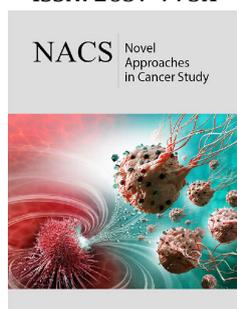


Immunotherapy the Present and Future of Cancer Treatment

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Abstract

Immunotherapy is based in reactivating the patient immune system specifically against the neoplasia, tumors have immunosuppression mechanisms that allow them to control and evade the immune response.

There are different immunotherapy approaches like tumor-targeting monoclonal antibodies, adoptive T cell transfer, anticancer vaccines, checkpoint inhibitors, most of these in important clinical trials in which the effects and toxicities are still evaluated. They are also beginning tested on a combination of immunotherapies and other non-immunological therapies in order to increase the survival of patients. Immunotherapy is still a young area and it needs to reach its peak, but it will surely be a great tool to treat and cure cancer.

Introduction

During many years' cancer treatments was restricted to surgery, chemotherapy or radiotherapy. The advances in cancer knowledge have revealed an interaction between malignant cells, their microenvironment and the immune system, which is crucial during oncogenesis and cancer progression; consequently, immunotherapy was developed, and it seems to work when other treatments do not. The main problem of immunotherapy is the tumor immunosuppressive microenvironment which is a dynamic status and is coordinated by multiple immunosuppressive signals. Personalized medicine is essential during immunotherapy to ensure the success of the treatment, it is necessary to consider tumor biomarkers, microenvironment, patient genetics, immune profile, and the general patient status [1]. Anticancer immunotherapies are classified as "passive" or "active" based on their ability to activate the host immune system against malignant cells.

Passive Immunotherapy

Tumor-targeting monoclonal antibodies

The tumor targeting monoclonal antibodies (mAb) can act by the following three ways:

- a) Altering the signaling of receptors expressed on malignant cells,
- b) Neutralizing trophic signals produced by malignant cells or by stromal components of neoplastic lesions,
- c) 3) Recognizing selectively tumor associated antigen and then activate antibody-dependent cellular cytotoxicity or complement dependent cytotoxicity, or well interfering with pathways of tumorigenesis (triggering apoptosis, inhibiting cells proliferation or blocking angiogenesis).

Clinical trials are being carried out to assess the safety or efficacy of tumor-targeting mAbs, engineered humanized or chimeric mAbs have been recently approved by the FDA. The mAbs are also being used combined with radioisotopes to attack selectively cancer cells [2,3].

Adoptive T cell transfer

The objective of the adoptive T cell transfer is to generate a vigorous immune mediated antitumor response, T cells are harvested from blood or tumor and manipulated ex vivo for its expansion and then re-infused into the patient, where they will mediate tumor destruction. The mechanism can be divided in two:

A. The isolation of tumor infiltrating lymphocytes; T cells and Natural killer are present in any solid tumor, but in an immunosuppressive tumor microenvironment, ex vivo T cell stimulation with cytokines enhance their efficacy. This therapy is actually used in melanoma patients.

B. The genetic modification of blood-derived T cells to allow for specific recognition of tumor cells. There are two common approaches for redirecting T cell specificity:

a) Gene modification with TCRs directed against tumor associated antigens. Some clinical studies have been conducted with modified TCR with limited efficacy and significant toxicity due to the destruction of self-antigens and

b) T cell receptor modified through the expression of a chimeric antigen receptor, CAR-T cell. The CAR-T cell has been used successfully in hematological malignancies targeting specific cell antigens; in solid tumors, the problem is the lack of specific tumor antigen [4,5].

Active Immunotherapy

Anticancer vaccines

There are two types of anti-cancer vaccines, the first one prophylactic anti-cancer vaccines that are developed to those chronic infections that are involved in carcinogenesis. On the other hand, non-prophylactic anti-cancer vaccines elaborated with tumor antigens to elicit an immune response versus cancer, the main obstacle is the identification of appropriate tumor antigen. The first anti-cancer vaccine approved by the FDA was for prostate cancer, it was done with autologous peripheral blood mononuclear cells and incubated with a fusion protein of a tumor antigen associated protein, and the objective is that dendritic cells present the antigen as part of the major histocompatibility complex. The most important prophylactic anti-cancer vaccine is the human papillomavirus which causes cervical cancer [6].

Checkpoint inhibitors

Malignant cells promote an immunosuppressive microenvironment with suppressive signal transduction; immune

checkpoints are responsible for the tolerance and immune activation. Cancer uses those checkpoints for its own benefit, inducing tolerance and evasion. The main checkpoints for cancer treatments by now are PD-1/PD-1L (Programmed death-1/-Ligand), CTLA-4 (cytotoxic T lymphocyte-associated antigen 4), LAG-3 (lymphocyte activation gene 3), among others [7].

Conclusion

The immune system is very powerful against cancer, but it controls the immunity by producing an immunosuppressive microenvironment. The objective of immunotherapy is to re-activate the patient immune system instead of attack cancer like other therapies used. Immunotherapy is the area of medical sciences that has advanced more in the last years but has not reached its peak, it seems that there is finally a way to effectively treat or even cure cancer, in the following years immunotherapy will complete change and everything seems to indicate that it would be used combined with other therapies to improve patient survival, but the studies are just starting, and antitumor effects and toxicities have yet to be fully explored.

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