MULTI-COURSE PHOTODYNAMIC THERAPY OF BASAL CELL SKIN CANCER OF THE CENTRAL FACE AREA (CLINICAL STUDY)

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Abstract

The results of an 11-year clinical observation and treatment of a patient with stage II basal cell carcinoma of the face (T2N0M0) are presented. History of the illness is associated with a long (from 2001 to 2008) inadequate treatment, due to the incorrect diagnosis. After the proper diagnosis was established, from 2008 to 2019 at the Center for Laser and Photodynamic Diagnostics and Tumor Therapy of P.A. Herzen Moscow Oncology Research Center, the patient underwent organ-preserving treatment using the multi-course photodynamic therapy (PDT) and drug targeted therapy. In total, 23 courses of PDT were conducted with photosensitizers of the chlorin series and 5-aminolevulinic acid during this period. Since 2018, the patient is in the process of targeted drug treatment with Vismodegib. In the course of targeted drug treatment, a follow-up examination in 2019 revealed continued growth of the residual tumor, and another course of PDT was carried out. Throughout the observation period, the patient tolerated the treatment well, without complications, with a good quality of life and satisfactory cosmetic effect.

Keywords: basal cell skin cancer, photodynamic therapy, photosensitizer, targeted therapy, vismodegib.

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МНОГОКУРСОВАЯ ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ ПРИ БАЗАЛЬНО-КЛЕТОЧНОМ РАКЕ КОЖИ ЦЕНТРАЛЬНОЙ ЗОНЫ ЛИЦА (КЛИНИЧЕСКОЕ НАБЛЮДЕНИЕ)

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Резюме

Приведены результаты 11-летнего клинического наблюдения и лечения пациентки с базальноклеточным раком кожи лица II стадии (T2N0M0). Анамнез течения заболевания связан с длительным (с 2001 по 2008 гг.) неадекватным лечением, вследствие отсутствия правильного диагноза. После установки диагноза, с 2008 по 2019 гг. в МНИОИ им. П.А. Герцена в Центре лазерной и фотодинамической диагностики и терапии опухолей пациентке проведено органосохраняющее лечение методом многокурсовой фотодинамической терапии (ФДТ) и лекарственной таргетной терапии. Проведено 23 курса ФДТ с фотосенсибилизаторами хлоринового ряда и 5-аминолевулиновой кислоты. С 2018 г. пациентка находится в процессе лекарственного лечения таргетной терапией висмодегибом. На фоне таргетного лекарственного лечения при контрольном осмотре в 2019 г. выявлен продолженный рост остаточной опухоли, проведен очередной курс ФДТ. Весь срок наблюдения пациентка переносила лечение хорошо, без осложнений с хорошим качеством жизни и удовлетворительным косметическим эффектом.

Ключевые слова: базальноклеточный рак кожи, фотодинамическая терапия, фотосенсибилизатор, таргетная терапия, висмодегиб.

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Basal cell carcinoma (BCC) is the most common skin cancer and the most common human malignancy [1]. The incidence of 2.75 million of cases diagnosed worldwide indicates its importance for public health care. Worldwide, upwards of 3.5 million of cases of non-melanoma skin cancer are diagnosed every year. BCC accounts for approximately 75% of these cases, that is not less than 2 million of new cases annually [2,3]. BCC occurs predominately in white people with 30% risk of development during lifetime [4]. The main principles of management of BCC include not only cure but also sparing of function with minimal cosmetic defect especially for tumors on face.

A photodynamic therapy (PDT) is reasonable for BCC with high risk of cosmetic defect following a surgical treatment or radiotherapy. PDT is a method of selective tumor destruction having the advantages of targeting destructive effect on tumor tissue comparing with other types of cancer treatment. Herewith, normal surrounding tissues are not affected offering multiple use of this method without compromising normal tissues and development of treatment resistance of the tumor, PDT has been widely used in the clinical practice for BCC since 1978 worldwide and since 1992 in Russia [5].

Another type of selective anticancer intervention for BCC is a targeted therapy. Vismodegib is an oral first-in-class inhibitor of Hedgehog pathway signaling. This is a small molecule which selectively inhibits a Smoothened (SMO) protein blocking a signal transfer into cell and prohibiting uncontrolled cell division [6]. The efficacy of Hedgehog pathway signaling inhibiting in the treatment of locally advanced and metastatic BCC of the skin was supported by phase II ERIVANCE international multicenter clinical trial. According to results of the trial, Vismodegib was approved by the US Food and Drug Administration (FDA) in 2012 and the European Medicines Agency (EMA) in 2013. In Russia vismodegib was registered in 26.09.2013 (LP-002252) and since that moment has been included into clinical practice of Russian oncologists for treatment of adults with metastatic and locally advanced BCC that has recurred after surgery or who are not candidates for surgery or radiation.

We present the case of long-term management in patient with extended BCC of the central area of the face.

Patient K, 11 y.o., noticed a wound-like skin lesion on the back of her nose in 2001. No self-treatment was performed. In 2002 because of non-healing wound she referred to a local dermatologist. Ointment applications were administered with no effect. In 2004 a laser ablation of the lesion was performed, but no healing or improvement was observed. For 5 years the patient referred to dermatologists in state and private clinics. Non-surgical treatment using various ointments with slight effect was performed. No morphological study was performed, the lesion continued to grow. In October, 2007 the patient was referred to the clinic of skin diseases in the medical university with continued growth of the lesion and new foci on the skin of the nose and adjacent parts of her cheeks. Neurotic excoriation and granuloma annulare were diagnosed; local therapy with Curiosin gel, NO-therapy, Longidaza 3000 ME, Actovegin gel, methyluracil ointment, 5% Xeroform ointment, Uriage gel was performed. There was a 50%–55% regression of lesions. In December, 2007 due to continued growth of the lesion and new focus on the right cheek the patient referred to a for-profit medical center, where a malignant tumor was suspected for the first time and she was referred to P.A. Herzen Moscow Oncology Research Center (MORC). In January, 2008 she presented in P.A. Herzen MORC where exfoliative cytology revealed BCC. The tumor affected all external nasal surfaces extending to cheeks. According to check-up data there were no regional and distant metastases. A clinical case was discussed on the extended consilium, photodynamic therapy (PDT) was recommended.

Taking into account the age of the patient, tumor localization, superficial tumor growth a topical 5-aminolevulinic acid-mediated PDT (ALA-PDT) was considered.

In April and December, 2008 two courses of PDT with ointment based on 5-ALA powder prepared *ex tempore* were performed (Fig. 1).

In February, March and November, 2009 five (two, one and two, respectively) courses of PDT with 5-ALA ointment prepared *ex tempore* were performed.

In December, 2009 for the cytologically confirmed tumor growth along the scar margin PDT with intravenous photosensitizer was considered.

In December, 2009 one course with photohem was conducted.

In April and November, 2010 two courses of PDT (one with Photogem and one with Photoditazine) was performed due to a continued tumor growth in the center and along the margin of the scar (April) and 0.5x0.3 cm tumor along the scar margin on the right side of the nose (November) (Fig. 2).

In December, 2011 one course of PDT with Radachlorin was performed due to the recurrence along the scar margin up to 0.3 cm in diameter. A contrast-enhanced magnetic resonance imaging (MRI) revealed no additional lesions in soft tissues of the right ala against the scar deformation; there was a skin and subcutaneous edema 1 cm above the nasal tip and along the left ala on the area up to 17x12 mm.

In August, 2012 one course of PDT with Radachlorin was performed due to the recurrence on the nasal tip, dorsum, and right and left lateral walls.

In September, 2013 there was no complete tumor regression following multiple courses of PDT and the patient was consulted by prof. Milanov N.O., academician of

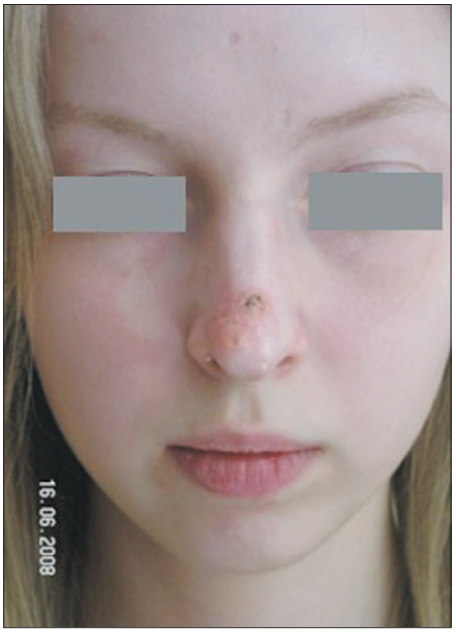


Рис. 1. Клиническая картина через 2 мес после первого курса ФДТ (июнь 2008 г.)
Fig. 1. Clinical picture after the first course of PDT (June 2008)

RAS, the head of the Plastic and Maxillofacial Surgery department in I.M. Sechenov First Moscow State Medicine University for chance for extended surgical intervention including reconstruction. Taking into account the presence of intact bone and chondral structures and benefit from previous PDT courses the subsequent multiple PDT courses were considered to be the method of choice.

In September, 2013 one course of PDT with photolon was applied on six foci of recurrent BCC located along the previous PDT area: the right lateral nasal wall near the ala (a dark-pink tumor of 1 cm in diameter), similar foci on the nasal tip (0.8x0.3 cm), the nasal dorsum (0.4 cm), and the nasal root (0.4x0.4 cm). A contrast-enhanced MRI revealed no significant changes in soft tissues of the face comparing with MRI data in 2011.

In March and December, 2014 two courses of PDT with Radachlorin were performed for the continued tumor growth on the lateral nasal wall (1.0 cm) and the nasal dorsum (1.0x1.5 cm), respectively.

In August, 2015 one course of PDT with Radachlorin was performed on five foci of BCC on the right cheek, the nasal tip, left ala, left lateral wall, and dorsum.

A contrast-enhanced MRI of facial skull in November, 2016 revealed no additional lesions in soft tissues of the nose against the scar deformation; there was a slight skin and subcutaneous edema on the right side. No fair MRI evidence for tumor lesion was obtained.

In May and December, 2016 two courses of PDT (Radachlorin and Levulon) were performed for recurrence on the left cheek, nasal dorsum, left lateral wall, and left cheek.

In March, May and December, 2017 three courses of PDT (Photolon, Radachlorin, Levulon) were performed for new tumor near the right internal canthus up to 1 cm in diameter and the continued tumor growth along the scar margin on the left cheek, left nasal lateral wall and nasal vestibule, the right cheek along the lower and upper scar margins. A contrast-enhanced MRI of facial skull in October, 2017: on native and post-contrast scans there are a scar area up to 28 mm in length on the level of zygomatic arch and a 9x13x8 mm tuberous soft-tissue component with well-defined contrast accumulation. No destruction or edema of bone structures and no subcutaneous fluid accumulations were revealed (Fig. 3).

In March and July, 2018 two courses of PDT with Radachlorin were performed for BCC on the nasal root, right

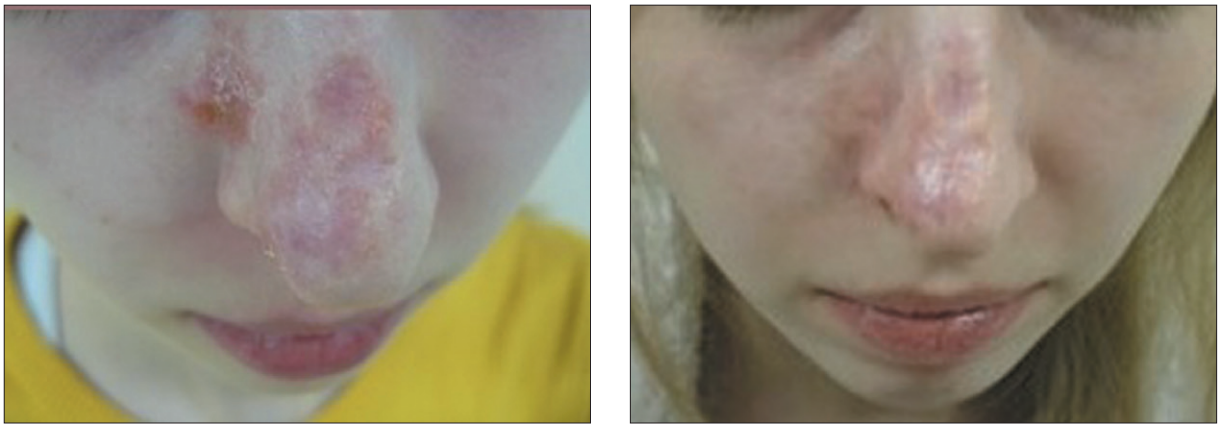
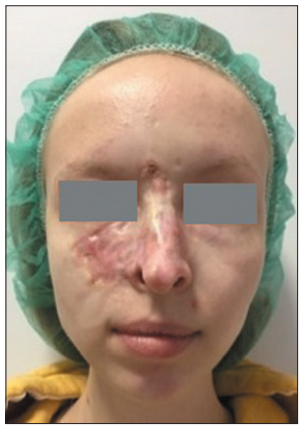


Рис. 2. Клиническая картина:
a – до проведения ФДТ (апрель 2010 г.);
b – после проведения ФДТ (июль 2010 г.)
Fig. 2. Clinical picture
a – before PDT (April 2010);
b – after PDT (July 2010)



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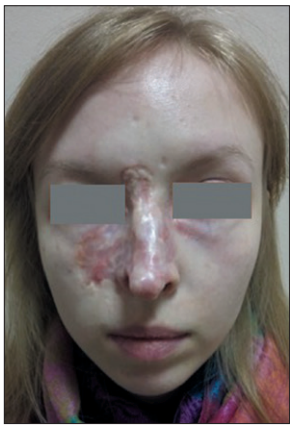


b

Рис. 3. Клиническая картина:
a – до проведения ФДТ (март 2017 г.);
b – после проведения ФДТ (июль 2017 г.)
Fig. 3. Clinical picture
a – before PDT (March 2017);
b – after PDT (July 2017)

zygomatic region, right infraorbital region, right buccal region, left lateral nasal wall, right nasal ala, nasal dorsum. A contrast-enhanced MRI of facial skull in January, 2018: a 28x6 mm scar in soft tissue of the right zygomatic region was seen; near the nasal ala within the subcutaneous tissue there was a 9x11x8 mm oval soft-tissue component with cord-like borders and homogenous well-defined contrast accumulation on delayed series. Accordingly, there was a 9x2 mm local thickening of the skin in the nasal root region on the right with contrast accumulation on delayed series (no dynamics since 2017). There were also local areas of hypervascularization in the forehead skin above the nasal root up to 5x3 mm in size (8x3 mm in October, 2017). A 4x5 mm local contrast accumulation within subcutaneous tissue of the half of the right nasal ala, which were not seen on scans performed on 23.10.2017; No destruction or edema of bone structures and no subcutaneous fluid accumulations were revealed.

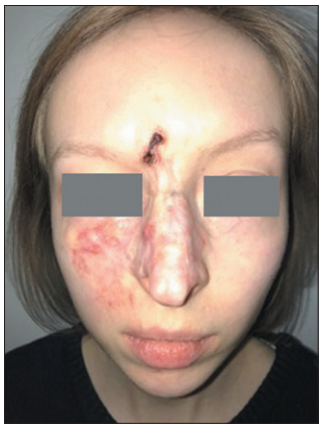
In July, 2018 a targeted therapy with Vismodegib (a daily dose of 150 mg) was considered. Since September, 2018 up to now a drug therapy has been conducted (Fig. 4).

In August, 2019 during follow-up examination on the background of the targeted therapy with Vismodegib a cytologically confirmed continued tumor growth on the right nasal ala was diagnosed.

An MRI in August, 2019: when comparing with the previous MRI (January, 2018), a positive dynamics was observed (previously detected areas on the lateral nasal wall, right nasal ala and forehead region without pathological contrast accumulation). There was a persisting lesion near the right nasal ala with no changes in size. Morphological confirmation of the continued tumor growth was performed by cytological analysis.

Taking into account a residual tumor, a course of PDT against the targeted therapy was considered on the extended consilium.

In November, 2019 one course of PDT with Photodita-



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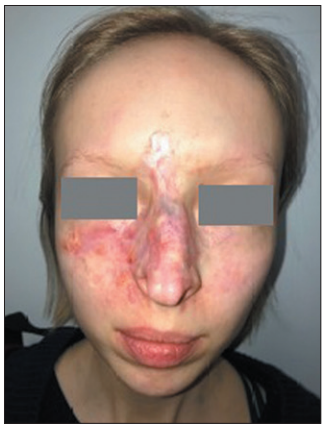

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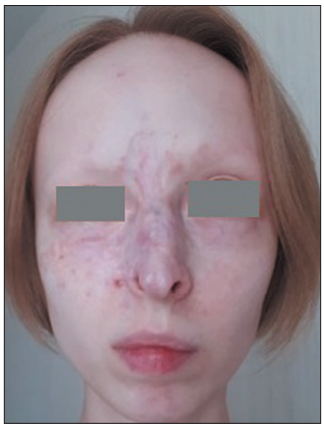

c

Рис. 4. Клиническая картина:
a– до проведения назначения висмодегиба (июль 2018 г.);
b – через 4 мес после начала лечения висмодегибом;
c – через 9 мес после начала лечения висмодегибом
Fig. 4. Clinical picture
a – before treatment with Vismodegib (June 2018);
b – after 4 months of treatment with Vismodegib;
c – after 9 months of treatment with Vismodegib

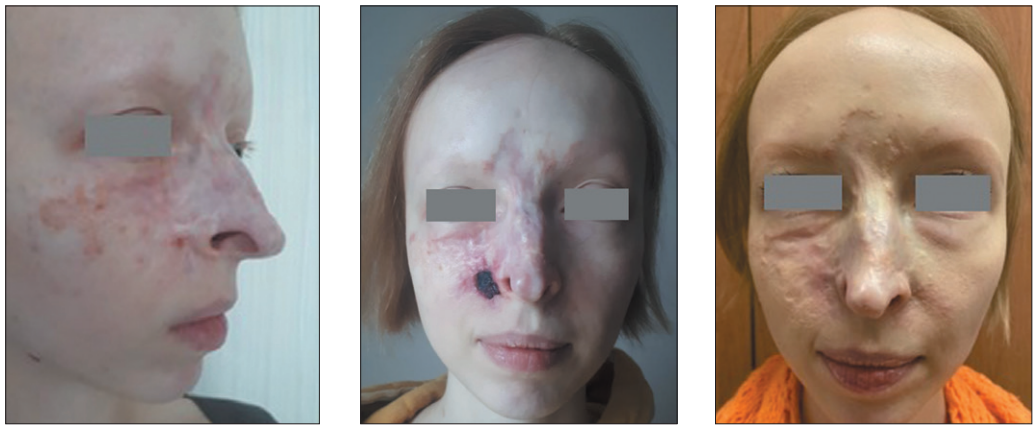

Рис. 5. Клиническая картина (2019 г.):
a – продолженный рост опухоли крыла носа справа до ФДТ;
b – некроз опухоли, 1 неделя после ФДТ;
c – полная регрессия опухоли, 3 мес после ФДТ
Fig. 5. Clinical picture (2019)
a – continued tumor growth on the right wing of the nose before PDT;
b – tumor necrosis, 1 week after PDT;
c – complete tumor regression, 3 months after PDT

zine for the residual tumor was performed. Three months later a complete regression of the tumor was registered (Fig. 5).

Discussion

This clinical case demonstrate a correct management of BCC of the central facial zone with PDT in the young patient, who had a tumor disease complicated by long-lasting incorrect treatment due to misdiagnosis, an absence of cancer alertness in her physicians and delayed morphological study for diagnosis confirmation. PDT was the very optimal strategy which allowed a preservation of the patient's face and stabilizing of initially locally advanced tumor of the central facial zone before market appearance of new generation drugs – targeted therapy for BCC.

The experience of long-term treatment (11 years) of the patient with PDT shows the efficacy of this organ-preserving method in multicourse mode for frequent recurrences of BCC. All courses of PDT were well-tolerated without complications and with good cosmetic and apparent antitumor effect.

5-ALA ointment prepared ex tempore is inefficient because a combination of additive agents responsible for 5-ALA delivery to pathologic tissue plays an important role for topical PDT. Only standardized formulations showed its efficacy in trials of all clinical phases should be used for topical PDT. There are publications showing a high efficiency of topical PDT with ALA-based agents (levulon, ameluz, metvix) for such types of BCC [7,8]. Probably, an inappropriate combination of additive agents did not allowed getting a significant benefit from first six courses of PDT in this patient.

Conclusion

This clinical case demonstrates the efficacy and utility of PDT combined with the targeted therapy with vismodegib in patients with BCC for continued tumor growth during the drug therapy or for repeated recurrences of tumor during multi-course PDT.

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