



## IMMUNOTHERAPY OF CANCER

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### ABSTRACT

**Aim:** The aim of the review is to give information about the available immunotherapeutic approaches for the treatment of cancer.

**Objective:** This review aims to brief about the mechanisms and efficiency of various types of immunotherapies that manipulates immune response to treat tumours.

**Background:** In primary cancer treatment strategies like chemotherapy and radiation therapy, relapse of tumour is a significant problem. So, alternative therapies that harnesses the immune system are now the current trend to eliminate the tumour cells and may prove more efficient in the near future.

**Reason:** Since our understanding of the immune system has increased substantially, there are a variety of pathways that manipulate the immune system in different manners to promote anti-tumour responses. This review elaborates on the different immunotherapies and their mechanisms.

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## INTRODUCTION

Neoplasms have antigens against which the host immune system is capable of reacting. Applications of immunisation to treat tumours have come into existence after the definite presence of tumour specific antigen in carcinoma was put forward by Phren and Main in 1957 [1]. However, the concept of tumour immunology came to light when gross in 1943 was able to immunise a mice against sarcoma induced by methyl cholanthrene [2]. It is clinically observed that patients with depressed immune system are more susceptible to cancer [3]. There are several in vitro techniques that identify these antigens which includes immunofluorescence, colony inhibition, complement fixation, immunodiffusion, lymphocyte mediated cytotoxicity, lymphocyte blastogenesis and various radioimmunoassays, indicating that the host responds immunologically to tumour [4]. This implies that cancer cells can be destroyed immunologically.

G. A Currie in 1972 classified potential methods of immunotherapy as passive, adoptive and active each of which are further classified into specific and non specific forms of immunotherapy. The classification was given as follows:

- Active specific immunotherapy :Tumour cells, extracts or chemically-modified tumour antigens, Foetal antigens

- Active non specific immunotherapy :Non-specific stimulants of the immune response BCG,C.parvum,etc.
- Adoptive specific immunotherapy: Xenogeneic or allogeneic sensitized lymphoid cells or extracts
- Adoptive non specific immunotherapy:Normal lymphoid cells allogeneic or xenogeneic.Anti-tumour effect of GVH disease
- Passive specific immunotherapy: Xenogeneic or allogeneic anti-tumour antisera,
- Passive non specific immunotherapy:Non-specific serum factors,Properdin,etc.
- This review gives information on non specific , non specific and adoptive immunotherapy of cancer.

### Non Specific Immunotherapy

Active non specific immunotherapy uses various agents that enhance antibody formation and nonspecifically trigger cellular immunity. There are many non specific immune stimulators that have been identified but the most evaluated are: corynebacterium parvum, levamisole and BCG.

### Bcg

In animals a single injection of BCG results in enhanced humoral immunity, increase in macrophage function, increased resistance to bacterial infection, accelerated homograft rejection and increased resistance to tumor challenge.(6)Intralesional BCG has also been effective in the treatment of intradermal local recurrences of breast carcinoma following a mastectomy.(7). Methe *et al* in 1969 treated acute

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lymphoblastic lymphoma with BCG in experimental rodents. BCG was directly given on large skin abrasions. However, the role of BCG is unclear in Mett's experiment as his patients were also given allogenic leukemic blast cells along with many other agents including poly I: Poly C, Corynebacterium parvum and amantadine. So his clinical success cannot be attributed to the effect of BCG. It can be concluded that BCG along with specific active immunotherapy may provide a synergistic therapeutic effect. (8) It is noticeable that Mett was the first to use BCG to treat leukaemia. However, he failed to confirm a clear observation about its effect. Eliber *et al* used immunotherapy with BCG along with surgical removal of the tumour. His findings suggested that the recurrence rate is minimal when immunotherapy is used as a surgical adjuvant. (9) The use of living BCG may cause generalised disseminated disease in an immune compromised host which may even lead to death of the individual. (10,11,12). This difficulty in using live stimulated interest in using extracts of BCG such as the cord factor and delipidated and deproteinized cell wall. (13) Delipidated and deproteinized cell walls from Mycobacterium tuberculosis H37Ra suspended in 1.25% mineral oil emulsion cured established tumours in guinea pigs in 33% of the cases. When the cord factor was used along with Delipidated cell wall, 83% of the cases showed improvement. The study concluded that the adverse effects of using live BCG can be avoided by using lyophilized, killed BCG alone, with CF in 1% emulsions of mineral oil or with BCG and CF in peanut oil. The percentage of cures was considerably high.

#### ***Corynebacterium Parvum And Levamisole***

*Corynebacterium parvum*, a gram positive anaerobic organism is a strong macrophage stimulator and T cell suppressor. When given intradermally or intralesionally, it is a T cell stimulator (14). Unlike BCG, *C. parvum* is evaluated as an adjuvant to chemotherapy. A study by Israel and Halpern suggests that the patients who have undergone chemotherapy along with *C. parvum* had prolonged survival. (15) Levamisole is an antihelminthic which was used for intestinal disorders in man. Its immunotherapeutic effect was discovered accidentally. However, levamisole is less potent when compared to *C. Parvum* and BCG. (16,17)

#### ***Specific Immunotherapy***

##### ***Activation of NKT Cells And NK Cells***

NK cells are components of the innate immune system that play a protective role against some viral infections and tumors (18,19). These functions are achieved by the ability to recognize and lyse target cells (20,21). iNKT cell activation by soluble  $\alpha$ -GalCer, leads to rapid activation of other immune cells, including NK cells, which express CD69, secrete IFN- $\gamma$ , become more cytotoxic, and proliferate (22). The DC-GalCer response, as assessed by the number of IFN- $\gamma$ -secreting iNKT cells, was much stronger and prolonged than that obtained with soluble  $\alpha$ -GalCer (23) intravenous delivery of a soluble antigen together with the synthetic CD1d-binding glycolipid  $\alpha$ -GalCer can lead to in vivo activation of NKT cells and induction of anti tumor T-cell immunity. (24)

##### ***Activation of Dendritic Cells***

Dendritic cells (DCs) are bone marrow-derived antigen presenting cells (APCs) that play an important role in the

induction and regulation of immune responses. It has been proposed that the manipulation of DCs as a "natural" vaccine adjuvant may prove to be a particularly effective way to stimulate anti tumor immunity. (25,26) The most common approach to using DCs for vaccines is preparing large numbers of autologous mature MDCs *ex vivo*, load them with antigens, and then injecting them back into the subject (27,28) Three general methods have been described for preparation of the dendritic cells (1) differentiating DCs from leukapheresis-derived monocytes with GM-CSF and IL-4, (29) (the most popular approach; IL-13 has been used by some groups in place of IL-4), (2) GM-CSF and TNF-mediated differentiation of CD34 hematopoietic progenitor cells into mixtures of interstitial DCs and Langerhans cells (30) (Flt3L or stem cell factor may be added to expand DC progenitors, and differentiation may be skewed toward Langerhans cells by adding TGF $\beta$  to the culture (31), or (3) directly isolating DCs from leukapheresis products by density gradient centrifugation (32) or with commercially available closed systems that use immunomagnetic beads.

#### ***Carbohydrate Vaccines***

Carbohydrate antigens can be categorized into two major groups: "(i) glycolipids such as GM2, GD2, GD3, and fucosyl GM1 (gangliosides), and Lewis y (Le y) and globo H (neutral glycolipids); and (ii) glycoproteins such as the mucin-related epitopes Tn (GalNAc  $\alpha$  -O-Ser/Thr), TF (Thomsen-Friedenreich, Gal  $\beta$  1  $\rightarrow$  3GalNAc  $\alpha$  -O-Ser/Thr) and STn (NeuAc  $\alpha$  2  $\rightarrow$  6GalNAc  $\alpha$  -O-Ser/Thr)". Natural and vaccine-induced antibodies against GM2 and STn have been detected in patients with cancer, and have been associated with prolonged disease-free periods and overall survival. (33) so, these antigens specifically kill the tumour cells.

Cancer carbohydrate antigens such as gangliosides (GM2, GD2, GD3, 9-O-acetyl GD3 and fucosyl GM1), neutral glycolipids (Ley and globo H), and mucin related epitopes (TF, Tn, and STn), are suitable targets for both active and passive immunotherapies because they are over expressed at the cell surface of malignant cells and poorly expressed or not accessible on most normal cells. Conjugate vaccines against GD3, GD2, globo H, Ley and TF have induced antibody responses in 60% or more of patients. These antibodies can react strongly with the cell surface of antigen-positive cancer cells and are said to be able to mediate complement lysis (34)

#### ***Adoptive Immunotherapy***

Adoptive immunotherapy is the transfer of lymphoid cells with anti tumor reactivity that can mediate anti tumor responses in the host. Several lymphocyte subpopulations may be suitable for use in adoptive immunotherapy. Resting lymphocytes incubated in interleukin-2 (IL-2) give rise to lymphokine activated killer (LAK) cells that can lyse malignant cells, but not normal cells. In patients with advanced cancers, treatment with high dose IL-2 alone or in combination with LAK cells can mediate the complete or partial regression of cancer in selected patients. (35)

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