inhibitors in hepatocellular carcinomas. J Lab Autom 3: 423-437.

24 Ku SH, Kim K, Choi K, Kim SH, Kwon IC (2014) Tumot-targeting multifunctional nanoparticles for siRNA delivery: Recent advances in cancer therapy. Adv Health Meter 3: 1182-1193.

25 Prieto J, Melero I, Sangro B (2015) Immunological landscape and immunotherapy of hepatocellular carcinoma. Nat Rev Gastroenterology Hepatol 12: 681-700.

26 Jaeger S, Igea A, Arroyo R, Alcalde V, Canovas B, et al. 2017) Quantification of pathway cross-talk reveals synergistic drug combinations for breast cancer. Cancer Res 77: 459-469.

27 Li H, Zeng J, Shen K (2014) PI3K/AKT/Mtor signalling pathway as a therapeutic target for ovarian cancer. Arch Gynecol Obstet 290: 1067-1078.

28 Hu-Lieskovan S, Robert L, Homet Moreno B, Ribas A (2014) Combining targeted therapy with immunotherapy in BRAF-mutant melanoma: promise and challenges. J Clin Oncol 32: 2248-2254.

29 Bournet B, Buscail C, Muscari F (2016) Targeting KRAS for diagnosis, prognosis and treatment of pancreatic cancer: Hopes and realities. Eur J Cancer 54: 75-83.

30 Zsiros E, Tanyi J, Balint K, Kandalaft LE (2014) Immunotherapy for ovarian cancer: Recent advances and perspectives. Curr Opin Oncol 26: 429-500.

31 Ho V, Lim TS, Lee J, Steinberg J, Szmyd R, et al. (2015) TLR3 agonist and sorafenib: Combinatorial therapy promotes immune activation and controls hepatocellular carcinoma progression. Oncotarget 6: 27252-2766.

32 McMenamin MM (2011) Translational benefits of gene therapy to date. Clinical Oncol Cancer Res 8: 10-15.

33 Mitsuyasu R (2013) Curing HIV: lessons from cancer therapy. Curr Opin HIV AIDS 8: 224.

34 Bordignon C, Notarangelo LD, Nobili N, Ferrari G, Casorati G, et al. (1995) Gene therapy in peripheral blood lymphocytes and bone marrow for ADA-immunodeficient patients. Science 270: 470-475.

35 Cartier N, Hacein-Bey-Abina S, Bartholomae CC, Veres G, Schmidt M, et al. (2009) Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy. Science 326: 818-823.

36 Freytag SO, Rogulski KR, Paielli DL, Gilbert JD, Kim JH, et al. (1998) A novel three-pronged approach to kill cancer cells selectively: concomitant viral, double suicide gene, and radiotherapy. Hum Gene Ther 9: 1323-1333.

37 Ferrua F, Brigida I, Aiuti A (2010) Update on gene therapy for adenosine deaminase-deficient severe combined immunodeficiency. Curr Opin Allergy Clin Immunol 10: 551-556.

38 El-Aneed A (2004) Current strategies in cancer gene therapy. Eur J Pharmacol 498: 1-8.

39 Barker SE, Broderick CA, Robbie SJ, Duran Y, Natkunarajah M, et al. (2009) Sub retinal delivery of adeno-associated virus serotype 2 results in minimal immune responses that allow repeat vector administration in immunocompetent mice. J Gene Med 11: 486-497.

40 Aiuti A (2002) Advances in gene therapy for ADA-deficient SCID. Curr Opin Mol Ther 4: 515-522.

41 Somia N, Verma IM (2000) Gene therapy: Trials and tribulations. Nat Rev Genet 1: 91-99.