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RESEARCH ARTICLE

THE THERAPEUTIC POTENTIAL OF PD-1 / PD-L1 INHIBITORS IN NON SMALL CELLS IN SMOKING METASTATIC LUNG CANCER

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ABSTRACT

Immune surveillance is a process of containing the multiplication of rapidly spreading tumor cells, causing the immune system to function improperly. Immunotherapy uses the immune system as a means of fighting cancer. Checkpoint inhibitors have shown great ability to fight cancer. These inhibitors work by modifying the tumor environment and preventing cancer cells from escaping the immune system. The aim of this paper is to highlight the therapeutic potential of PD-1 and PDL-1 inhibitors in lung cancer. The method used for this research was the qualitative exploratory, with the purpose of bringing the population's knowledge about immunotherapy for the treatment of metastatic non-small cell lung cancer in smokers. Given the above, direct or indirect contact with tobacco derivatives makes the likelihood of lung cancer possible, showing that the greater the degree of mutations expressed by the cell, the greater the chance of developing PD-L1 overexpression. Consequently, treatment will work more effectively. Given the questions presented, it was concluded that PD-1 / PD-L1 inhibitor therapy is a restricted and individualized treatment.

INTRODUCTION

Cancer is a set of multifactors that alter cellular metabolism, generating mutations in the genome[1]. When there is a change in these genes, the cell multiplies quickly and in a disorderly manner[2]. Lung cancer is associated with 30% of cancer deaths[3]. The second most common among men and women, with an incidence of 13% in relation to other types of cancer[4]. Tobacco use is related to the triggering factor of several diseases, among them, 90% is related to lung cancer[5,6]. Lung cancer can be classified histologically, according to the World Health Organization, into non-small cell lung cancer (CPNPC) and small cell lung cancer (CPCP). The two classes express different mechanisms, so they are treated differently[17]. The immune system is of paramount importance for the individual's homeostasis. It is able to regulate and prevent disorders resulting from gene mutations[7]. Immune surveillance consists of three correlated phases. The elimination, equilibrium, and escape phases. In this last phase, successive mutations in cancer cells occur, in an attempt to not be recognized by the immune system[6].

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In this stage, disorderly growth of the tumor occurs and mechanisms are developed by the mutant cells to escape and prevent the action of the immune system. As, for example, immune suppression induced by the tumor, in which defective cells release factors that inhibit T lymphocytes, preventing their effective action[7,8]. Thus, when the TCD8 cells recognize the antigens, they are elevated and the tumor cell's degradation process begins, as a defense mechanism the cancer cell fails to express the characteristic antigen recognized by the immune system, or else it starts to produce cytokines capable of suppressing the functioning of the immune system, or inhibitors capable of inactivating the TCD8 cell, such as PDL-1[8]. Although the body has the immune capacity to fight tumor cells, these cells have the ability to express inhibitors, such as PDL-1, which are able to inactivate the functioning of the TCD8 cell through its ligands, such as PD-1[9]. The checkpoint inhibitors that have been developed have shown great ability to fight cancer[10]. These inhibitors act by modifying the tumor environment and preventing cancer cells from escaping the immune system, thus preventing their proliferation[10,11]. Immunotherapy uses the immune system as a means of fighting cancer, with the administration of antibodies that stimulate the immune response, thus transforming it into a treatment with a specific specificity and also creating immunological memory[11].

The purpose of this study was to explore an alternative therapy for the treatment of non-small cell lung cancer, providing the patient with a possibility of survival and reduction of suffering regarding the most commonly used treatments. Thus, the choice of the theme proposed in the article comes from the observation that the emergence of new techniques has contributed to attest to the increased survival of patients affected with lung cancer, depending also on the patient's stage and characteristics particular to the individual's system. This research is also relevant, as immunotherapy has been shown to be very effective and to know it in more detail, allows for academic and professional enrichment. This work is justified in the evidence of the therapeutic potential of PD-1 and PDL-1 inhibitors in non-small cell metastatic lung cancer in smokers. In comparing the smoking and non-smoking public with the development of lung cancer, in elucidating the mechanisms of PD-1 and PDL-1 in lung cancer and addressing the effectiveness of the treatment of PD-1 and PD-L1 inhibitors with degree of tumor immunogenicity.

METHODOLOGY

The method used to carry out this research was the qualitative exploratory, with the purpose of bringing the population's knowledge about immunotherapy for the treatment of non-small cell metastatic lung cancer in smokers. In order to obtain the necessary data for the study, bibliographic research was carried out to evaluate the effectiveness of the combined use or not of this therapeutic alternative. The data were collected between the specific interval from 2009 to 2019. The bibliographic survey was carried out by searching national and international scientific publications, using the systems: Scielo (Scientific Electronic Library Online); Medline (International Health Sciences Literature Database); books and other sources like academic Google. The following keywords were used to collect the articles: Lung cancer, PD1 and PDL1 expression pathways and smoking. The inclusion and exclusion criteria were respectively: Articles published in the last 10 years, publications in international scientific journals. In contrast, the exclusions were articles with a year prior to 2009. The criteria for authorial citation were respected to exclude any possibility of plagiarism.

RESULTS AND DISCUSSION

Exposure to carcinogens, such as tobacco derivatives, enables the appearance of mutations and, consequently, the appearance of tumors. Tobacco has dozens of carcinogenic substances in its composition and this contributes to the increased likelihood of developing lung cancer. The type of exposure, whether direct or indirect, may or may not define the appearance of the pathology, as compared in Table 1.

Table 1 - Distribution of lung cancer cases, in hospitals in Curitiba, according to the smoking variable

Category	Number of Cases	%
Smokers	155	59%
Ex-Smokers	79	30%
Non smokers	29	11%
Total	263	100%

Source: Lustosa et al, 2015.

The formation of cancer, properly speaking, is a slow process that needs, in almost its totality, a cumulative exposure to a carcinogenic source[12]. Tobacco and tobacco products have been used for decades. This use has brought a series of consequences that are related to the development of several pathologies, among them, 90% are related to lung cancer[13,14]. Among the compounds present in the composition of tobacco and its derivatives, approximately 4,700 are considered toxic and about 50 are identified as carcinogenic substances[12]. According to the National Cancer Institute (INCA 2019), 85% of lung cancer cases are directly or indirectly linked to tobacco use. Its use is associated with one of the main causes of preventable death in the world[15]. The smoke released by cigarettes contains several toxic substances that can be divided into two phases: particulate and gaseous. The gas phase involves compounds such as carbon monoxide, ammonia, ketones, formaldehyde, acetaldehyde, acrolein. The so-called particulate phase is composed of nicotine[16]. The cigarette end releases smoke three times more concentrated in nicotine and carbon monoxide, and up to 50 times more carcinogenic compounds than the smoke inhaled by the smoker himself[16]. Tobacco use significantly increases the likelihood of lung cancer. The substances contained in its composition are capable of modifying, at the level of DNA, the synthesis of proteins in cells. This modification often occurs irreversibly, leading to cell mutation and the appearance of cancer cells[13].
The development of lung cancer in ex-smokers can manifest itself about 10 to 15 years after smoking cessation. This condition can be hypothetically associated, due to the irreversible damage caused by exposure to tobacco. The likelihood of developing lung cancer in ex-smokers is proportional to the time of exposure. The longer the exposure time, the greater the chance of developing cancer[14]. Most of the patients affected by lung cancer are ex-smokers and others never smoked. They are affected by the fact of secondhand smoke and radiation exposure, even in the thoracic region, also by exposure to chemical compounds considered to be carcinogenic, air pollution and diesel engine exhaust. Thus, being a smoker, the risk increases even more of the development of cancer[17]. For treatment efficacy based on PD-1 and PD-L1 inhibitors, the tumor cell needs to manifest specific characteristics, including the degree of immunogenicity. Since it is an essential factor in identifying the type of cancer that best suits the treatment. As discussed in table 2:

Table 2. Degree of Immunogenicity

Type of cancer	Somatic mutations by mega dna base
Melanoma; Renal cell carcinoma; NSCLC	5 a 10 Mb
Pancreas; prostate	0,1 a 1 Mb

Source: Elaborated by the author, 2019. Adapted from Pedro Silvares, 2017.

Normal and tumor cells can express proteins related to the immune response with similar structural characteristics. These apparently identical proteins are expressed in different ways. In cancer cells, this expression is exacerbated[7]. The hyperexpression of these proteins provides a potential for T cell recognition and activation on these peptides [18]. The interaction that occurs between the T cell receptor and the ligand present in these anomalous cells can generate mechanisms of immunological inhibition, as expressed in the

PD-1 / PDL-1 pathway. The relationship between these two complexes results in the possible suppression of the tumor on the immune system[8,18]. The therapy related to the checkpoint block is seen individually. Since, the tumor has several mechanisms to suppress the immune system and behaves differently in each organism[19,20]. The great challenge is to identify specific biomarkers present in cancer cells and select patients who are more likely to benefit from this type of treatment, avoiding ineffective exposures and directing treatment in an assertive manner[19]. Although anti PD-1 and PD-L1 therapy is effective, it is not effective on all types of cancer. Patients can be classified according to the degree of sensitivity to treatment, varying between sensitive, primary resistant or acquired resistant. The sensitive ones are the ones that obtain the stabilization of the tumor. Primers have no benefit whatsoever when using the treatment. And those acquired in one moment obtained results, but in a certain moment the disease started to progress[21]. Mechanisms that, presumably, may be involved in the resistance of anti PD-1 / PD-L1 therapy can be highlighted: the presentation of the tumor cell and the increase of effector T lymphocytes, the activity and effectiveness of tumor-specific immune responses, the interaction of tumor cell and PD-L1 by tumor-specific T lymphocytes, the degree of immunogenicity and the induction of immunological memory [21].

Among the mechanisms that are possibly related to the ineffectiveness of immunotherapy, we can highlight the degree of immunogenicity, which are quantified through a test that aims to target possible patients who will benefit from treatment. This test aims to quantify the mutational tumor load. The higher the degree of immunogenicity, the greater the effectiveness of the treatment, and the lower the degree of immunogenicity, the lower the expression of PD-1 in the tumor cell and, consequently, the less effective the treatment will be [21,22]. The expression of ligands such as PD-1 and PD-L1 in tumor cells prevents the recognition of the same by the immune system. However, there has been an advance in research aimed at inhibitors of these ligands, becoming a viable alternative for the treatment of metastatic lung cancer. PD-1 or programmed death protein belongs to the group of cell surface molecules. It has 288 amino acids in its composition and has a ligand PD-L1 (B7-H1, CD274) that is associated with the homeostatic functionality of the T cell. In contrast, it has routes that block the functionality of these cells, compromising the antitumor and antiviral response [23, 24]. Specifically, the PD-L1 ligand emits negative signs of inhibition. It binds to its receptor (PD-1), present in activated T cells, in order to suppress the immune response and stimulate the exhaustion of T cells or induce its apoptosis, via modulation of the cell-tumor-immune cell interaction, causing the immune system to malfunction and promote tumor evasion [25, 20]. Through the identification and knowledge of the PD-1 and PD-L1 pathways, new treatment approaches aiming at modulating the tumor microenvironment, blocking the checkpoint are being developed and applied in several types of cancer such as: metastatic melanoma, cancer non-small cell lung cancer (NSCLC), renal cell carcinoma (RCCs) and bladder or urothelial cancer [20]. The new class of drugs is intended to inhibit the PD-1 / PD-L1 pathway, thus modulating the tumor microenvironment. Blocking the interaction between ligand and receptor proves to be very effective in redefining the functioning of T cells and, thus, making it return to develop its normal functions [20].

The class of drugs used for the treatment of immunotherapy are defined as monoclonal antibodies, antibodies produced in laboratories, which target the blocking of cancer cells or T lymphocytes. For CPNPC there are some drugs available, among them Nivolumab and Durvalumabe, examples of PD-1 and PD-L1 inhibitors, respectively[17]. Nivolumab is a human monoclonal antibody, whose mechanism is the inhibition of PD-1 present in the T cell with the ligands expressed in the cancer cell PD-L1 and PD-L2, enabling the recognition of the tumor cell by the immune system[26]. Durvalumab is completely human and has the mechanism of inhibiting PD-L1 in cancer cells by blocking its interaction with PD-1 present in T cells, increasing the immune system's response against the tumor [17, 27].

FINAL CONSIDERATIONS

According to the aspects presented in this work, it was possible to conclude that compared the number of lung cancer cases expressed by smokers and non-smokers, the direct or indirect contact with tobacco derivatives, makes the probability of the development of lung cancer viable. In this sense, the non-exposure to these agents allows a lesser chance in the development of the pathology. The degree of immunogenicity is directly proportional to the expression of PD-L1 ligands in cancer cells. The greater the degree of mutations expressed by the cell, the greater the probability that it will develop mechanisms, such as the over expression of PD-L1, and thus inhibit the immune response. Such factors presented are decisive for the choice of immunotherapy. The markers being over expressed, there is a more effective treatment response.

In view of the questions presented, it was possible to conclude that PD-1 / PD-L1 inhibitor therapy is a restricted and individualized treatment. In order to have the expected effect, the patient must have specific characteristics such as the expression of these ligands. To be successful in the treatment outcome, the personal response of each organism must be evaluated.

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