Immunotherapy with dendritic cells for gynecological neoplasias: a new therapeutic approach?

M.A. Michelin[1], E.F.C. Murta[2]

[1]Discipline of Immunology; [2]Discipline of Gynecology and Obstetrics
Oncological Research Institute (IPON), Federal University of Triângulo Mineiro, Uberaba, MG (Brazil)

Summary

The immune system consists of a complex collection of mediators and cells that act in a coordinated way to eliminate neoplastic cells. One of immunotherapy's promises is the development of cellular vaccines, or more specifically, vaccines with dendritic cells. However, we still have a lot left to study and learn, since we already know that patients with tumors of the same histological grade can have completely different behaviors when given the same immunological stimulus. We believe that antitumor immunotherapy will lead to a personalized vaccine, since the scheme of treatment, the stimuli and the dosages need to be tailored to each patient.

Key words: Immunotherapy; Dendritic cells; Neoplasia.

Introduction

Using the immune system as a tool to treat neoplasias is one of science's oldest dreams. The origin of modern immunotherapy stems from studies performed in Europe and the United States at the start of the nineteenth century, which observed tumor regression in association with other infections, such as erysipelas [1].

The tumor microenvironment is, in fact, made up of a collection of neoplastic cells, but also of various components of the immune system. The particular constitution and character of this microenvironment determine the type of anti-tumor response, since at the same time as there are immune system cells that powerfully destroy neoplastic cells, such as natural killer and dendritic cells, the tumor cells themselves can create a suppressor environment in which myeloid suppressor cells and T regulatory lymphocytes predominate [2-6]. Understanding the complexity of this tumor microenvironment and the escape mechanisms used by tumors is of fundamental importance to the development of new immunotherapies.

During the last 100 years, there have been huge advances in immunology, which today have allowed us to take the first steps in developing an effective immunotherapy. Various kinds of immunotherapies have been and continue to be developed; from the point of view of applicability, some have not passed *in vitro* tests, while others are already in clinical use. Many components of the immune system have already been used as a tool in the effort to destroy tumors, such as immunostimulants, antibodies, cytokines, and cellular therapies.

Among the cytokines that are already in use, the one that has the most beneficial effects and the fewest side effects is IFN-alpha. This cytokine is used to treat various types of tumors, such as renal carcinoma, melanoma, head and shoulder tumors, non-Hodgkin's lymphomas, chronic myeloid leukemia, and cervical tumors. Published studies show that IFN-alpha can act directly on tumor cells, interfering with growth and differentiation, affecting intracellular signaling and perhaps the tumor's capacity for mitosis. Moreover, it is suspected that this cytokine can also act in an indirect way or by stimulating the immune system to exercise its anti-tumor action. Our research group has spent several years analyzing the use of IFN-alpha in patients with cervical intraepithelial neoplasia grade 3 (CIN 3). The data shows that this cytokine can act to stimulate patients' immune systems, since a reversion to the Th1 pattern, both locally and peripherally, occurs [7-9].

In addition, we know that the immune system consists of a complex collection of mediators and cells that act in a coordinated way to eliminate neoplastic cells. One of promises of immunotherapy is the development of cellular vaccines, or more specifically, vaccines with dendritic cells.

Immunotherapy with Dendritic Cells

Since the 1960s, there have been great advances in cell immunology. In 1973, Steinman and Cohn published an article in which they affirmed: "A novel cell type has been identified in adherent cell populations prepared from mouse peripheral lymphoid organs (spleen, lymph node, Peyer's patch). Though present in small numbers (0.1-1.6% of the total nucleated cells) the cells have distinct morphological features. The nucleus is large, retractile, contorted in shape, and contains small nucleoli (usually two). The abundant cytoplasm is arranged in processes of varying length and width and contains many large spherical mitochondria. In the living state, the cells undergo characteristic movements, and unlike macrophages, do not appear to engage in active endocytosis. The term, dendritic cell, is proposed for this novel cell type" [10]. This article heralded a great discovery, describing DCs for the first time.

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This cell type originates in the bone marrow, via pluripotent CD34+ cells, and develops into two different types, plasmocytoid DCs and myeloid DCs. The first type originates in the lymphatic system, is present in a lower proportion than myeloids, and is found in lymphatic organs, such as the thymus, the spleen, the lymph nodes, and the bone marrow. Myeloid DCs are comprised of Langerhans cells, located in the stratified epithelium; dermal DCs, located in the dermis; and interstitial DCs, located in the interstices of the tissues [11-13].

DCs leave the bone marrow in a premature form; during this phase, they have a large capacity for antigen processing and presentation, although they have a low ability to stimulate the lymphocytes. The migration process to the lymph node after antigen capture and the cytokines produced at the point of inflammation or of tumor response are crucial to the maturation and activation of the DCs, since this activation and migration implies the expression of new costimulatory molecules that are essentially made to activate the T lymphocytes [14, 15].

The first attempts to use DCs as anti-tumor immunotherapy took place in the 1990s. The clinical use of this type of cell in therapy to treat different types of tumors – such as renal tumors, melanoma, cervical cancer, and prostate cancer – has taught us a great deal. However, there are still gaps in various areas of our knowledge that need clarification, as, for instance, the best form of differentiation, the dosage, the mode of administration, and, above all, the mechanisms that these cells use i*n vivo* to induce this anti-tumor response.

Our research group has worked on developing new protocols for the differentiation of these cells, as well as studying the mechanisms involved in the process of tumor regression after vaccination. After immunotherapy with autologous DCs in patients with different types of advanced-stage tumors, differentiated *in vitro* based on the patient's own blood and pulsed with tumor antigens obtained by biopsies of the patients themselves, the systemic immunological profile changes. We have seen evidence that there is a stimulation of innate immune response, with an increase in T helper lymphocytes (CD4+) expressing IL-2, IFN-gamma, IL-12, TNF-alpha and IL-10 after the start of treatment. The same effect was observed for T cytotoxic lymphocytes (CD8+) expressing IL-2. The percentage of total T lymphocytes (CD3+) remains elevated during the whole of immunotherapy, while the levels of regulatory T cells (CD4+/CD25+/FOXP3+) go down after the start of treatment [16].

However, our experience shows that despite the fact that the vaccine stimulates an initial immune response, in which there is regression and/or stabilization of the tumor, after some months, this response is reduced, and the tumor progresses. Therefore, we believe that a new tumor escape mechanism arises, and for this reason, we need to improve the protocol for the differentiation and stimulation of DCs.

Immunotherapy with DCs gives great hope for the treatment of tumors. Nevertheless, much more still needs to be done. We know that using autologous cells in immunotherapy is of fundamental importance, because when heterologous cells are used, these very cells must be irradiated to avoid rejection, which leads to a huge loss of function, since these cells must be able to migrate and to express new adhesion molecules and the mediators needed to adequately activate T lymphocytes. Another important point is the need to develop the cells on an industrial scale so that they will be more accessible to the population requiring treatment.

Conclusions

There are still a number of factors limiting the development of new protocols for treatment in humans, which range from ethical precepts to the understanding of the basic mechanisms involved in the interaction between the innumerable and complex components of the immune system.

Immunotherapy with DCs is immunology's promise for the treatment of neoplasias. However, we still have a lot left to study and learn, since we already know that patients with tumors of the same histological grade can have completely different behaviors when given the same immunological stimulus. We believe that antitumor immunotherapy will lead to a personalized vaccine, since the scheme of treatment, the stimuli, and the dosages need to be tailored to each patient.

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Address reprint requests to:
E.F.C. MURTA, M.D.
Oncological Research Institute (IPON)/
Discipline of Gynecology and Obstetrics
UFTM, Av. Getúlio Guaritá, s/n, Bairro Abadia
38025-440 Uberaba-MG (Brazil)
e-mail: eddiemurta@mednet.com.br.