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BIOLOGICAL RESPONSE MODIFIERS

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BIOLOGICAL RESPONSE MODIFIERS

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Much of what used to be called immunotherapy is now included in the term biological response modifiers. Biological response modifiers (BRMs) are defined as "those agents or approaches that modify the relationship between the tumor and host by modifying the host's biological response to tumor cells with resultant therapeutic effects." Most of the early work with BRMs centered around observations of spontaneous tumor regression and the association of tumor regression with concurrent bacterial infections. The BRM can modify the host response in the following ways:

1. Increase the host's antitumor responses through augmentation and/or restoration of effector mechanisms or mediators of the host's defense or decrease the deleterious component by the host's reaction.

2. Increase the host's defenses by the administration of natural biologics (or the synthetic derivatives thereof) as effectors or mediators of an antitumor response.

3. Augment the host's response to modified tumor cells or vaccines, which might stimulate a greater response by the host or increase tumor-cell sensitivity to an existing response.

4. Decrease the transformation and/or increase differentiation (maturation) of tumor cells.

5. Increase the ability of the host to tolerate damage by cytotoxic modalities of cancer treatment.

I. Principles of BRM Use

A. As an adjuvant therapy to definitive primary therapy, i.e., surgery, radiotherapy, chemotherapy, hyperthermia.

1. Application as a primary therapy alone is unlikely.

2. Examples of application as adjuvant therapy:

a) Malignant melanoma - surgery + BRM

b) Squamous cell carcinoma - radiotherapy + BRM

c) Acute myelogenous leukemia - chemotherapy + BRM

B. Goals of primary therapy:

1. Reduction of tumor size - diminish to finite tumor load ($<10^5$ cells).

2. Depletion of blocking factors

a) Decreases tumor antigens

b) Decreases circulating antibodies and circulating antigen-antibody complexes

c) Suppression of immunoglobulin production

C. Goals of BRM Therapy

1. Stimulate animal's immune system to recognize tumor cells (afferent)

a) Increase antigenicity of tumor cells

1. Alteration of cell surface

2. Alteration of internal structures

b) Selectively increase T- or B-cell populations

c) Increase amount of antigen presented to the immune system without increasing the number of tumor cells

d) Use of cross-reacting antigens

2. Increase the immune system's ability to kill tumor cells (efferent).

II. Current Classifications of Biological Response Modifiers

Immunomodulator and/or Immunostimulating Agents

BCG
Brucella abortus
Cornybacertium parvum
Cimetidine
"Immune" RNAs
Levamisole
Muramyl dipeptide (MDP)
Malic anhydride-divinyl ether (MVE-2)
Mixed bacterial vaccines (MBV)
Picibanil (OK-432)
Prostaglandin inhibitors (aspirin, indomethacin)
Thiobendazole
Tilorones
Tuftsin

Interferons and Interferon Inducers

Interferons (alpha, beta, gamma)
Poly ICLC
Pyrimidinones
Tilorones
Viruses

Thymosins

Thymosin alpha-1
Thymosin fraction 5
Other thymic fractions

Lymphokines and Cytokines

Chalones
Colony-stimulating factor (CSF)
Interleukin 3 (IL-3)
Lymphocyte activation factor (LAF-interleukin 1 [IL-1])
Lymphotoxin
Macrophage activation factor (MAF)
Macrophage inhibitory factor (MIF)
T-cell growth factor (TCGF - interleukin 2 [IL-2])
Thymocyte mitogenic factor (TMF)
Transfer factor
Tumor-necrosis factor (TNF)
B-cell growth factor (BCGF)

II. Current Classifications of Biological Response Modifiers (cont)

Monoclonal Antibodies

Monoclonal antibodies
Anti-T cell
Anti-T-suppressor cell
Antitumor antibody endotoxin
(including antibody fragments and/or conjugates with drugs, toxins, and isotypes)

Antigens

Tumor-associated antigens
Vaccines

Effector Cells

Macrophages
NK cells
T-cell clones
T helper cells

Miscellaneous Approaches

Allogeneic immunization
Bone marrow transplantation and reconstitution
Plasmapheresis and ex vivo treatments (activation columns and immunoabsorbents)
Virus infection of cells (oncolysates)
Blood constituent therapy (serum factors)

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