Immunotherapy

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Immunotherapy involves manipulation of host's immune system to achieve beneficial immune response against invading organisms. Besides the well establised, universally implemented active/passive immunisation schedules in prophylaxis / treatment, immunotherapy has shown potential promise as an adjuvant in cancer therapy, in combination with chemo and or radiation therapy. Immunotherapeutic agents are generally more effective when tumour mass (antigenic) is small.

Local Immunotherapy: Immunotherapeutic agents like BCG, Corynebacterium parvum, Dinitrochlorobenzene (DNCB), Purified protein derivative (PPD), Lymphokines etc are inoculated directly into region of tumour deposit. Primary squamous skin tumours respond to topical DNCB, malignant melanoma to vaccinia virus. In addition to curing the local lesion, they augment systemic tumour immunity.

Systemic Immunotherapy: It may be broadly classified into (1) Active (2) Passive (3) Adoptive, all of which may be specific or non-specific in nature.

1. Desensitisation: Small dose of the allergen is given s. c. or i. m. to ameliorate allergic symptoms (ragweed, grass pollen, hay house dust, mites, hymenopterous insect stings etc). The mechanism of desensitisation is supposed to be the production of IgG or blocking antibodies which bind to allergen before it interacts with mast cell bound IgE, thus

preventing mast cell degranulation and allergic manifestations. Purified preparations and slow release preparations are currently being exploited.

2. Active Immunisatian: Involves provocation of immunological response to a selected microbial agent or its antigen. While protection is diminished after some time, future exposure results in rapid return of immune response.

(a) Live, attenuated viruses as vaccines- act like natural infection and stimulate longer lasting antibody (AB) production but hazards are risk of reversion to greater virulence.

b) Killed virus vaccines, whole virions stimulate development of circulating antibody against coat proteins of virus.

c) Intranasal aerosol vaccines for respiratory disease viruse to stimulate local antibody production at portal of entry.

d) Synthetic vaccines- antigenically active polypeptides for human vaccination.

Purification of vaccines by newer methods, elimination of nonviral proteins, subunit vaccines to include those viral components required to stimulate protective antibody, attenuation of virus by genetic manipulation like production of recombinants and vaccines from recombinant DNA are under extensive studies.

In tumour therapy, altered tumour cells (irradiated, mitomycin- C, or neuraminidase treated), tumour extracts (purified tumour antigens) or similar preparations are used to invoke an immune response in the patient. Immunising preparation should maintain its antigenic properties, be devoid of replicating potential and not act as a source of metastases. In a study by Graham and Graham, a vaccine of autologous tumour cells(lung cancer) pretreated with Concanavalin A, neuraminidase and Complete Freunds Adjuvant given 2-4 months post operatively elicited statistically significant increase in survival.

3. Active (non-specific) immunisation exploits non specific stimulation of immune system to enhance cell-mediated immune responses (CMIR). 3n-pentadecylcatechol component of poison ivy/oak, urushiol, a chemical hypersensitising agent is highly effective in generating local T cell mediated immune response.

Bacillus Calmette Guerin (B. C. G.) besides its use in leprosy and malignancy is also used as prophylaxis in malaria, possibly due to the understanding of its immunopotentiating action. In cancer therapy, BCG and C. parvum were found effective in patients with a functional immune system. BCG increases Naturual Killer (NK) cell activity, enhances production of stem cells, activates macrophages to become more/ cytocidal, and may augment intracellular content of some enzymes that act on some carcinogens. In malignant lymphomas, lymphocytic and macrophage infiltrations are seen in regressing tumours after BCG treatment. Best results were obtained with small tumour loads (skin and sub cutaneous tissue involvement). Visceral metastases rarely respond to this therapy. Successful results in ALL, AML and bladder cancer (intravesical BCG therapy) have been reported but these results were not confirmed by further workers. Adverse reactions encountered are local skin reactions on scarification, granulomatous hepatitis responsive to anti-TB treatment and immune complex glomerulonephritis.

C. parvum: Vaccines prepared from heat killed, formaldehyde treated suspensions, can be given IV, orally, inj parenterally or directly into lesion. It activates NK cells on IV route and macrophages. Intralesional injection causes regression of tumours. However the initial enthusiastic results have not been confirmed by large scale clinical studies.

Levamisole: An antihelminthic drug used in rheumatic arthritis, stimulates CMIR and endogenous interferon production. It is useful as an adjuvant to surgery in breast and lung cancer, but shows little promise in bladder cancer.

Inosiplex (P-acetamidobenzoic acid salt of NN dimethyl amino-2-propanol : inosine complex (3: 1 molar ratio) increases T cell function, macrophage activity and enhances AB production. It is reported to restore the T cell suppression seen in post-radiation therapy and to potentiate anti-viral and anti-tumour activity of interferon.

Isoprinosine an antiviral compound, enhances lymphocytic response to mitogens and possess interferon like effect. It is relatively nontoxic.

Glucan (B 1 : 3 poly-glucose), a component of cell wall of S. cerevisae is found to stimulate RES, increase humoral and CMIR and enhance antitumour activity.

Vit. A, its analogues, tilorone, L-fucose, poly A: U, poly I : C, thiabendazole, tolazoline and several microbial extracts are being studied as immunotherapeutic agents in cancer. Systemic, non-specific immunotherapy with lymphokines, thymic hormones, transfer factors, interferon and interleukins have also been studied.

Lymphokines are non-Ig, generally glycoproteins, secretory products of activated lymphocytes with a wide range of potent physiological effects in inflammation and immunity. They have a multiplicity of intracellular effects and are biologically active at extremely low concentration.

Interferons are species specific glycoproteins produced by a wide variety of vertebrate cells upon viral and non-viral nucleotide stimulation. It inhibits cell division, enhances NK cell activity and augments immunity.

Therapeutic trials in human osteosarcoma (Strander 1971), laryngeal papilloma, breast cancer, lymphoma and basal cell

carcinoma have yielded promising results. The tumours usually reappear on cessation of treatment. Interferon is now being produced in larger quantities from Namalva strain lymphoblastoid cells and by recombinant DNA technology.

Interleukin-2 In a recent report IL-2 given intralesionally in 6 bladder cancer cases showed regression of tumour.

Thymic hormones play an important role in regulation and differentiation of T cells. Multiple factors with thymic activity, thymosin, thymopoietin and facteur thymique serique (FTS) have been isolated and used in congenital T cell deficiency, autoimmune disease (SLE) and in tumour therapy.

Transfer Factor is a dialysable moiety from leucocyte that transfer cell mediated immunity immediately to the recipient even in very small doses and is free of risk of sensitisation upon repeated administration. Transfer factor was found to be a complex of polypeptide and oligonucleotide. Its use in primary immunodeficiency diseases gave disappointing results.

Passive Immunotherapy

Passive immunisation involves use of immune serum globulin (ISG) from actively immunised animals or humans. Duration of immunity provided is brief. Generally used are ISG hepatitis A and B, zoster serum immune globulin; diphtheria antitoxin, tetanus immunoglobulin and rabies, pertussis, measles, rubella immunisations in post-exposure therapy. Pooled, normal, human immunoglobulins have been tried in bacterial infections, in patients with ganeralised antibody deficiency or hypo-gama-globulinemia and in treating individuals at risk with normal immunity.

As early as 1900 Ehrlich conceived the idea of a "magic bullet" in cancer treatment i. e. utilising specific antisera to specifically target cytotoxic agents to tumour cells. The advent of monoclonal antibodies has revolutionised the whole concept. Currently a "carrier" approach with monoclonal antibodies linked to radioisotopes (alpha particle emitting radionuclies Ra 224), to chemotherapeutic drugs, toxins (diphtheria toxin, plant toxin, abrin and ricin) and liposome encapsulated lymphokines like IFN, muramyl dipeptide (MDP) show great promise in tumour specific therapy. As the amount of antibody that can bind to tumour cell is limited by the number of antigen receptors on tumour cell, highly toxic substances in minute doses (toxins) are ideal. Cocktail of monoclonal antibodies are used to circumvent pitfalls of tumour heterogenecity and antigen shedding. Isolation of the putative antigens and raising of specific monoclonal antibodies in preparation of vaccines eg. in malaria, is another fast growing area of research.

Antilymphocyte globulin (ALG). The globulin fraction obtained by injecting human lymphocytes into rabbits, goats or pigs is generally used in organ transplant-prolongation of homograft survival. It is also used in treatment of autoimmune diseases, severe glomerulonephritis, polyarteritis nodosa, SLE, disseminated sclerosis, myasthenia gravis etc.

Adoptive immunotherapy

Immune reactions to tumour antigens on cell membranes are of the delayed hypersensitivity type which can be transferred from one individual to another with lymphoid cells. It can be non-specific by transfer of normal lymphoid cells or specific by tranfer of lymphoid cells presensitised to tumour antigens.

Reports on inhibition of growth of tumours after passive transfer of tumour sensitised lymphocytes in animals and humans are seen. In 1963 Woodruff and Nolan obtained partial success by treating advanced human cancer with high dose of spleen cells from a non cancer individual undergoing splenectomy. Vasudevan et al (1974) characterised the cytotoxic lymphocyte population involved in specific killing of tumour cells. Cytotoxic T cells (CTL) are formed normally as host immune response to cell associated antigens (viral, infectious or malignant transformation). Lymphocytes are initially enriched in vitro for CTL maintained in continuous proliferation in culture by repeated stimulation with antigen and T cell growth factor (interleukin 2), cloned and AG-specific CTL used in tumour therapy. Loss of tumour-specific antigens during tumour progression and tumour heterogenecity have suggested a nonspecific approach using (IL-2) lymphokine activated killer cells and lymphokine induced cytotoxic cells. Another non-specific approach is stimulation of NK cell and macrophages as non specific effector cells. T cell and NK cell resistance can develop, so activation of macrophages (MDP-liposomes) is an elegant approach.

Immune RNA: To avoid development of reaction to xenogeneic proteins and graft versus host disease, Pilch (1971) advocated the use of immune RNA from lymphoid cells of sensitised animals. Stabilisation of disease and positive response was seen in patients with hypernephroma. Symes (1968) used immunised porcine mesenteric lymphnode cells in tumour therapy. Its main draw back was the severe anaphylactic shock in some cases and only a single dose could be given.

Other modalities in cancer therapy include Immunological Reconstitution approach. Bone marrow transplant, thymus transplant and stem cells from foetal liver are currently being studied.

Antigenic tumours continue to grow even in the presence of specific sensitised lymphocytes, cytotoxic in vitro but unable to fully function in vivo due to immunosuppressive factors in circulation. Selective abrogation of suppressor cell activity could be beneficial. Antigen–antibody or immune complexes (IC) induce suppressor T cells and inhibit anti tumour activity of macrophages. Protein A of Staph. aureus Cowan 1 is a powerful immunostimulating agent. It can bind plasma blocking factors (IC) and modulate reactivity of both cellular and humoral factors in tumour host. Tumours are reported to regress on adsorbing factors (IC) and modulate reactivity of both cellular and humoral factors in tumour host. Tumours are reported to regress on adsorbing plasma of host over protein A, collodion charcoal/ silica gel bound protein A (Ray et al).

Besides immuno stimulation, immuno suppression may also be required as in organ transplant and treatment of autoimmune diseases. Irradiation with sublethal doses to whole body (200-600 rads) is immunosuppressive.

Active immunisation programme in prophylaxis against infectious diseases has been one of the success stories of medicine of this century. More promising clinical trials suggest that immunotherapy may be beneficial for selected cancer cases, in combination with other modalities. With the newer techniques for isolation and purification of antigens, production of monoclonal antibodies, advances in recombinant technology and genetic engineering, a gleam of optimism can be discerned in the fast growing field of immunotherapy.

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Abbreviations used in this article:

AG—Antigen Ig—Immunoglobulin

ALL—Acute Lymphoblastic Leukemia

AML—Acute Myelogenous Leukemia

RES—Reticulo endothelial system