PHOTODYNAMIC THERAPY TREATMENT OF ORAL CAVITY CANCER IN PATIENTS WITH COMORBIDITIES

Panaseykin Y.A.[1], Kapinus V.N.[1], Filonenko E.V.[2], Polkin V.V.[1], Sevrukov F.E.[1], Isaev P.A.[1], Ivanov S.A.[1,3], Kaprin A.D.[2,3,4]
[1]A. Tsyb Medical Radiological Research Center – branch of the National Medical Research Radiological Center of the Ministry of Health of the Russian Federation, Obninsk, Russia
[2]P. Hertsen Moscow Oncology Research Institute – branch of the National Medical Research Radiological Center of the Ministry of Health of the Russian Federation, Moscow, Russia
[3]Peoples Friendship University of Russia (RUDN University), Moscow, Russia
[4]National Medical Research Radiological Center of the Ministry of Health of the Russian Federation, Obninsk, Russia

Abstract

We report the experience of radical treatment by photodynamic therapy of patients with squamous cell carcinoma of oral cavity with serious side diseases. Completed treatment of two patients with serious side diseases (HIV infection with associated pulmonary hypertension of high degree and cardiac pathology) suffered from cancer of oral cavity. Extensive surgical treatment and/or aggressive course of chemoradiation therapy were not indicated to them due to concomitant pathology. Both patients were diagnosed with squamous cell carcinoma of oral cavity, with appropriate stage Ist. cT1N0M0. Patients received treatment by photodynamic therapy with chorine photosensitizer in dose 1.0 mg/kg. Options of photodynamic were: output power – 1.5W, power density – 0.31 W/cm^2, light dose – 300 J/cm^2. After one time session of photodynamic therapy, in both cases full response was diagnosed (according to RECIST 1.1). In one case the second session of photodynamic therapy was performed due to concomitant disease of oral cavity – multiply lesions of leukoplakia and after was diagnosed full remission of all lesions. Major adverse event was pain during the first 5-7 days after treatment, curable by painkillers. Follow-up (IQR) was 12 and 18 month respectively with no evidence of progression. It is available to avoid extensive surgical treatment and aggressive course of chemoradiation therapy (as an alternative) with the use of photodynamic therapy. Photodynamic therapy is minimally invasive method of radical treatment of localized squamous cell carcinoma of oral cavity with minimal adverse events, and could be especially relevant in patients with serious concomitant diseases.

Key words: oral cavity cancer, HIV infection, photodynamic therapy, leukoplakia.

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Contacts: Панасейкин Ю.А., e-mail: deus2@bk.ru

ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ ПРИ РАКЕ ПОЛОСТИ РТА У СОМАТИЧЕСКИ ОТЯГОЩЕННЫХ БОЛЬНЫХ

Ю.А. Панасейкин[1], В.Н. Капинус[1], Е.В. Филоненко[2], В.В. Полькин[1], Ф.Е. Севрюков[1], П.А. Исаев[1], С.А. Иванов[1,3], А.Д. Каприн[2,3,4]
[1]МРНЦ им. А.Ф. Цыба – филиал ФГБУ «НМИЦ радиологии» Минздрава России, Обнинск, Россия
[2]МНИОИ им. П.А. Герцена – филиал ФГБУ «НМИЦ радиологии» Минздрава России, Москва, Россия
[3]ФГАОУ ВО «Российский университет дружбы народов», Москва, Россия
[4]ФГБУ «НМИЦ радиологии» Минздрава России, Обнинск, Россия

Резюме

В настоящей работе продемонстрирован опыт радикального лечения соматически отягощенных пациентов с плоскоклеточным раком слизистой оболочки полости рта при помощи фотодинамической терапии. Проведено лечение двух соматически отягощенных пациентов (ВИЧ инфекция с ассоциированной легочной гипертензией высокой степени и выраженной кардиальной патологией), которым

было не показано выполнение обширных хирургических вмешательств и/или проведение агрессивной химиолучевой терапии в связи с наличием выраженной сопутствующей патологии. У обоих пациентов был диагностирован плоскоклеточный рак слизистой оболочки полости рта, распространенность опухолевого процесса соответствовала стадии I cT1N0M0. Пациентам была выполнена фотодинамическая терапия с фотосенсибилизатором хлоринового ряда в дозе 1,0 мг/кг. Параметры облучения: выходная мощность – 1,5 Вт, плотность мощности – 0,31 Вт/см^2, световая доза – 300 Дж/см^2. После одного курса фотодинамической терапии у обоих пациентов диагностирована полная резорбция первичного опухолевого очага (по RECIST 1.1), но в первом клиническом случае был проведен повторный курс фотодинамической терапии в связи с сочетанной патологией слизистой оболочки полости рта – множественными очагами лейкоплакии. В результате лечения так же была отмечена полная регрессия всех очагов лейкоплакии. Основным нежелательным явлением являлась боль в течение первых 5-7 дней после вмешательства, успешно купируемая ненаркотическими анальгетиками. Период наблюдения (IQR) пациентов составил 12 и 18 мес соответственно, без признаков рецидива и метастазов. Благодаря использованию методики фотодинамической терапии у пациентов удалось избежать проведения обширных хирургических вмешательств, а также отказаться от агрессивной схемы химиолучевой терапии, как альтернативы хирургической методике. Фотодинамическая терапия является малоинвазивной методикой радикального лечения локализованного плоскоклеточного рака полости рта с минимальным количеством осложнений, поэтому особенно актуальной эта методика является у пациентов с выраженной сопутствующей патологией.

Ключевые слова: рак полости рта, ВИЧ инфекция, фотодинамическая терапия, лейкоплакия.

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Контакты: Панасейкин Ю.А., e-mail: deus2@bk.ru

Introduction

According to international and Russian clinical guidelines, the main method of treating oral cancer is the surgical method. In the absence of contraindications, it is recommended to remove the primary lesion within intact tissues [1]. Based on the results of a routine morphological study and evaluation of prognostically unfavorable factors, such as extranodal spread of metastases in the lymph nodes of the neck (ENE +), positive (R1), or close margins (<5mm) of resection, primary tumor with a prevalence of pT3-4, metastases to regional lymph nodes pN2 -3, metastases in the IV and V locoregional groups, the presence of perineural, perivascular, perilymphatic invasion, the method of adjuvant treatment (radiation or chemoradiotherapy) is developed, or dynamic monitoring in their absence is carried out [2,3,4].

An alternative to the surgical technique is external beam radiation therapy (EBRT) or chemoradiotherapy (CRT) alone, with a total focal dose of up to 72 Gy in the area of the primary focus and up to 63 Gy in the area of subclinical distribution [5]. It is possible to use brachytherapy as an independent method of radical treatment of oral cancer using radionuclides Ir-192, CF-252, and others [6,7]. Chemotherapy and targeted therapy are used in combination and/or alone, mainly as a palliative technique in patients who are not indicated for other curative treatments. At the same time, highly toxic schemes with platinum preparations and immunotherapy with pd-L1 inhibitors are recommended in the first line [8,9,10].

Surgery is an invasive method of treatment with the possible development of various complications, up to lethal. At the same time, it is not always possible to conduct full-scale social and cosmetic rehabilitation, which reduces the quality of life. In addition, this type of treatment is not recommended in elderly and/or somatically burdened patients.

CRT, as an alternative to surgical treatment, is most effective with platinum drugs, leading to the development of adverse reactions such as nephrotoxicity, cardiotoxicity, polyneuropathy, hearing loss, and others. With chemoradiation therapy, for the eradication of a tumor of the oral cavity in an independent variant, delivery of the total doses exceeding the tolerance of the surrounding normal tissues is required, which, in turn, leads to the development of such complications as mucositis, osteomyelitis, hyposalivation, long-term non-healing ulcerative processes in the oral cavity and at the site of radiation delivery. Thus, the choice of treatment tactics in elderly and/or somatically burdened patients is a difficult task for an oncologist. Treatment of oral cancer should not only be radical, with a minimum number of complications but should also maintain the patient's quality of life at the "preoperative" level [11].

Photodynamic therapy (PDT) can be used as an independent, radical option for the treatment of malignant neoplasms of the oral cavity, corresponding to stage T1-T2 and with an invasion depth of up to 7 mm, in the absence of alternative methods of radical treatment, such as surgery, EBRT, and CRT. In a retrospective meta-analysis comparing the results of treatment of malignant neoplasms of the oral cavity (surgical method and PDT), the effectiveness was comparable, however, after PDT, there was a significant improvement in the quality of life compared with the surgical method [11].

In the analysis of 43 studies of the effectiveness of PDT in a total of 2121 patients with malignant neoplasms of the head and neck (mainly of the oral cavity), with T1-T2 prevalence, the best response was found in cancer of the

tongue. Complete regression was observed in 94.4% of cases, and 5-year survival was 84.2% [12]. PDT can also be used as a palliative treatment for locally advanced head and neck tumors when other local treatment methods (surgery, radiation therapy) have been exhausted [13,14]. During PDT, not only remote irradiation with laser light can be performed but also interstitial irradiation to reduce the volume of massive tumor foci [15]. In this case, it is possible to achieve remission and/or symptomatic improvement in the form of a decrease in pain, bleeding, and tumor decay. A multicenter study was conducted to evaluate the effectiveness of PDT as a palliative treatment for locally advanced unresectable head and neck cancer, which resulted in a clinical response in 53% of patients. Tumor size decreased by more than 50% in 28% of patients. Complete regression of neoplasms was noted in 17% of cases. The median survival in the study was 226 days, which is longer than after conventional chemotherapy. In addition, there were no significant side effects associated with PDT in patients [16]. The use of PDT does not exclude the possibility of simultaneous or sequential use of other treatment methods, such as surgery, chemoradiotherapy, chemo– and immunotherapy [12,16,17].

Clinical observation 1

Patient P., born in 1978, addressed to the A. Tsyb Medical Radiological Research Centre with complaints of an ulcerative defect in the mucosa of the alveolar bone of the lower jaw on the right (Fig. 1a).

Examination in the retromalar region on the right revealed a tumor with uneven, indistinct edges, ulceration, and bleeding on contact. Moreover, multiple diffuse foci of erosive-ulcerative leukoplakia were noted (Fig. 1b) with the formation of islet foci of stage 2 epitheliitis, moderately painful on contact. Regional lymph nodes were not enlarged.

Histological examination against the background of leukoplakia revealed invasive moderately differentiated squamous cell carcinoma.

Computed tomography revealed a rounded area of increased accumulation of a contrast agent near the angle of the lower jaw. The area was with fuzzy boundaries, with maximum visible dimensions of 10x8 mm, and an invasion depth of up to 4 mm. No destructive changes from the side of the adjacent part of the body of the lower jaw were observed. According to ultrasound data, no enlarged lymph nodes in the neck were found in the supraclavicular and subclavian areas.

The main diagnosis was cancer of the retromolar region on the right of stage I cT1N0M0. During the additional examination, the patient was diagnosed with severe comorbidity – HIV infection of stage 4A (against the background of antiretroviral therapy) and HIV-associated high pulmonary hypertension. Severe cardiac pathology was also diagnosed – chronic heart failure, circulatory disorders 2A, functional class 2 with preservation of the ejection fraction of 56%. Dilated cardiomyopathy was also revealed. The patient had a history of chronic viral hepa-

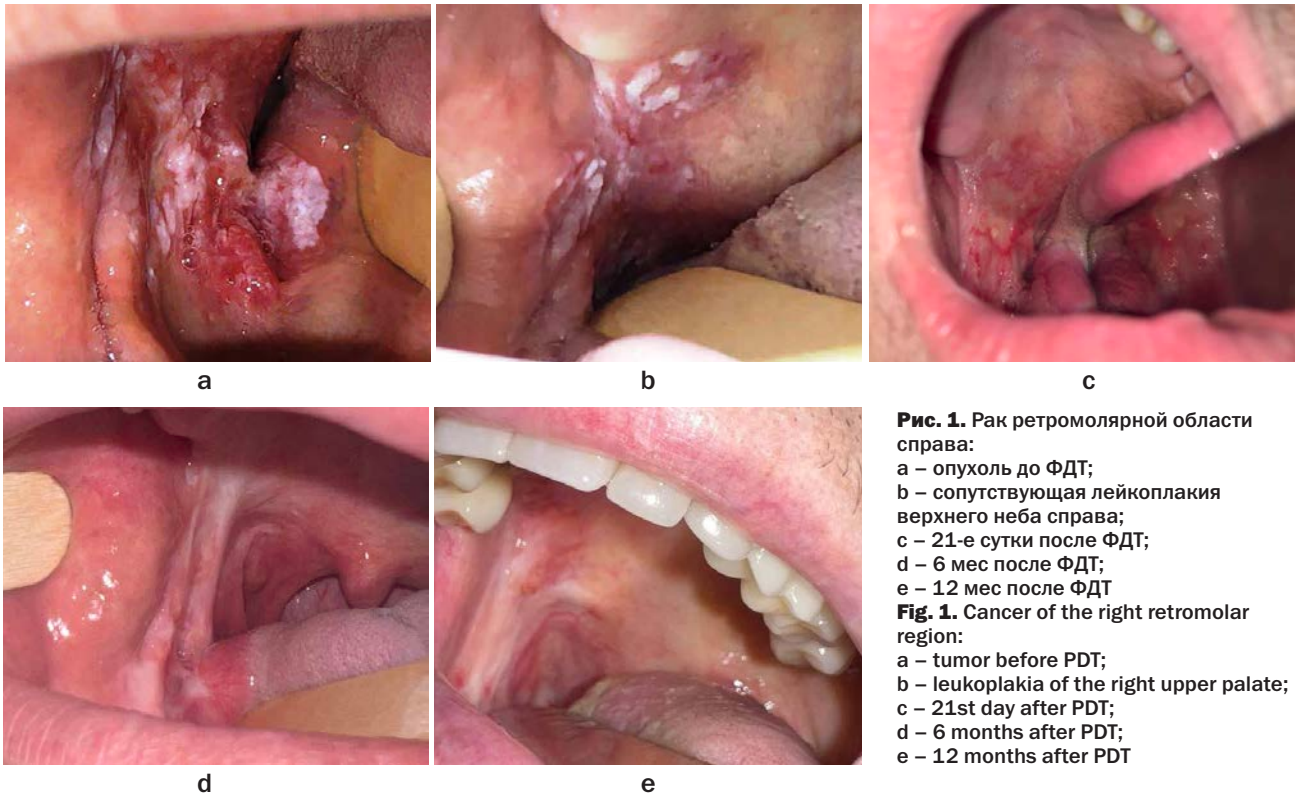

Рис. 1. Рак ретромолярной области справа:
a – опухоль до ФДТ;
b – сопутствующая лейкоплакия верхнего неба справа;
c – 21-е сутки после ФДТ;
d – 6 мес после ФДТ;
e – 12 мес после ФДТ
Fig. 1. Cancer of the right retromolar region:
a – tumor before PDT;
b – leukoplakia of the right upper palate;
c – 21st day after PDT;
d – 6 months after PDT;
e – 12 months after PDT

titis C without replication and chronic obstructive pulmonary disease of bronchitis type. From the endocrinological pathology, primary hypothyroidism in the subcompensation stage, metabolic syndrome, insulin resistance, and obesity of the 2nd degree were diagnosed. A varicose disease of the lower extremities of stage 2 was also present.

Thus, according to the P-POSSUM scale, the risk of lethal complications during surgery reached 40%.

An interdisciplinary consultation was held with the participation of surgeons, radiologists, chemotherapists, and specialists from the PDT department. Taking into account the long-term immunosuppression, multiple foci of leukoplakia, the presence of inflammatory changes in the oral mucosa, and high risks of complications when radical doses of radiation therapy are administered against the background of comorbidities, a decision of conducting an independent PDT course was made.

The patient underwent PDT with the photolon photosensitizer, administered intravenously at a dose of 1.0 mg/kg. For pain management, Ketorolac solution 1.0 ml IM, Promedol 2% 1.0 ml IM, and Relanium 0.5% 2.0 ml IM were used with additionally made local anesthesia with ropivacaine solution. Three hours after the introduction of the photosensitizer, PDT was performed with the laser light source – "Latus 2" (662 nm), remote irradiation of the neoplasm at a power density of 0.31 W/cm^2, the light energy density of 300 J/cm^2, with the number of fields – 1, and the procedure time of 16 min.

After PDT, initial signs of hemorrhagic necrosis, and edema were noted. By the 10th day, a hemorrhagic scab was formed in the form of a fibrin film. By the 14th day, marginal rejection of necrotic tissues, and by the 21st day, active epithelialization (Fig. 1c) occurred.

The patient was discharged from the hospital on the 3rd day after PDT.

Epithelialization of the wound defect occurred on an outpatient basis with drugs with anti-inflammatory and reparative properties. Complete healing with a good functional and cosmetic effect was noted after 8 weeks.

At the follow-up examination 6 months after the treatment, new foci of leukoplakia of small sizes up to 10 mm were diagnosed (Fig. 1d) and a second course of PDT was performed.

Currently (12 months from the start of the treatment), the patient is under dynamic observation without signs of disease progression (Fig. 1f) with a preserved somatic status (ECOG 0).

Clinical observation 2

Patient A., born in 1932, addressed to the A. Tsyb Medical Radiological Research Centre with complaints of a mass in the area of the buccal mucosa on the right.

During a clinical examination of the mucosa of the right cheek in the posterior sections, a tumor of an erosive-ulcerative nature of growth, with fuzzy, uneven edges, up to 1.2 cm in size, was determined (Fig. 2a). Regional lymph nodes were not enlarged.

A moderately differentiated nonkeratinizing squamous cell carcinoma was concluded from the histological examination. To clarify the prevalence of the process, and the presence of regional and distant metastasis, an instrumental examination was performed. According to MRI in the area of the buccal mucosa, a focus of increased accumulation of a contrast agent was identified, with fuzzy boundaries and maximum visible dimensions of 12x8 mm, with an invasion depth of up to 6 mm. Destructive changes from the side of the adjacent part of the body of the lower jaw were not observed. An ultrasound examination of the mucous membrane of the right cheek revealed a hypoechoic formation with a fuzzy, uneven contour, and an invasion depth of 4.7-5 mm. Enlarged lymph nodes in the neck, supraclavicular and infraclavicular areas were not detected.

The main diagnosis was cancer of the buccal mucosa of stage II cT2N0M0. The patient had several comorbidities. From cardiac pathology, the patient suffered from arterial hypertension stage II, risk 4, and coronary heart disease with atherosclerosis of the aorta, heart valves,

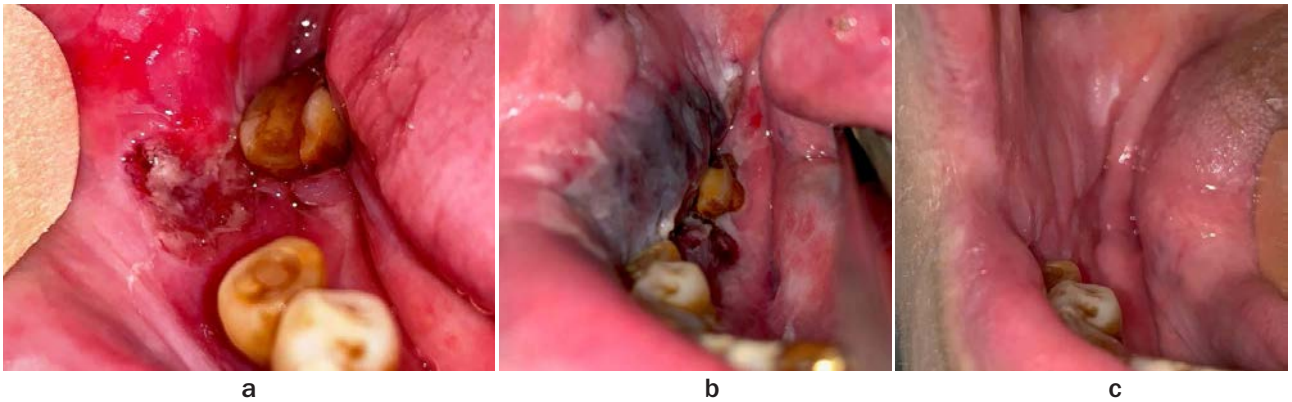

Рис. 2. Рак слизистой правой щеки: a – опухоль до ФДТ; b – 3-е сутки после ФДТ; c – 18 мес после ФДТ
Fig. 2. Cancer of the mucous membrane of the right cheek: a – tumor before PDT; b – 3st day after PDT; c – 18 months after PDT

coronary arteries, circulatory disorders 2A, chronic heart failure, with functional class 2, and preserved ejection fraction of 67%. In history, surgery for an abdominal aortic aneurysm was performed. Besides, chronic kidney disease, stage 4, with a glomerular filtration rate of 28 ml/min, and a varicose disease of the lower extremities 3 tbsp presented.

Taking into account the prevalence of the tumor process, severe comorbidity, age, and extent of the proposed surgical intervention, PDT was proposed as an alternative independent treatment at the inter-departmental consultation.

The patient underwent PDT with photolon administered intravenously at a dose of 1.0 mg/kg. Ketorolac solution 1.0 ml IM, Promedol 2% solution 1.0 ml IM, Relanium 0.5% 2.0 ml IM, and additional local anesthesia with ropivacaine solution were used to stop the pain syndrome.

PDT was carried out three hours after the injection with the laser light source – "Latus 2" (662 nm), remote irradiation of the neoplasm at a power density of 0.31 W/cm^2, the light energy density of 300 J/cm^2, with the number of fields – 1, and the procedure time of 16 min.

The patient was discharged from the hospital on the 3rd day after PDT. The signs of hemorrhagic necrosis and edema were noted locally (Fig. 2b).

At the follow-up period of 18 months, no signs of local recurrence and metastasis were detected (Fig. 2c).

Рис. 3. Сеанс ФДТ
Fig. 3. PDT treatment

Discussion

In the presented clinical examples, PDT was performed on patients from different age groups (43 and 89 years, respectively), in whom, according to the clinical and instrumental examination, the cN0 status of regional lymph nodes was confirmed and the depth of invasion of the primary focus was 4 and 6 mm, respectively. PDT was chosen as an alternative treatment option since surgical intervention or chemoradiotherapy was associated with the risk of developing severe complications due to the presence of severe comorbidities.

PDT was not accompanied by technical difficulties (Fig. 3). In both cases, one irradiation field was sufficient to cover the tumor lesion of the oral mucosa and areas of the potential subclinical lesion (0.5 cm from the visible boundaries of the tumor). In addition, it did not require a long stay in the hospital, the patients were discharged on the 3rd day after treatment.

Adverse events included pain (grade 1 CTCAE) and edema (grade 1 CTCAE), which were managed with nonsteroidal anti-inflammatory drugs and decongestant therapy.

Both patients were diagnosed with complete resorption of the primary tumor focus (according to RECIST 1.1) against the background of a single course of PDT. However, in the first clinical case, a second course of PDT was performed due to a combined pathology of the oral mucosa – multiple foci of leukoplakia. A complete regression of all foci of leukoplakia was noted. The follow-up period (IQR) of patients was 12 and 18 months, respectively, without signs of recurrence and metastases.

Conclusion

The presented clinical experience demonstrates the possibilities of PDT as a minimally invasive, effective method of radical treatment of T1-T2 cancer of the oral mucosa. PDT with chlorin-type photosensitizers may be an alternative treatment option for elderly and somatically burdened patients in whom major surgery and/or aggressive chemoradiotherapy are associated with the development of serious complications. This method is particularly relevant in the treatment of combined pathology of the oral mucosa, such as oncopathology and mucosal leukoplakia. However, for a comprehensive assessment of efficacy and adverse events and the development of indications and contraindications, an analysis of a larger number of patients is required.

In the case of malignant neoplasms of the oral cavity, at certain treatment stages, with both radical and palliative goals, it is possible to use such modern technology as PDT, which has a pronounced antitumor effect and, at the same time, is distinguished by the selectivity of tumor tissue damage, the absence of significant local and systemic side effects and the possibility of repeating courses.

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