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Immunotherapy of head and neck squamouscell carcinoma (HNSCC). Immune checkpoint blockade

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ABSTRACT: Treating patients with squamous cell carcinoma of the head and neck is a significant problem. There is an increase in the incidence of malignant neoplasms in this region. Surgery, radiotherapy and chemotherapy are often not sufficient methods of treatment. Thorough analysis of processes occurring in the tumor microenvironment has allowed to distinguish three stages that make up the reaction of the human body to hostile antigens, which are tumor antigens. Understanding these mechanisms has resulted in the introduction of a new term immune-oncology. It is an area of cancer treatment that focuses on use of the patient's immune system to combat the disease. Immunotherapy has had positive effects in cancer patients. The use of immune checkpoint inhibitors, such as anti-CTLA-4 and PD-1 monoclonal antibodies has enabled the modulation of T cell functions, consequently eliminating immunosuppression in the tumor microenvironment. Clinical trials were conducted using nivolumab and ipilimumab, which confirmed their clinical usefulness. The approval by FDA of nivolumab in treatment of recurrent and metastatic squamous cell carcinoma of the head and neck has increased the overall survival time of patients as well as disease free survival. Statistical data indicate an advantage of immunotherapy over other treatment methods at an advanced stage of cancer. This work aims to discuss basic issues related to immunotherapy, in particular immunotherapy in patients with squamous cell carcinoma of the head and neck.

KEYWORDS: squamous cell carcinoma of the head and neck, immunotherapy, CTLA-4, PD-1, nivolumab, ipilimumab

INTRODUCTION

Head and neck cancers are ranked sixth in terms of prevalence. Around 600,000 new illnesses are observed in the world annually [1]. About 90% of head and neck cancers are squamous cell carcinomas [2]. The most common causative factors are alcohol consumption and smoking tobacco products. Over recent years, a significant increase in the incidence of squamous cell carcinoma of the head and neck has been observed in young people, before 45 years of age, which results from infection with oncogenic human papillomavirus, HPV [3].

Therapeutic approach to patients with squamous cell carcinoma of the head and neck depends on disease location and severity. Usually in stage III and IV the treatment of choice is surgical resection, radiotherapy or chemotherapy or a combination of these three methods [4]. An aggressive approach in 15–50% of head and neck cancers did not prevent cancer recurrence, and distant metastases are observed in 4–26% cases [5, 6]. Appearance of foreign antigens in the body, including tumor antigens, activates the immune system and an attempt of their elimination.

Unfortunately, the immune system is often ineffective in fighting the disease, which has led to many clinical trials expanding knowledge in this field. As a consequence, a new field of science called immune-oncology has been distinguished.

IMMUNO-ONCOLOGY

The main aim of immune-oncology is to use the immune system to suppress the cancer process. The human immune system has two types of immune response: humoral and cellular.

The first is responsible for the production of antibodies after antigen recognition with Th lymphocytes (T helper cells), which, by generating cytokines after identifying the antigen–antibody complex, activate B cells for further proliferation. The second mechanism is based upon direct reaction of the T-lymphocyte cell with the antigen, which stimulates the production of cytokines responsible for, i.a., stimulating macrophages [7]. In response to uncontrolled spreading, the patient's immune system activates both processes. Cancer cells have the ability to "mask", which results from the reduction of antigen expression on their surface and production of proteins that reduce immune system activity. In addition, substances that cause increased, uncontrolled spreading are present in the tumor microenvironment [8]. As a consequence, active and passive cancer immunotherapy was distinguished. Active immunotherapy consists in direct influence on the patient's immune system, which is to increase its activity. Passive immunity is based on direct influence on the tumor [9].

Stimulation of the defense system has been made possible by strengthening the function of immune cells with cytokines, immunomodulators, the use of cancer vaccines and by modulating T lymphocyte activity.

An example of a protein responsible for the regulation of leukocyte activity is interferon alpha (a cytokine classed as a glycoprotein). Interferon alpha has been registered for the treatment of hairy cell leukemia, Philadelphia chromosome-positive chronic myelogenous leukemia, cutaneous T cell lymphoma, follicular type non-Hodgkin's lymphoma, advanced stage of kidney cancer and in patients with stage II AJCC melanoma (American Joint Committee on Cancer) [10]. Immunostimulants increase cytokine activation. This includes, among others, BCG (Bacillus Calmette-Guerin) used in complementary treatment of patients with bladder cancer [12].

In contrast to non-specific cytokine activity, cancer vaccines stimulate specific T-lymphocytes. A distinction is drawn between prophylactic and therapeutic preparations. The former prevent the occurrence of a harmful factor that can contribute to development of cancer. An example is the HPV vaccine, which effectively reduces the incidence of cervical cancer [13]. The therapeutic nature of vaccines is confirmed by a phase III clinical trial performed on Sipuleucel-T registered by the Food and Drug Administration, FDA for treatment of prostate cancer [14].

IMMUNOLOGICAL CHECKPOINT BLOCKERS

Special attention should be drawn to the type of active immunotherapy consisting in modification of the function of T-lymphocytes. It is important to firstly explain the weakening immune response to cancer cells. The theory of "escape" from immune surveillance proceeds in three stages: elimination, balance and escape.

From the onset of cancer, first there is increased activity of the defense system. Antigen – presenting cells; APC stimulate naive T lymphocytes. The emergence of effector T lymphocytes (e.g., cytotoxic T lymphocytes) follows without co-inhibitory signals, which leads to a quick phase of elimination. This process is additionally supported by cytotoxic natural killer cells which produce a series of cytokines. However, as the cancer process develops, the immune system breaks down. The equilibrium phase shall then begin.

Cytokines and molecules with immunosuppressive activity are continuously produced in the tumor microenvironment. Thanks to this, cancer cells avoid elimination through rapid multiplication, masking of antigens and production of factors inhibiting complement activation in the escape phase [15].

Knowing this mechanism, the key goal has been to reverse immunosuppression. Antibodies against the inhibitory activity of selected leukocytes (immune checkpoint blockers) were used. Treatment of tumors with immune checkpoint blockers consists in strengthening the immune system so that it recognizes and eliminates tumor cells, inducing an anti-cancer immune response, and multiplying effector cells [16, 17, 18].

CTLA – 4

Special attention should be given to the anti-cytotoxic T lymphocyte antigen-4 antibodies (cytotoxic T lymphocyte - associated antigen 4; anti-CTLA-4; ipilimumab, pembrolizumab). CTLA-4 has an inhibitory effect on the immune system (early cellular response). As a transmembrane protein, it competes with the CD28 costimulatory molecule for affinity for CD80/CD86 ligands located on antigen-presenting cells. Combination of a costimulant with the B7 ligand family (CD80CD86) induces T-lymphocyte activation. On the other hand, CTLA-4 binding (has a higher affinity for CD80/CD86) with APC cells contributes to inhibition of lymphocyte function [19]. The discovery of anti-CTLA-4 (ipilimumab, tremelimumab) has shed a new look at cancer immunotherapy.

Ipilimumab has been approved by the FDA for treatment of advanced melanoma (inoperable or metastatic) due to the results of many clinical trials [20]. It has been proven that the use of a monoclonal antibody in melanoma patients increases the ove-

Tab. I. Selected clinical studies in head and neck squamous cell carcinoma using pembrolizumab.

NCT NUMBER	NUMBER OF PATIENTS	RESEARCH STAGE	TREATMENT	RECEPTOR
NCT03245489	20	I	Pembrolizumab + Klopidogrel + ASA	PD-1
NCT02718820	22	I	Pembrolizumab + Docetaxel	PD-1
NCT02586207	39	I	Pembrolizumab + Cisplatyna + RT	PD-1
NCT02769520	45	II	Pembrolizumab	PD-1
NCT03246685	87	II	Pembrolizumab + Imprime PGG	PD-1
NCT02841748	100	II	Pembrolizumab	PD-1
NCT03082534	83	II	Pembrolizumab + Cetuximab	PD-1
NCT03057613	37	II	Pembrolizumab + IMRT	PD-1
NCT02892201	24	II	Pembrolizumab	PD-1
NCT02718820	22	I/II	Pembrolizumab + Docetaxel	PD-1
NCT02289209	48	II	Pembrolizumab + Reirradiation	PD-1
NCT02609503	29	II	Pembrolizumab + IMRT	PD-1
NCT03085719	26	II	Pembrolizumab + RT	PD-1

RT – radiotherapy; IMRT – intensity-modulated radiation therapy; ASA – acetylsalicylic acid

rall survival time. Studies have also been carried out with the use of Ipilimumab in patients with lung cancer. The results, however, were not as spectacular as in the case of melanoma [21].

PD-1

The PD-1 molecule is a transmembrane protein that, unlike CTLA-4, is involved in inhibition of the delayed immune response. Its ligands are PDL-1 and PDL-2; their combination on an APC cell with a T-lymphocyte causes disruption of effector functions, and thus it causes defense mechanism to slow down [22]. These molecules significantly impact processes occurring in the tumor microenvironment. They may occur on both tumor cells and on cells involved in the immune response. PDL-1 expression within malignant tissue may correlate with the survival of patients. This is not always directly proportional. Increase in PDL-1 expression was found in cervical cancer. These patients' prognosis was much better. This fact constitutes unquestionable proof to the need to assess PDL-1 depending on tumor location and histopathological type [23].

It is also important to correlate PDL-1 expression and the amount of tumor infiltrating lymphocytes (TIL). In practice, this may result in an increased neoplastic infiltration mass and lower overall survival. This dependence is observed, among others, in head and neck cancer [24]. Significant improvement in the survival rate of head and neck cancer patients resulted was brought by the introduction of nivolumab - anti-PD-1 antibodies. Initial clinical study showed surprisingly good results in treatment of melanoma, lung cancer and kidney cancer.

The survival rate in patients undergoing immunotherapy was higher [25, 26]. Nivolumab has been approved by the Food and Drug Agency for treatment of melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin's lymphoma, urothelial carcinoma, colorectal cancer, and hepatocellular carcinoma as well as head and neck cancer [27].

IMMUNOTHERAPY IN HEAD AND NECK SQUAMOUS CELL CARCINOMA PATIENTS

In squamous cell cancer of the head and neck patients, PD-1 and CTLA-4 expression was correlated with tumor grade. The expression of receptors in the tumor microenvironment and patients' peripheral blood before was after surgical treatment was compared. Higher values of PD-1 and CTLA-4 were found in the tissue than in the blood, which means that T cells in the tumor were more influenced by inhibitory molecules [28].

In the case of well-differentiated squamous cell carcinoma in the larynx, the value of PD-1 and CTLA-4 expression was lower than in the high-grade cancer [29]. A similar relationship occurs in oral cavity, pharyngeal, and laryngeal cancer. PD-1 expression was not shown in normal nasopharyngeal tissue. In contrast, in patients with cancer, PD-1 expression was significant [30].

Association of HPV virus with PDL-1 was observed among tumors localized in the oral pharynx. High PDL-1 expression in HPV-positive cancer has become an additional positive prognostic factor [31].

Tab. II. Selected clinical studies in head and neck squamous cell carcinoma using nivolumab.

NCT NUMBER	NUMBER OF PATIENTS	RESEARCH STAGE	TREATMENT	RECEPTOR
NCT02764593	120	I	Nivolumab + Cisplatyna + Cetuximb + IMRT	PD-1
NCT03317327	20	I	Nivolumab + RT	PD-1
NCT03247712	18	I/II	Nivolumab + SR + RT	PD-1
NCT02684253	40	II	Nivolumab + SBRT	PD-1
NCT03341936	58	II	Nivolumab + Lirilumab	PD-1
NCT03544723	40	II	Nivolumab	PD-1
NCT03317327	20	I/II	Nivolumab + RT	PD-1
NCT03247712	18	I/II	Nivolumab + SR + RT	PD-1
NCT03349710	1046	III	Nivolumab + Cetuximab + Cisplatyna + Fluorouracyl	PD-1
NCT02741570	930	III	Nivolumab + Cetuximab + Cisplatyna + Karboplatyna + Fluorouracyl	PD-1

RT – radiotherapy; IMRT – intensity-modulated radiation therapy; SBRT – stereotactic body radiation therapy; SR – surgical resection.

Data from 2017 indicate that several dozen studies have been carried out over the past few years using immunological checkpoints in squamous cell carcinoma of the head and neck. The primary purpose of monoclonal antibodies has become PD-1, PDL-1 and CTLA-4. Results of four works conducted by Keynote-012 (phase Ib), Keynote-055 (phase II), CheckMate-141 (phase III) and NCT01693562 (phase II/III) were presented. It was shown that the response to treatment was on average 20% [32].

Patients with recurrent or metastatic head and neck squamous cell cancer who have not responded to treatment with platinum-based chemotherapy demonstrate an average survival of <6 months. A poor prognosis led to the performance of a Phase I Keynote-012 trial, which assessed the effect of pembrolizumab on the course of disease. One hundred ninety--two patients with histopathologically confirmed squamous cell carcinoma of the head and neck were qualified. The average age was 60 years. The cancer process was evaluated every 8 weeks using imaging examinations. After 24 weeks of taking pembrolizumab, the drug was discontinued in the event of remission. In the 12th month, the number of respondents was 38%. However, the average disease-free survival was 2 months [33].

CheckMate -141 evaluated the efficacy of nivolumab in patients with head and neck cancer. The study group consisted of patients with squamous cell carcinoma (in the oral cavity, pharynx and larynx) within 6 months of the end of the chemotherapy. The study comprised 361 people. The analysis pointed to an increase in survival time from 5.1 months (in the case of standard therapy) to 7.5 months (in patients undergoing immunotherapy) [34]. Thanks to the positive results, nivolumab was registered by the FDA for treatment of recurrent and metastatic squamous cell carcinoma of the head and neck.

There are numerous clinical studies checkpoint-blocking antibodies in patients with squamous cell carcinoma of the head and neck. Statistical data indicates a longer survival time and an increased quality of life. Selected studies with pembrolizumab and nivolumab are presented below [Tab. I; Tab. II].

SUMMARY

Despite the dissemination of knowledge about head and neck cancer, still 80% of patients at the moment of diagnosis present an advanced stage of the disease. Classic methods of oncological treatment such as surgery, radiotherapy and chemotherapy are in many cases insufficient. Increasing knowledge about immunological mechanisms during carcinogenesis has allowed for the introduction of new therapeutic standards. Immunotherapy based on the modification of immune checkpoints is a breakthrough in oncological therapy. There is evidence suggesting the efficacy of monoclonal antibodies in treatment of, i.a., advanced forms of non-small cell lung cancer (NSCLC), melanoma, Hodgkin's lymphoma and kidney cancer. Sue to a significant proportion of relapses, malignant neoplasms in the head and neck have also become the target of immunotherapy. High immunosuppression makes it beneficial to use immunotherapeutic treatment in the form of blocking checkpoints, among others, PD-1 (nivolumab, pembrolizumab). Therefore, it appears advisable to conduct further clinical trials. The acquired knowledge will serve to specify therapeutic methods that will improve treatment results in head and neck cancers in the future.

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