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Vaccines in non-small cell lung cancer: Rationale, combination strategies and update on clinical trials

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Abstract

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer related mortality worldwide and despite some advances in therapy the overall prognosis remains disappointing. New therapeutic approaches like vaccination have been proposed and several clinical trials are ongoing.

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Many tumor antigens have been identified so far and specific tumor vaccines targeting these antigens have been developed. Even if the ideal setting for vaccine therapy might be the adjuvant one, vaccines seem to be potentially beneficial also in advanced disease and combination therapy could be a promising treatment option.

In the advanced setting anti-MUC-1 vaccine (belagenpumatucel) and anti-TGF-β_2 vaccine (BPL-25) have entered in phase III trials as maintenance therapy after first line chemotherapy. In the adjuvant setting the most relevant and promising vaccines are directed against MAGE-A3 and PRAME, respectively.

We will review the key points for effective active immunotherapies and combination therapies, giving an update on the most promising vaccines developed in NSCLC.

Keywords: Non-small cell lung cancer; Vaccine therapy; Tumor antigens; Adjuvant vaccines

1. Introduction

NSCLC remains the leading cause of cancer related mortality worldwide. Major advances in treatment have been achieved in the last few years, mainly in terms of molecular targeted therapies; however, most patients only have palliative therapeutic options and overall prognosis remains disappointing [1].

Development of strategies able to induce antitumor activity is an active and promising area of research. The concept that tumors could be recognized by the immune system was proposed in the late 19th century when observations of rare spontaneous tumor regressions after infectious episodes were reported [2]. Unfortunately such regressions are displayed only in few tumors like melanoma and renal cancers as most cancers display in vivo no or weak immunogenicity [3,4]. In fact tumor cells seem to be antigenic, but not immunogenic, either due to presentation of weakly recognized antigens or because of the inability of the immune system to recognize them. Basis of cancer immunotherapy is the artificial external activation of the immune system against the tumor [5]. This requires the appropriate presentation of a tumor antigen by the antigen-presenting cells able to stimulate and expand tumor-specific T-cells [6].

At present, even if several trials have been conducted so far and many are currently ongoing, NSCLC vaccines do not have clinical indication in daily medical practice, unless within the a clinical trial.

In this paper we will review the rationale of cancer immunotherapy, focusing on vaccination in NSCLC; we will discuss the basis of choosing the best setting of patients to be treated with vaccines; then we will describe the main antigens which can be targeted in NSCLC, providing a summary of the leading clinical trials, with a focus on the adjuvant setting which might be very promising.

2. Cancer immunotherapy: rationale

The immune system can play a dual function in tumor development: it can either favor or inhibit tumorigenesis and can act in the initial or late phases of tumor development. The involvement of chronic inflammation in tumorigenesis has been clearly shown in several animal models of spontaneous or chemically induced carcinogenesis [7–13]. Chronic inflammation or infection, for instance, can lead to the generation of a protumoral environment that in individuals predisposed to cancer can increase the incidence of tumors. Typical examples are the predisposition of inflammatory bowel disease patients to develop colorectal cancer [14] or liver tumor development in patients affected by helicobacter pylori [15]. Most of these effects are mediated by cells of the innate arm of the immune system that are educated by the local microenvironment to acquire protumoral characteristics (tumor associated macrophages and myeloid derived suppressor cells [16,17]). In addition, the tumor microenvironment plays an important role in tumorigenesis and tumor progression and may be a target for therapy (for a thorough review please see [18]). Patients with NSLC display conditions of low oxygen (hypoxia) in the tumors that selects for tumor variants with diminished apoptotic potential [19]. Like many other solid tumors, NSCLC is also characterized by an increased angiogenesis, likely due to the release by the tumor of pro-angiogenic factors like VEGF in response to hypoxia [20]. Fibroblasts and stromal cells also participate in generating a pro-tumoral environment by inducing the upregulation of aromatases that favor tumor growth [21] and by recruiting and promoting the differentiation of protumoral immune cells [22].

The immune system however participates also to tumor immune surveillance and could be exploited to develop effective anti-tumor immunity. Indeed, it is believed that tumor associated antigens that are either overexpressed, arise from mutations or are expressed ectopically, can be processed and presented by dendritic cells, a process called cross-presentation [23]. Dendritic cells are professional antigen presenting cells that can migrate to draining lymph nodes for activation of T cells into effector cells (either CD4+ T helper cells or CD8+ cytotoxic T cells) [24]. However, the induction of immunity to tumors can be hampered by tumor cells at several levels, a phenomenon called immune evasion [25,26]. The tumor can favor the development of tolerogenic dendritic cells that instead of inducing effector T cells can drive the differentiation of T regulatory cells that dampen the activity of effector cells [27–32]. In addition, tumor cells can release or express several factors that can directly inhibit the activity of effector T cells like TGF-β