New therapeutic perspectives in prostate cancer – Provenge imunotherapy

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Abstract

Along with progresses in understanding the complex interactions between tumor cells and the immune response of the host and the very dynamic development of genetic engineering techniques, the newer and more efficient immunotherapeutic techniques which generate less secondary effects are gaining more attention when approaching neoplasic pathology. PROVENGE (Sipuleucel-T) falls in this category and it is the first therapeutic cancer vaccine to demonstrate effectiveness in patients who suffer from advanced to the late stage of the disease, asymptomatic, hormone-refractory prostate cancer.

Key words: immunotherapy, hormone-refractory prostate cancer, therapeutic antineoplastic vaccine

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Introduction

Immunology has in time evolved from theoretical knowledge to the profoundly skeptical and fact-based science we know today. Immunotherapy in its many approaches is the highest type of the applicability of immunology in medicine.

Along with progresses in understanding the complex interactions between tumor cells and the immune response of the host and the very dynamic development of genetic engineering techniques, the newer and more efficient immunotherapeutic techniques which generates less secondary effects are gaining more attention when approaching neoplasic pathology.

Immunotheraputic strategies in prostate cancer include: cytokine and anticytokine therapy, activated T killer lymphocytes, dendritic cells or other antigen presenting cells, which are ex-vivo exposed to tumor antigens or cells. All these above mentioned are ways to stimulate the specific antitumor immunity and they proved to induce a favorable clinical and biological outcome for patients with prostate cancer [1].

PROVENGE (Sipuleucel-T) falls in this category and it is the first antineoplasic therapeutic vaccine approved by FDA (Food and Drug Administration) in the therapy of metastatic hormone refractory prostate cancer (T4N1M1c) [2].

PROVENGE – action mechanism

PROVENGE obeys to the principles of active immunotherapy and uses autologous immune cells which are trained to specifically activate one of the most efficient anti-tumor immune links: T lymphocytes [3].

The first step of this revolutionary therapy is to perform a leukapheresis that is meant to isolate peripheral mononuclear cells (*„peripheral blood mononuclear cells", PBMC*) [4]. Among these cells, the antigen presenting cells (APC – macrophage, dendritic cells, B lymphocytes) hold a key role in strategy that PROVENGE uses to modulate antitumor immune response [5].

Once isolated, APC are activated in vitro by PAP-GM-CSF. This is a recombinant human protein, which consists of prostatic acid phosphatase (*„prostatic acid phosphatase" PAP*), linked to granulocytes-macrophage colony-stimulating factor (*GM-CSF*). PAP is an antigen intensely expressed in prostate tumor cells, while GM-CSF is used as immunostimulant [6].

Antigen presenting cells activated by GM-CSF exposure take over PAP, which undergo intracellular decomposition under the action of an enzyme system and turn into antigenic peptides (epitopes) on the surface of the cellular membrane. APC are ex vivo taught to direct the immune response toward PAP [7].

Once they have been auto-transplanted to the patient, activated APC generate the immune message designed in the laboratory through their ability to present epitopes (peptide sequences generated during intracellular decomposition of PAP and T lymphocytes). The immunologic consequence is that antigen specific activation of corresponding T lymphocytes takes place. This is the most important moment of the PROVENGE strategy against prostate cancer: T cells identify and destroy prostate tumor cells that express the target molecule (in this case the human prostatic acid phosphatase) [8].

Two important aspects deserve recognition: ex vivo activation of APC eludes immunosuppression in a tumor context, and using autologous cells excludes any incompatibility in the HLA system (*Human Leukocyte Antigen*) because the antigen is expressed in the context of self CMH molecules (*Major Histocompatibility Complex*) [9].

The final product, Sipuleucel-T, contains APCs and other cellular types involved in immune response such as T cells, natural killer cells and very small quantities of intact PAP-GM-CSF. Each dose of PROVENGE brings to the host's immune system hundreds of million of activated autologous antigen presenting cells [9, 10].

Among the techniques used to evaluate APC activation, there are the phenotyping techniques (the evaluation of surface expressing of certain markers such as the class II histocompatibility antigens) and the functional techniques (the evaluation of the ability to take up, process and stimulate T cells) [11].

In PROVENGE therapy, the evaluation of APC activation is evaluated by flow cytometry studies, which detect the CD54 differentiation marker (also known as *ICAM 1 – intracellular adhesion molecule 1*). This molecule expresses itself significantly on the surface of the APC after growing in a culture along with the PAP-GM-CSF fusion protein. Moreover, in vitro studies showed that CD54 positive cellular types are responsible for taking up the antigen. In the same time, ICAM-1 plays an important role in activating the specific immune response as it mediates and amplifies the interactions between APC and T cells. This makes the CD54 mo-lecule essential for an efficient cooperation of immune cells and is also used as a criterion to measure the power of Sipuleucel-T [12, 13].

The impact of PROVENGE therapy over the immune response is complex and unpredictable. Along the designed effect (that of destruction of the positive PAP cells), it also elicits humoral immune response. Sipulecucel-T immunomodulation is associated to measurable serologic levels of specific antibodies (M and G isotypes), which are directed against the PAP-GM-CSF fusion protein and the prostatic acid phosphatase. However the neutralizing humoral response is transitory; it has also been demonstrated that a T cell mediated response against the fusion protein develops for patients undergoing PROVENGE therapy. The clinic meaning of activating two sides of the specific immune response (both cellular and humoral) remains a subject of further studies and interpretation [13].

Hypothetically, this therapeutic vaccine can generate a continuous antineoplasic immune response. Further study is needed to confirm the activation of anti-tumor immunologic memory.

PROVENGE – adverse reactions

This new therapeutic approach of the neoplasic patient also has its side effects. The majority of adverse reactions is immediate and occurs after the first dose. They are usually acute infusion reactions, in relation to the dose, but secondary to the cytokine imbalance, and they usually improve by slowing the perfusion rate. In the majority of cases, the immediate reactions consecutive by PROVENGE administration can be prevented by acetaminophen or antihistaminic premedication. Clinically, the most frequent immediate reactions are nausea, vomiting, increasing fever, chills, back pain, headache, fatigue, dyspnea, and bronchospasm. The majority of side effects are mild or moderate in terms of severity. Data from controlled clinical trials shows that acute reactions (linked to the dose) show in small percent of PROVENGE treatment patients (3,5%) [14].

Among late events that occur during Sipuleucel-T immunomodulatory therapy are eosinophilia, rhabdomyolysis, myasthenia gravis, and myositis. An important complication of PROVENGE administration is the occurrence of cerebral vascular accidents. No fatal events have been recorded [15].

Another important aspect is that active antioneoplasic immunotherapy isn't free of the dramatic side effect of the conventional therapy (both chemotherapy and radiotherapy) that the tumoral stage would impose.

Clinical studies

PROVENGE immunotherapy has up to now been used for over 1000 patients diagnosed with hormone refractory metastatic prostate neoplasm.

The adverse effects of Sipuleucel-T therapy have been investigated in the frame of 3 randomized multicenter, double-blind, placebo-controlled clinic studies. The patients included in the study have undergone three episodes of leukapherese during weeks 0, 2 and 4. Each leukapherese has been continued with PROVENGE or placebo administration. Inactive autologous immune cells were administered to the witness group. For all patients, the curating doctor had total freedom in choosing a therapeutic approach imposed by the evolution of the disease. The exception from this rule was the immunosuppressive therapy,which goes against the objective of the PROVENGE therapy to stimulate antitumor immune response [16].

All these studies showed an increase in life expectation for patients treated with PROVENGE. In the first phase III trial, the average life expectation of patients treated with Sipuleucel-T was of 25,9 months compared to that of 21,4 months of the placebo treated patients. The second trial also found a bigger survival period for patients undergoing PROVENGE therapy. The third trial, IMPACT, included over 500 patients and the average survival rate of patients taking Sipuleucel-T was 25,8 months compared to that of 21,7 month of patient from the witness group. The results presented in March 2010 during the Genitourinary Cancer Symposium of the American Clinic Oncology Association showed that Sipuleucel-T increased the survival rate to 3 years (approx. 40% more than the survival rate of he placebo group: 32,1% vs. 23%) [17].

PROVENGE is being currently tested for patients with non-metastatic prostate adenocarcinoma and the results are promising.

Conclusions

The last decades have generated and increased interest of immunology researchers which has resulted in new ways of manipulating and controlling the immune system, aiming to suppress inadequate, exaggerated or altered response (as it is the case of auto-immune diseases, allergies and transplant rejections), to stimulate protective or corrective immune response in case they are insufficient or depressed (as it is the case of immunodeficiency of advanced cancer).

After a decade of research and over a thousand

patients that underwent this revolutionary therapy, PROVENGE inaugurates a new era in anti-tumor therapy. As of April 2010 it becomes the first antineoplasic therapeutic vaccine approved by FDA. Up to now, PROVENGE therapy generated an increase in life expectancy and an improvement in the quality of life for patients with advanced prostate neoplasm.

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Rezumat

Pe măsura progreselor în înțelegerea interacțiunilor complexe dintre celulele tumorale şi răspunsul imun al gazdei, alături de dezvoltarea explozivă a tehnicilor de inginerie genetică, noi modalități imunoterapeutice eficiente şi cu efecte secundare cât mai mici, câştigă teren în abordarea patologiei neoplazice. În acest registru se înscrie PROVENGE, primul vaccin terapeutic antitumoral, care şi-a dovedit eficiența la pacienții cu stadiu tumoral avansat, hormonorezistent.

Cuvinte cheie: cancer prostatic hormonorezistent, imunoterapia, vaccin terapeutic antineoplazic