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Pembrolizumab as an immunotherapy drug in the treatment of a patient with recurrent (unresectable) cancer of the lower lip

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Advances in immunotherapy have changed approaches to the treatment of recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC). The US Food and Drug Administration (the FDA) has approved both pembrolizumab monotherapy for first-line treatment of the tumours expressing the programmed cell death receptor-1 (PD-L1; combined positive score of ≥ 1) in patients with R/M HNSCC and pembrolizumab administration in combination with platinum and fluorouracil regardless of the level of PD-L1 expression. Pembrolizumab is a humanized monoclonal antibody class drug that activates the anti-tumour immune response.

Objective — to present treatment outcomes for recurrent (unresectable) cancer of the lower lip that was treated using a pembrolizumab monotherapy regimen.

Patient H., born in 1968, received a 20-month combined therapy for cancer of the lower lip. He had radical surgical removal of the primary tumour and two surgical resections of metastases, as well as courses of both remote gamma-therapy and polychemotherapy. Nevertheless, the disease progressed from $T_2N_0M_0$ to $T_4N_1M_0$. In the area of the chin and right cheek, the patient developed a defect of the skin and subcutaneous tissue measuring 18×10 cm with purulent-necrotic margins and an external fistula of the oral cavity. He was also bothered by unbearable pain in the area of the tumour and an unpleasant odour from the mouth and from the tumour. The patient was prescribed immunotherapy with pembrolizumab since an immunohistochemical examination revealed an RD-L1-positive tumour. One year after the start of immunotherapy, which included 17 courses of cancer treatment, the wound healed and the patient's quality of life significantly improved. No adverse reactions were observed during immunotherapy. Computed tomography revealed a 25 x 15 mm nodule at the level of the lower jaw on the right and a lymph node of about 10 mm in diameter in the area of the lower parts of the right parotid salivary gland. Distant metastases were not detected. Currently, immunotherapy is ongoing. The issue of surgical removal of pathological formations is under consideration.

This case demonstrates the positive outcomes of a pembrolizumab monotherapy regimen in a patient with R/M HNSCC.

Keywords
recurrent and/or metastatic squamous cell cancer of the head and neck, immunotherapy, pembrolizumab.

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According to the International Agency for Research on Cancer (GLOBOCAN), which covers data on 36 cancer types from 185 countries, head and neck cancer is the seventh most common cancer in the world, accounting for 3 % of all cancers, with approximately 900,000 new cases and half a million deaths annually [6]. In 2018, new cases of lip and oral cavity cancer were registered in 354,864 patients, which accounted for 2.0 % of the 36 main cancer locations, and 177,384 (1.9 %) died from this disease [6]. The cumulative risk of lip and oral cancer and mortality from this disease from birth to 74 years is higher in men than in women: 0.66 vs. 0.26 and 0.32 vs. 0.14, respectively. Among all cancers occurring in the head and neck region, including the oral cavity, oropharynx, hypopharynx, and larynx, squamous cell carcinoma accounts for approximately 90 % [27].

The most frequent risk factors for head and neck cancer include tobacco use, excessive alcohol intake, and HPV infection [1].

Until recently, the two standard methods for treating HNSCC were primary surgery followed by adjuvant radiotherapy (RT) or chemoradiotherapy (CRT) and definitive CRT [26].

Conventional treatment results in recurrence and/or metastatic head and neck squamous cell carcinoma in more than 65 % of patients [1], with only one-third of patients responding to treatment and an average survival period of 6—8 months [19].

In recent years, the high potential of immunotherapy, which uses the immune system's own capacity, has been established. Normally, tumour cells are recognized and destroyed by the immune system, particularly by activated T cells. It has been proven that tumour cells can suppress T-cell activity using the immune checkpoint pathway PD-1 (programmed cell death 1) due to the expression of ligands PD-L1/2 (programmed cell death ligand 1/2). These ligands bind to PD-1 on T-cells, which leads to suppression of their proliferation and cytolytic activity and the induction of apoptosis. This contributes to the functional inactivation or exhaustion of T cells and, as a result, the suppression of the anti-tumour immune response and the immune system's failure to destroy tumour cells. Thus, increased PD-L1 protein expression allows cancer cells to evade the body's immune response. Instead, targeting the PD-1/PD-L1/2 pathway allows for the activation of anti-tumour immunity and better cancer treatment [2, 14, 20, 23, 28].

Thus, tumour immunotherapy is aimed not at the direct destruction of tumour cells, which is inevitably accompanied by a number of severe side effects, but at the elimination of tumour-induced immunosuppression, with the help of which it evades immune surveillance. This enables the human body to mount an effective immune response against the tumour, even if the neoplasia was initially immunoresistant.

In September 2014, the FDA approved pembrolizumab, the first immune checkpoint inhibitor targeting the PD-1/PD-L1 pathway, for the treatment of unresectable or metastatic melanoma with disease progression [17]. Pembrolizumab is a humanized monoclonal antibody that binds PD-1 receptors and blocks their interaction with PD-L1 and PD-L2, triggering an anti-tumour immune response [17].

The PD-1 inhibitors such as pembrolizumab and nivolumab were the first drugs to show a durable response and improved survival in patients with R/M HNSCC. Based on the findings of the study of the Ib KEYNOTE-012 phase in tumours with > 1 % PD-L1 expression, pembrolizumab was initially fast-tracked by the FDA in 2016 for the treatment of patients with R/M HNSCC and those who experience disease progression during or after platinum-containing chemotherapy. The study showed a sustained response to pembrolizumab (18 % response rate with a median overall survival of 8 months) [8, 25].

The Phase III study KEYNOTE-048 was soon conducted, in which 882 patients with R/M head and neck squamous cell carcinoma were randomly assigned to three groups in a ratio of 1 : 1:1. The first group received pembrolizumab, the second group received pembrolizumab with chemotherapy (5-fluorouracil and platinum drugs), and the third group received a standard treatment regimen using a triplet: cis- or carboplatin, 5-fluorouracil, and cetuximab (the regimen in the EXTREME study) [7].

Pembrolizumab monotherapy (hazard ratio (HR) — 0.78; 95 % CI: 0.64—0.96) and pembrolizumab administration in combination with chemotherapy (HR = 0.77; 95 % CI: 0.63—0.93) provided a statistically significant improvement in overall survival compared to the EXTREME regimen in patients whose tumours expressed PD-L1 (CPS ≥ 1). There were fewer grade 3—4 adverse events with pembrolizumab alone compared to the EXTREME regimen (17 % vs. 69 %) [7].

Based on the findings of KEYNOTE-048, the FDA approved both pembrolizumab monotherapy for first-line therapy for the tumours expressing the programmed cell death receptor-1 (PD-L1; combined positive score of ≥ 1) in patients with R/M HNSCC and pembrolizumab administration in combination with platinum and fluorouracil regardless of the level of PD-L1 expression [7]. Studies on the efficacy of pembrolizumab as first-line monotherapy in patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma are currently ongoing.

Objective — to present treatment outcomes for recurrent (unresectable) cancer of the lower lip that was treated using a pembrolizumab monotherapy regimen.

Patient H., born in 1968, was admitted to the oncology center in March, 2020 with complaints of a tumour in the area of the lower lip on the left and skin neoplasms on the left upper arm and in the left axillary area.

According to the patient, the lower lip tumour appeared at the end of 2019. The skin neoplasms on the left upper arm and in the left axillary area were noted in 1994 and 2010, respectively. He did not seek medical attention.

Objectively, on the mucous membrane of the lower lip, 0.1 cm from the commissure to the left, there was a tumour of an irregular shape, about 2.5 × 1.8 cm in size, a grey-pink colour, and in the form of an ulcer. Ulcer-like tumours creeping over the skin, grey-pink in colour, measuring 18 × 15 cm and 2.5 × 1.5 cm, respectively, were found on the left upper arm and the anterior chest wall. The skin around the tumours was not affected. Regional lymph nodes (LNs) were not enlarged.

A neck ultrasound revealed LN hyperplasia on both sides of the submandibular area.

Biopsy of neoplasms of the lower lip (20.03.2020) revealed squamous cell carcinoma of the lip, G1; biopsy of the skin of the shoulder on the left and the skin in the axillary area on the left revealed squamous cell non-keratinous skin cancer, G2.

On March 30, 2020, the patient underwent an operation: resection of the lower lip with Blokhin plastic surgery and excision of multiple skin tumours on the left upper arm, the anterior chest wall, and the left axillary area. Primary tension healed his wounds.

According to the pathohistological report (PHR) dated April 02, 2020, all tumours were removed within healthy tissues.

Upon discharge from the hospital, a diagnosis of primary multiple cancer was established: cancer of the lower lip of stage II $T_2N_0M_0$; $pT_2N_1M_0$; cl. gr. III; multiple skin cancers of stage II $RT_{3(3)}N_0M_0$; cl. gr. III on the left upper arm and the anterior chest wall, and in the left axillary area. The patient was under a surgeon-oncologist's surveillance.

Three months later (July 24, 2020), the patient complained about the presence of a tumour formation in the left submandibular area. During an ultrasound of the neck (July 24, 2020), a metastatic lesion of the regional LNs in the left submandibular area was suspected. A cytological examination (July 24, 2020) revealed cancer cells in the smears.

On August 5, 2020, the patient underwent suprascapular-hypoglossal lymph node dissection on the left side of the neck. According to the PHR, two of the seven LNs of the neck on the left were affected by carcinoma metastases.

In the postoperative period, from September 14, 2020 to October 9, 2020, the patient underwent a course of remote gamma-therapy for the area of the postoperative scar. The single irradiation dose (SID) was 2 Gy, and the total irradiation dose (TID) was 40 Gy.

On November 19, 2020, the patient was again admitted to the oncology center on account of the malformation in the submaxillary area on the right. Ultrasound: metastatic lesion of the submandibular LN on the right. Cytological conclusion: cancer cells. Diagnosis: cancer of the lower lip, stage II $T_2N_0M_0$, $pT_2N_0M_0$. Condition after combined treatment in 2020. Continuation of the disease: metastatic lesion of the submandibular LN on the right. Cl. grade IIa.

On November 26, 2020, an operation was performed: suprascapular-hypohyoid dissection of neck lymph nodes on the right. PHR: a squamous cell carcinoma metastasis with evidence of medical pathomorphosis was found in one of the eight LNs of the neck on the right, and reactive follicular hyperplasia was discovered in the other LNs.

From December 14, 2020 to December 30, 2020, a course of radiation therapy was administered to the area of the postoperative scar: SID — 2 Gy, TID — 20 Gy.

Despite the treatment, the disease progressed, and pain appeared in the area of the jaw and neck on the right. The physical and psychological domains of quality of life have significantly deteriorated. During the control ultrasound on April 20, 2021, metastases in the soft tissues of the neck to the right of the abscess were suspected. A spiral computed tomography of the neck and larynx was performed on April 23, 2021. A relapse of the disease was established. It was manifested by the presence of a pathological process in the soft submandibular tissues on the right, with spread to the muscular diaphragm of the oral cavity on the left, and signs of initial destructive changes in the lower jaw at the point of contact. Secondary (metastatic) changes were established in the LNs located in the parotid and middle jugular areas on the right. A trepan biopsy of the soft tissue masses in the neck on the right (May 5, 2021) showed squamous cell carcinoma, G1.

Diagnosis: cancer of the lower lip, stage II $T_2N_0M_0$, $pT_2N_0M_0$. Condition after combined treatment in 2020. Recurrence of the disease (2021); progression of the disease to $T_4N_1M_0$; cl. gr. II. tumour abscessation. Cancer intoxication.

The patient was prescribed palliative courses of polychemotherapy (PCT) according to the scheme: paclitaxel — 175 mg/m^2, cisplatin — 75 mg/m^2.

After three courses of PCT (paclitaxel, cisplatin; docetaxel, cisplatin), a certain stabilization of the process was noted, but in September 2021, the disintegration of the tumour began to intensify. From October 18, 2021 to October 28, 2021, two more PCT courses were administered according to the scheme, including cisplatin and gemcitabine. However, the tumour continued to disintegrate. The defect in the skin and subcutaneous tissue measured 18 × 10 cm and had purulent-necrotic margins. The patient presented with an external fistula of the oral

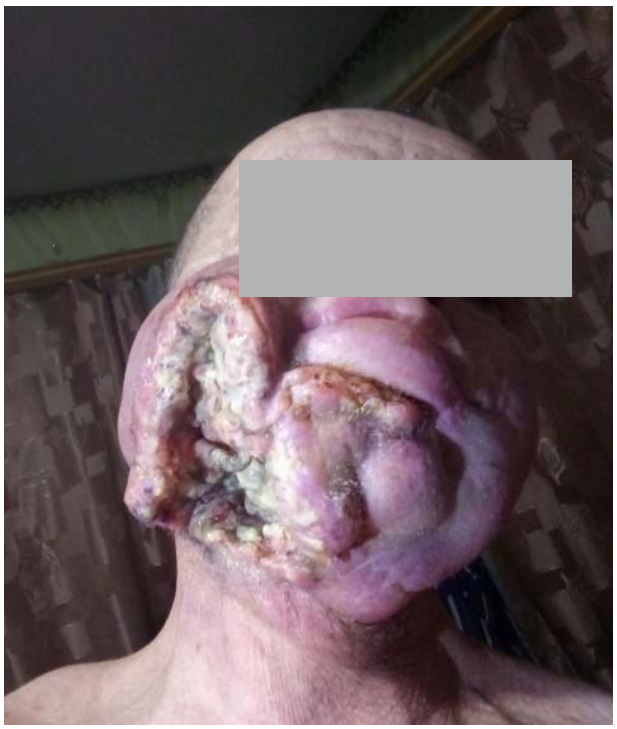

Figure 1. **The state of the site affected by squamous cell carcinoma of the lower lip before immunotherapy (pembrolizumab)**

cavity, through which saliva and food were secreted, and the patient was bothered by unbearable pain in the tumour area, bad breath, and a smell from the tumour (Fig. 1).

The poor outcomes of the combined cancer treatment urged us to resort to immunotherapy since, according to the data of the immunohistochemical study (November 23, 2021), the tumour was RD-L1 positive.

Immunotherapy was started on November 29, 2021. The patient received 17 courses of immunotherapy with pembrolizumab (single dose of 200 mg of pembrolizumab every 3 weeks). During treatment, pronounced positive dynamics were observed (reduced skin defect and tissue disintegration in the area of the left cheek). After the first course of treatment, the pain significantly decreased and disappeared completely after the second course. The quality of life improved significantly. After three courses, the external fistula of the oral cavity healed, and a small, irregularly shaped skin and subcutaneous tissue defect, measuring 2.5 × 2.2 cm and with active granulations, remained in the area of the lower jaw on the right. A year after the start of treatment with pembrolizumab, the skin defect was not observed (Fig. 2).

According to the neck and larynx CT scan (October 3, 2022), there were signs of the disease's continuation. At the level of the lower jaw on the right and in the area of the lower parts of the right parotid salivary gland, a nodular formation, measuring 25 × 15 mm, and LN, measuring about 10 mm in diameter, were determined on the basis of the pathological density and were unevenly enhanced. Lymph nodes of the neck at other scan levels were not enlarged. The larynx, soft tissues of the pharynx, and the root of the tongue were without visible areas of pathological enhancement. The vascular bundles of the neck had a normal course and diameter. The thyroid gland was not enlarged, and no inflammatory changes were determined. Distant metastases were not detected.

Immunotherapy with pembrolizumab was continued.

No adverse reactions were observed in the course of immunotherapy. Indicators of general and biochemical analysis of blood, urine, and thyroid function at all stages of immunotherapy were within the physiological norm.

Treatment of head and neck squamous cell carcinoma requires a multidisciplinary approach. Typically, patients with early-stage disease, defined as tumour stage T1—2 and nodal stage N0, are treated with surgery or radiation therapy as the only treatment options after diagnosis [21]. Radiation alone or concurrent chemotherapy and radiation are recommended for early-stage cancer when surgical resection is less appropriate or results in poor long-term functional or cosmetic outcomes [5].

A surgical approach was chosen for this patient. The tumour of the lower lip was excised within healthy tissues simultaneously with multiple skin tumours on the left upper arm, the anterior chest wall, and the left axillary area. As a rule, this approach in these conditions provides a good result, with cure rates of 70—90 %, but about a quarter of patients eventually require radiation and/or chemotherapy in the adjuvant setting [22].

The patient had a recurrence of lip cancer three months after surgery, although he did not belong to the high-risk group for recurrence according to the criteria defined in the EORTC 22931 and RTOG 9501 studies (positive surgical margins, two or more involved regional LNs, extranodal tumour spread, tumour T3 or T4, perineural or lymphovascular invasion, embolism of tumour vessels) [4, 12].

With a median survival of 7.4 months for patients treated with platinum-based chemotherapy and some patients becoming resistant to platinum and dying within 4 months, recurrent or metastatic HNSCC is a significant problem [16, 18, 23].

CRT was decided for the patient, which improves progression-free survival, locoregional control, and overall survival, according to EORTC 22931 and

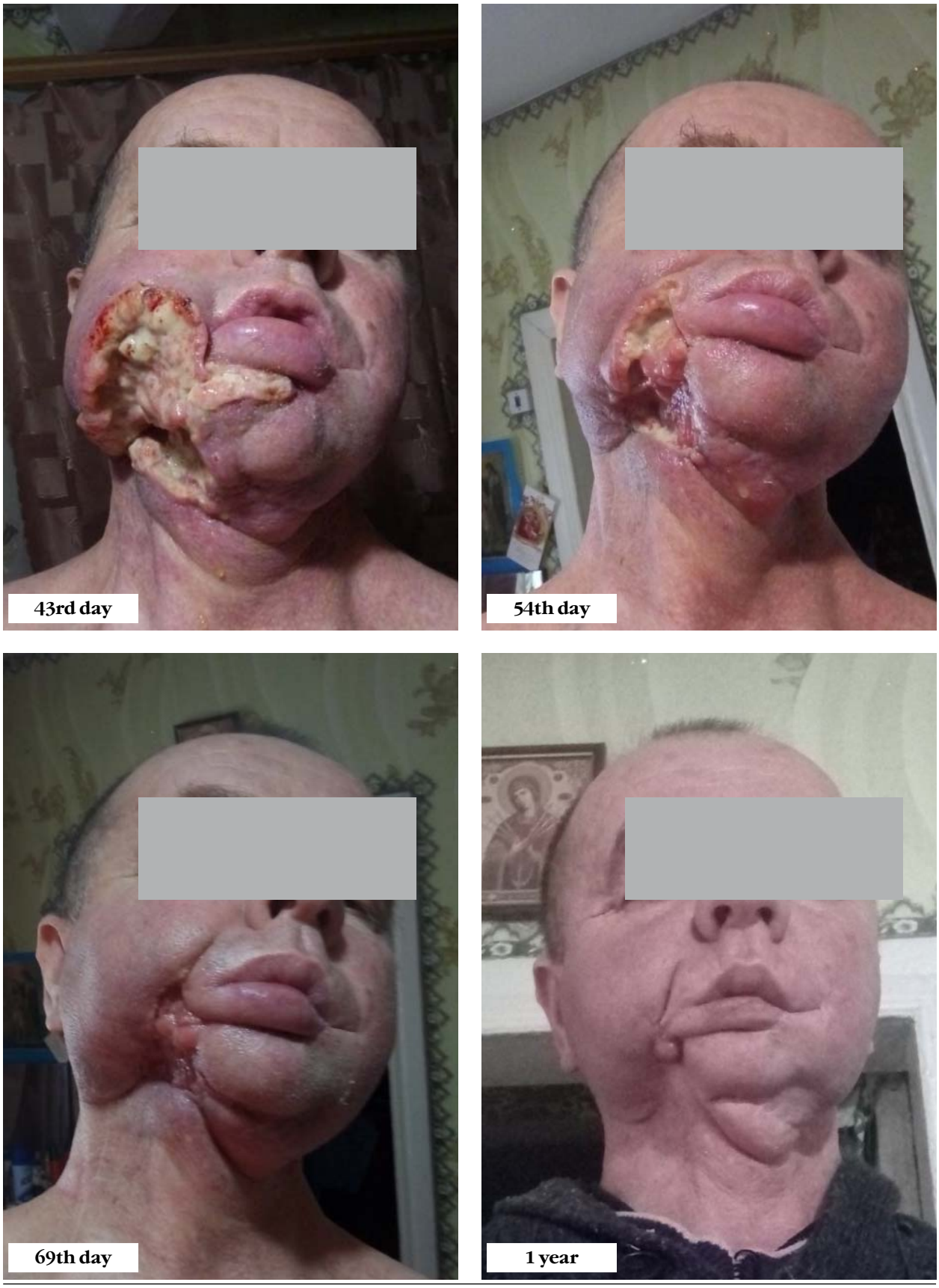

Figure 2. **The state of the site affected by squamous cell carcinoma of the lower lip during immunotherapy (pembrolizumab)**

RTOG 9501 studies [4, 12]. However, the patient's condition was worsening, and a year after the start of treatment, the disease progressed to $T_4N_1M_0$.

Advances in immunotherapy have led to a paradigm shift in the treatment of incurable R/M HNSCC. HNSCC tumour cells have high levels of PD-L expression (ranging from 50—60 % [11] to 85 % [23], depending on the assay method). The presence of an inhibitor of the PD-1 immune checkpoint, such as pembrolizumab, significantly increases the potential for treating patients.

In this patient, the standard treatment (surgical removal of the tumour followed by chemotherapy and radiotherapy) was ineffective. In view of this and after obtaining data on the expression of PD-L1 by the tumour, the patient was offered immunotherapy with a pembrolizumab monotherapy regimen according to the FDA's recommendations. 17 courses of pembrolizumab were conducted during the year. After the first courses of monotherapy, the patient had a significant improvement in quality of life due to the reduction and later disappearance of pain and tissue swelling, as well as the progressive reduction of the skin defect and healing of the external fistula of the oral cavity (after three courses). The positive effect of pembrolizumab on domains of quality of life in patients with R/M HNSCC was also noted in the KEYNOTE-040 study [10].

After a year of treatment with pembrolizumab, there was no skin defect. The CT scan revealed signs of the disease's continuation: a 25× 15 mm nodule at the level of the lower jaw on the right and a LN about 10 mm in diameter in the area of the lower parts of the right parotid salivary gland. No other regional neoplasms or distant metastases were found.

The impressive positive effect of immunotherapy with pembrolizumab in the patient is certainly related to the inhibition of the PD-1/PD-L1 pathway, but the influence of previous chemotherapy cannot be excluded. After all, chemotherapy disrupts the architecture of the tumour microenvironment, which can help overcome immune exclusion and cause antigen release [13].

Data from the literature show that moderate side effects are observed in 62—64 % of patients treated with pembrolizumab for R/M HNSCC: fatigue, decreased appetite, nausea, pruritus, rash, and hypothyroidism [3, 8, 25]. Side effects of 3—4 degree, including hyponatremia, increased levels of alanine aminotransferase and aspartate aminotransferase, atrial fibrillation, congestive heart failure, diarrhoea, and pneumonitis, were significantly less common in pembrolizumab monotherapy groups than in investigator-selected [9] groups or groups receiving pembrolizumab in combination with chemotherapy [7].

In our study, no adverse reactions were recorded during the course of immunotherapy. Indicators of general and biochemical analysis of blood, urine, and thyroid function at all stages of immunotherapy were within the physiological norm.

Pembrolizumab monotherapy significantly improved the patient's quality of life during the year of treatment. The analysis of questionnaires of patients enrolled in the KEYNOTE-040 study revealed a stabilization of quality-of-life indicators in patients who received pembrolizumab, while in those who received standard treatment (methotrexate, docetaxel, or cetuximab), they decreased [15].

Currently, the patient is being treated with pembrolizumab. The issue of surgical removal of malformations is under consideration.

This case demonstrates the positive outcomes of pembrolizumab immunotherapy in a patient with recurrent (unresectable) cancer of the lower lip.

Declaration of interests

The authors who participated in this study stated, that they had no conflict of interest regarding this manuscript.

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Ethics approval and written informed consents statements

The project has been reviewed and approved by the Committee on Human Rights Related to Research Involving Human Subjects of Regional Clinical Oncology Center of the Kirovohrad Regional Council. Patient gave his written informed consent prior to study inclusion.

Authors contributions

The authors have contributed equally to conception and design, acquisition and interpretation of data, drafting the article.

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Випадок лікування хворого з рецидивним (нерезектабельним) раком нижньої губи із застосуванням імунотерапії препаратом пембролізумаб

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Прогрес в імунотерапії спричинив зміну підходів до лікування рецидивного та/або метастатичного плоскоклітинного раку голови та шиї (Р/М ПРГШ). Нещодавно FAD схвалила пембролізумаб (препарат класу гуманізованих моноклональних антитіл, який активізує протипухлинну імунну відповідь) для першої лінії терапії Р/М ПРГШ у режимі монотерапії у разі експресії пухлиною рецептора програмованої смерті клітин-1 (PD-L1; за комбінованою позитивною шкалою ≥ 1) або в поєднанні з платиною і фторурацилом незалежно від рівня PD-L1-експресії.

Мета — представити результат лікування хворого з рецидивним (нерезектабельним) раком нижньої губи із застосуванням імунотерапії препаратом пембролізумаб у режимі монотерапії.

Хворий Г., 1968 року народження протягом 20 міс отримував комбіновану терапію раку нижньої губи (радикальне оперативне видалення пухлини і двічі — її метастазів, курси дистанційної гамма-терапії, курси поліхіміотерапії), але захворювання прогресувало від $T_2N_0M_0$ до $T_4N_1M_0$. У ділянці підборіддя і правої щоки утворився дефект шкіри та підшкірної клітковини розміром 18 × 10 см з гнійно-некротичними краями, виникла зовнішня нориця ротової порожнини, також хворого турбував нестерпний біль у ділянці пухлини, неприємний запах з рота та від пухлини. Хворому призначено імунотерапію препаратом пембролізумаб, оскільки, за даними імуногістохімічного дослідження, пухлина виявилася PD-L1-позитивною. Через рік (17 курсів) після початку імунотерапії рана загоїлася, а якість життя хворого суттєво поліпшилася. Під час імунотерапії не спостерігали будь-яких побічних реакцій. За даними комп'ютерної томографії, на рівні нижньої щелепи справа та в ділянці нижніх відділів правої привушної слинної залози визначалися відповідно вузлове утворення розміром 25 × 15 мм та лімфатичний вузол діаметром близько 10 мм. Віддалених метастазів не виявлено. Нині імунотерапія триває. Розглядається питання щодо хірургічного видалення патологічних утворень.

Описаний випадок наочно ілюструє сприятливий вплив пембролізумабу в режимі монотерапії у хворого з Р/М ПРГШ.

Ключові слова: рецидивний та/або метастатичний плоскоклітинний рак голови та шиї, імунотерапія, пембролізумаб.

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