Efficacy of Photodynamic Therapy with Chlorine-Based Photosensitizer in the Treatment of Basal Cell Carcinomas

T.P. Artsemyeva[1] and D.A. Tzerkovsky[2,*]

[1]*Department of Hyperthermia and Photodynamic Therapy, N.N. Alexandrov National Cancer Center of Belarus, Lesnoy, Republic of Belarus*

[2]*Laboratory of Morphology, Molecular and Cellular Biology with Group of Experimental Medicine, N.N. Alexandrov National Cancer Center of Belarus, Lesnoy, Republic of Belarus*

Abstract: The aim of this study is to evaluate a safety and antitumor efficacy of photodynamic therapy (PDT) with chlorine-based photosensitizer (PS) for treatment patients with basal cell skin carcinomas (BCC).

Material and Methods: The work was performed on the basis of the Department of hyperthermia and photodynamic therapy. The object of the study were 172 patients with a verified diagnosis of BCC (T1N0M0, I stage), who received treatment from 2007 to 2022. PS «Photolon» (RUE «Belmedpreparaty», Republic of Belarus) was administrated intravenously at a dose of 2.0-2.5 mg/kg. The session of PDT was performed 2.5-3 h after intravenous injection of PS using semiconductor lasers (λ=660±5 nm) with exposure doses 50-250 J/cm² and power density – 0.15-0.5 W/cm². Frequency and severity of side effects after treatment session was assessed based on the criteria CTCAE (Version 4.03; 2010). The antitumor efficacy was evaluated 3 months after treatment. Clinical outcome was evaluated visually and morphologically by cytological or histopathological examination. Performance criteria were as follows (according to WHO, 1979).

Results: The phenomenon of skin phototoxicity due to violation of the light regime (hyperemia, burning, slight swelling of the soft tissues of the face; CTCAE, I-II grades) was registered in 5.8% of cases (n=10). Serious adverse reactions (anaphylactic shock, Quincke's edema, severe pain syndrome) after the administration of PS and photoirradiation were not identified. Complete and partial regressions of tumors was observed in 93.0% and 4.7% of patients, respectively. The objective answer was 97.7%. The frequency of local relapses of the disease 1, 2, 3, 4 and 5 years after PDT was 3.1%, 3.1%, 4.6%, 4.6% and 6.9%, respectively.

Conclusion: PDT is a well-tolerated and highly effective therapeutic option in patients with BCC.

Keywords: Basal cell carcinoma, chlorine-based photosensitizer, photodynamic therapy, tolerability, safety and antitumor efficacy.

INTRODUCTION

Basal cell carcinoma (BCC) is a serious medical problem of modern clinical oncology. BCC is the most common type of carcinoma worldwide, accounting for 75% to 90% of non-melanoma skin cancers and affecting around two-three million people each year, with a steadily increasing incidence [1, 2]. Despite the minimal risk of metastasis of this type of tumor (no more 0.5%), BCC is locally invasive and can infiltrate and destroy the subcutaneous tissue, bone and cartilage, reaching vital structures (major vessels or central nervous system); complications like bleeding and infections can affect the prognosis of patients, especially when elderly and debilitated [3].

The key methods of treatment of BCC are surgical excision with Mohs microsurgery, curettage with or without electrosurgery, cryosurgery, topical drug preparations (an immune-response modifier «Imiquimod» 5% cream, Hedgehog inhibitors «Vismodegib» and «Sonidegib»), chemotherapy with «5-Fluorouracil» 5% and contact radiotherapy [4].

The recurrence rate of BCC after surgical excision is 4.7-35.9%, electrocoagulation – 10.0-20.6% cryodestruction – 4.0-22.0% and with local chemotherapy – 10.0-25.0% [5, 6].

The development of new methods of treatment of BCC are relevant. These therapies should be characterized by high efficacy, minimal amount of adverse reactions and complications, and good cosmetic effect. One of these therapeutic options of treating patients with BCC is PDT. It is based on the local or systemic application of a photosensitive compound – the photosensitizer (PS), which is accumulated in pathological tissues [7]. Photoirradiation of these tissues leads to the formation of reactive oxygen species in them. Thus, a direct cytotoxic effect is realized. In addition to directly acting on tumor cells, PDT damages and restricts tumor microvasculature, and causes a local inflammatory response that stimulates an immune response against

*Address correspondence to this author at the Laboratory of Morphology, Molecular and Cellular Biology with Group of Experimental Medicine, N.N. Alexandrov National Cancer Center of Belarus, Lesnoy, Republic of Belarus; Tel: +375173899536; E-mail: tzerkovsky@mail.ru

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the tumor. All of these reactions lead to the death of tumor cells and tissues [8].

Teams of authors from a number of clinical and scientific Centers published the results of using PDT with different types of PS in patients with BCC [9, 10].

The aim of this study is to evaluate a safety and antitumor efficacy of PDT with chlorine-based PS «Photolon» for treatment patients with basal cell skin carcinomas.

MATERIALS AND METHODS

Patients

PDT was performed in 172 patients (97 male, 75 female) with morphologically verified BCC (T1N0M0, stage I, primary form). All patients received treatment at the Department of hyperthermia and photodynamic therapy from 2007 to 2022. In the vast majority of cases tumors had the so-called «uncomfortable» localization (paraorbital region, nasal and nasolabial folds, skin behind the ear, skin auricles and external auditory canal), which traditionally presents difficulties for surgical and/or radiation treatment. The average age was 54.4±11.2 years. In the overwhelming majority of patients (n=133, 77.4%), the primary focus was located in the face (nose, cheek, forehead). The distribution of patients according to the localization of the primary focus and to the clinical forms is presented in Table **1**.

Ethical Aspects

All patients were informed about possible adverse reactions with intravenous administration of PS and PDT session, as well as the need for strict adherence to the light regimen for 3-5 days, and the timing of the antitumor response to treatment. All patients signed an informed consent for treatment by PDT (Helsinki declaration of 1964 (revised 2013).

Photosensitizer

PS «Photolon» (RUE Belmedpreparaty, Republic of Belarus, registration number 16/11/886; 08 November 2016) is a complex of chlorin e6 trisodium salt with

Table 1: Characteristics of Tumors in Patients

Sites of tumor foci	Total number of patients		Clinical form	Total number of patients	
	n	%		n	%
Scalp	12	7.0	Superficial	48	27.9
External ear	14	8.1	Ulcerative	72	41.9
Neck	3	1.7	Nodular	47	27.3
Trunk	10	5.8	Morpheaform	5	2.9
Face	133	77.4	**Total**	**172**	**100**
Total	**172**	**100**			

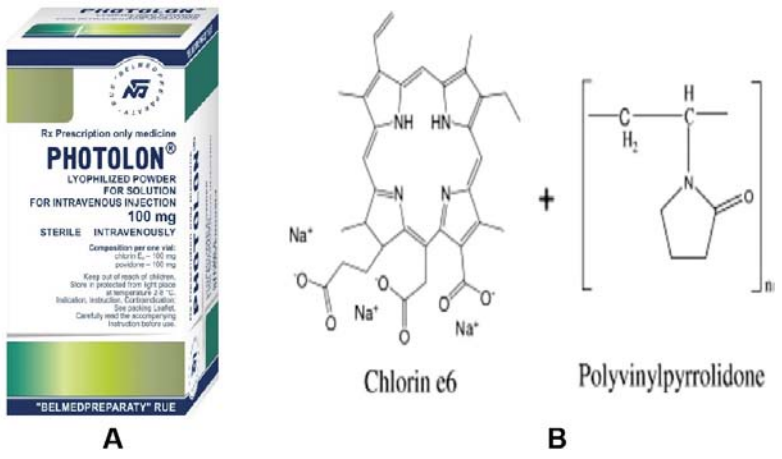

Figure 1: A, **B.** Belorussian photosensitizer «Photolon» (RUE «Belmedpreparati», Republic of Belarus).

povidone with a K-value of 17. The calculated doses of PS were dissolved in 200 ml 0.9% sodium chloride solution and injected intravenously over 30 minutes at a doses of 2.0-2.5 mg/kg body weight, in a darkened room (Figure **1**).

Photodynamic Therapy

The tumor photoirradiation session was carried out 2.5-3 h after the injection of PS with the use of a semiconductor lasers «UPL PDT laser» («Lemt BelOMO», Republic of Belarus, λ=665±5 nm) and «PDT LASER» (Institution Institute of Molecular and Atomic Physics of the National Academy of Sciences of Belarus, Republic of Belarus, λ=660±5 nm) (Figure **2**).

The exposure doses were varied from 50 J/cm^2 to 250 J/cm^2, power density of laser radiation – from 0.15 W/cm^2 to 0.5 W/cm^2 and the time of photoirradiation of one focus varied depending on the size and location of the tumor and ranged from 3 to 25 min. The area of irradiation included a section of healthy tissue, retreating from the edge of the tumor to 5 mm.

The Tolerability and Safety of the Photodynamic Therapy

Frequency and severity of side effects after treatment session was assessed based on the criteria CTCAE (Version 4.03; 2010).

The Antitumor Efficacy of the Photodynamic Therapy

Clinical and cosmetic outcomes were evaluated after 1 and 3 months. Clinical outcome was evaluated visually and morphologically by cytological or histopathological examination. Performance criteria were as follows (according to WHO, 1979):

1. Complete regression (CR) – absence of all signs of the disease, 100% resorption of tumor foci in 1 to 3 months after PDT;

2. Partial regression (PR) – reduction of the total tumor size by 50% or more with subsequent stabilization established after 1 month and confirmed 3 months after the PDT session;

3. Stabilization of the process – no increase in the size of the tumor nodes, the appearance of new nodes or other signs of disease progression within 3 months;

4. Progression of the process – an increase in the total size of the tumor node by 25% or more, or the development of new foci.

The frequency of objective responses to the treatment included the frequency of complete and partial regressions of tumors.

RESULTS

In all patients, no hematological and/or hepato- or nephrotoxicity was noted after PS infusion. Patients observed the light regimen (sun protection glasses, room with tinted windows) within 3-5 days. Adverse reactions (light hyperemia itching and burning of externally exposed areas of sunlight skin; CTCAE, version 4.03, I-II grades) were registered in 10 cases (5.8%). Serious adverse reactions (anaphylactic shock,

A B

Figure 2: A. Medical laser device «UPL PDT» (Lemt BelOMO, Republic of Belarus, λ=665±5 nm).

B. Medical laser device «PDT LASER» (Institution Institute of Molecular and Atomic Physics of the National Academy of Sciences of Belarus, Republic of Belarus, λ=660±5 nm).

Table 2: Antitumor Efficacy of the PDT in Patients with BCC

Criteria for antitumor efficacy	Indicators, %
Complete regressions	93.0
Partial regressions	4.7
Stabilization	1.7
Progression	0.6
Objective responses	97.7
Local recurrence (1 year)	3.1
Local recurrence (2 year)	3.1
Local recurrence (3 year)	4.6
Local recurrence (4 year)	4.6
Local recurrence (5 year)	6.9

Quincke's edema, severe pain syndrome) after the administration of PS and photoirradiation were not identified.

After PDT, standard signs of photochemical reactions occurring in tumors were noted: hyperemia in the irradiation zone, cyanosis of the skin over and around tumors formed due to circulatory disorders, pinpoint hemorrhages, tissue edema.

Signs of photochemical ischemic necrosis of irradiated tissues were registered 1-3 days after PDT. Edema of the tissues surrounding the tumor persisted for 2-5 days. Next, a scab formed, which was rejected after 2-4 weeks, followed by tissue epithelialization within 4-7 weeks.

Data on the antitumor efficacy of PDT are presented in Table **2**.

The data obtained are illustrated by the following clinical examples (Figures **3**, **4**, **5**).

DISCUSSION

Photodynamic therapy (PDT) is one of the promising areas in the treatment of BCC. PDT is a method which based on the significant increase of the cytotoxicity of drugs with photoirradiation of the tumor tissue. According to numerous studies of photochemical reactions include a direct interaction of excited molecules with the help of photoirradiation the PS on the substrate and forming transient radicals that react with oxygen [7]. Interaction initiates a complex cascade of free radicals, such as singlet oxygen, hydroxyl radical, hydrogen peroxide and superoxide anion radical, causing the development of oxidative stress syndrome [11]. As a result, PDT effectively induced tumor-cell apoptosis, autophagy and necrosis, and tumor destruction [12, 13]. Along with the direct cytotoxic effect in PDT, an important role is played by damage to the endothelium of blood vessels. As a result, due to damage to the capillaries, the blood

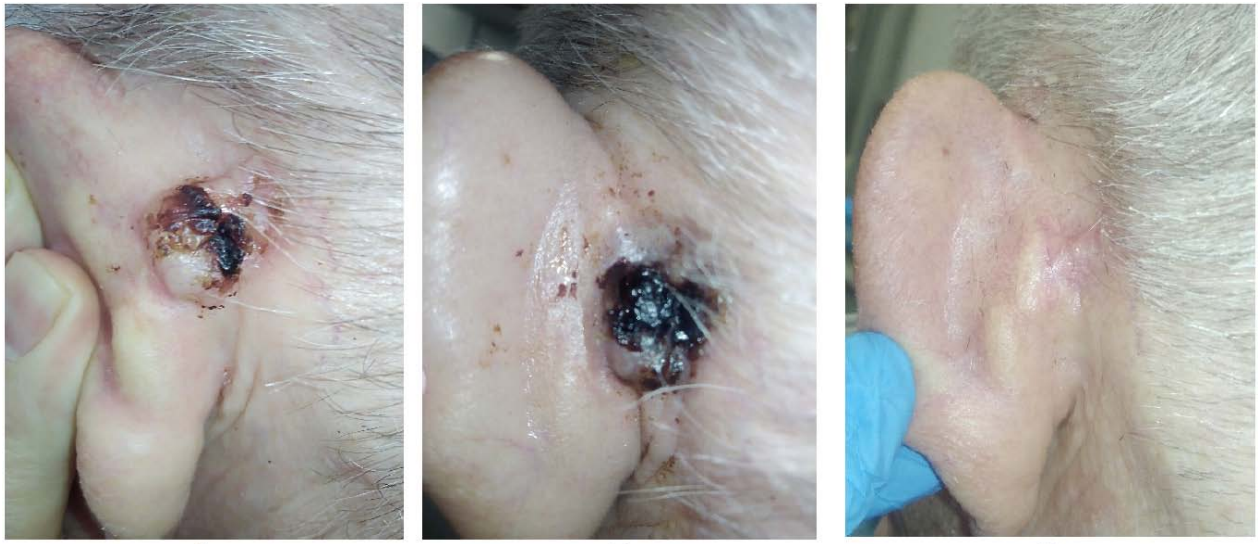

Figure 3: Patient F., 62 years. Diagnosis – BCC of the auricle, nodular form, T1N0M0, I stage.

A – status localis before PDT (PS «Photolon» at a dose 2.5 mg/kg + photoirradiation (200 J/cm²; 350 mW).

B – 3rd day after PDT (cyanosis and swelling of soft tissues in the area of photoirradiation – signs of emerging photochemical necrosis).

C – 3 month after PDT (complete regression of the tumor).

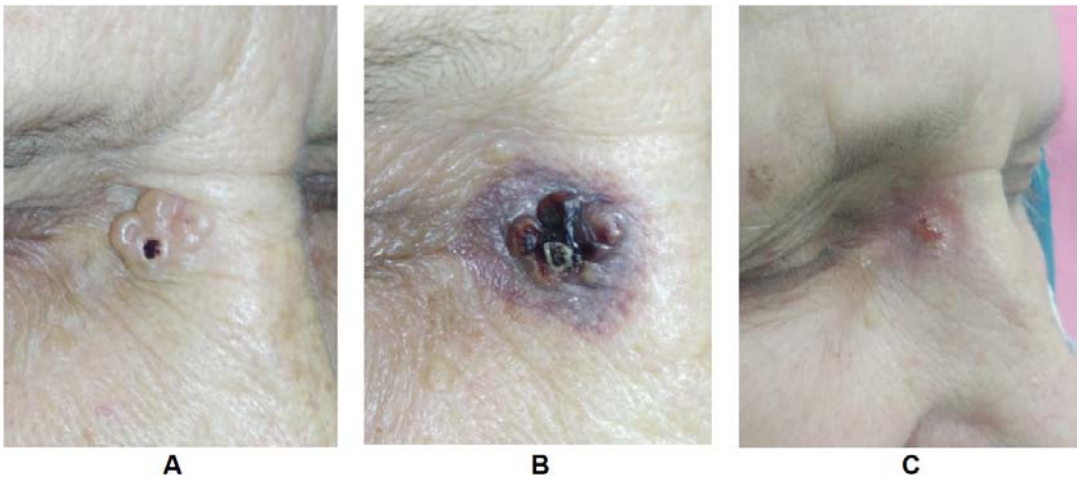

Figure 4: Patient R., 59 years. Diagnosis – BCC of the side of the nose, nodular form, T1N0M0, I stage.

A – status localis before PDT (PS «Photolon» at a dose 2.5 mg/kg + photoirradiation (150 J/cm²; 350 mW).

B – 3rd day after PDT (cyanosis and swelling of soft tissues in the area of photoirradiation – signs of emerging photochemical necrosis).

C – 3 month after PDT (the wound surface is in the stage of epithelialization in the zone of photoirradiation. There were no clinical signs of tumor growth – complete regression of the tumor).

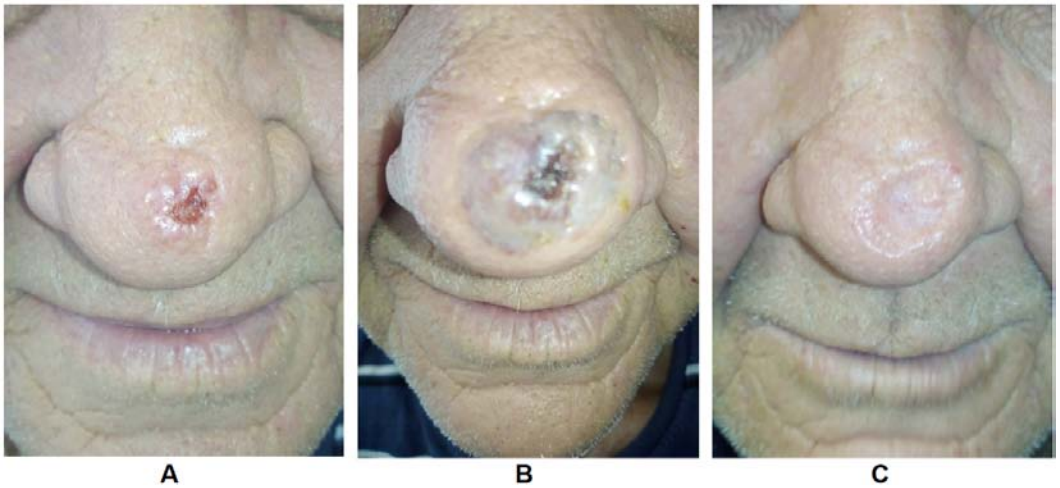

Figure 5: Patient G., 64 years. Diagnosis – BCC of the tip of the nose, erosive-ulcerative form, T1N0M0, I stage.

A – status localis before PDT (PS «Photolon» at a dose 2.5 mg/kg + photoirradiation (200 J/cm²; 350 mW).

B – 3rd day after PDT (cyanosis and swelling of soft tissues in the area of photoirradiation – signs of emerging photochemical necrosis).

C – 1 month after PDT (in the zone of photoirradiation there is a connective tissue scar in the formation stage. There were no clinical signs of tumor growth – complete regression of the tumor).

supply to the tumor is disrupted and ischemic necrosis occurs, leading to the death of the tumor [7].

In the European countries and Russia, considerable experience has been accumulated in the use of PDT with «5-aminolevulinic acid» (5-ALA), hematoporphyrin and chlorine derivatives in the treatment of BCC. Essential shortcomings in the use of these PS are the limited penetration depth of laser radiation (from 2 to 3 mm depending on the wavelength), the long period of cutaneous phototoxicity and the high cost of some PS [14, 15].

The results obtained are systematized and presented in Tables **3** and **4**.

Lasers with a wavelength of radiation of 630±5 nm for PDT of tumors with topical forms 5-ALA are used. In this case, the depth of penetration of this radiation into biological tissues is 2-3 mm. Therefore, PDT with

Table 3: Selected Results of the Use of 5-ALA for PDT of BCC

Author, country	Patients, n	PS, mg/kg	PDT parameters	Side effects	Antitumor efficacy
Nguyen K.P. Netherlads 2019 [16]	superficial BCC, n=30	MAL cream (MetvixVR) 160 mg/g	The incubation time was 3-5 h. λ=630 nm ED1=20 J/cm^2 ED2=55 J/cm^2 Group 1 – illumination at 3 and 4 h, Group 2 – illumination at 3 and 5 h	No serious adverse reactions occurred.	*Complete response* (for groups 1 and 2 – 3 months) = 63.6% and 70.0% *Complete response* (for groups 1 and 2 – 12 months) = 80.0% and 100.0% A *local recurrence* was observed in 10.0% (12 months, group 1)
Filonenko E. Russia 2020 [17]	superficial BCC, n=82 primary BCC – 64.6% recurrent BCC – 35.4%	12% 5-ALA drug Levulon gel	The incubation time was 3 h. λ=630 nm ED=350 J/cm^2	Mild or moderate pain with no cessation of a treatment There were no complications. No serious adverse reactions occurred.	*Complete response* = 95.8% A *local recurrence* was observed in 6.1% cases in the period from 7 to 58 months after PDT. *Overall relapse-free survival rate* (patients with primary and recurrent tumors): 1-year rate – 96.4% vs. 77.8%; 3-year – 91.6 % vs 77.8 % (p=0.06)
Woźniak Z. Poland 2020 [18]	recurrent BCC, n=50	20% ointment 5-ALA	The incubation time was 4 h. λ1=405 nm λ2=638 nm ED=48 J/cm^2 P=400 mW	Mild skin burning, edema, erythema or slight pain which subsequently disappeared during the next 3-4 days. No serious adverse reactions occurred.	*Complete response* = 87.0%, *partial response* = 9.0%, *no effect* = 4.0%
Gomez C. Spain 2021 [19]	superficial (n=56), nodular (n=118) BCC, n=174	16 % MAL cream (Metvix®)	The incubation time was 3 h. λ=630 nm ED=90 J/cm^2	Side effects for sBCC and nBCC: erythema perilesional (81.5%;61.1%), edema perilesional (61.8%;81.3%), мild pain (100%; 100%). No serious adverse reactions occurred.	*Complete response* (sBCC vs. nBCC) in the 1 year = 97.4% and 97.2%. *Complete response* (sBCC vs. nBCC) in the 3 year = 96.1% and 95.2%. A *local recurrence* was observed in 1.8% (sBCC) and 4.2% (nBCC) cases in the period from 1-3 year after PDT.
Hellen R. Ireland 2022 [20]	superficial BCC, n=28	methyl 5-ALA	The incubation time was 3 h. λ=405-800 nm ED=75 J/cm^2 rate=55 mW/cm^2	Median pain scores were 0/100 (IQR 0) and 0/100 (IQR 5) during treatments one and two. No serious adverse reactions occurred.	The *response rate* at day 28 was 100%. *Recurrence rates* were 8.3% at 3 months, 16.7% at 6 months, 27.8% at 9 months, 30.6% at 12 months.

Table 4: Selected Results of the Use of Chlorine-Based PS for PDT of BCC

Author, country	Patients, n	PS, mg/kg	PDT parameters	Side effects	Antitumor efficacy
Sukhova T.E. Russia 2015 [21]	ulcerative/ superficial BCC, n=34	Radachlorine solution, 1.75-3.5 mg/cm^2 volume: 0.5-1.0 ml per 1 cm^2	The incubation time was 15 min. λ=662 nm ED=300 J/cm^2 rate= 0.14-0.39 W/cm^2	Marked increase in blood pressure (8.9%). No serious adverse reactions occurred.	*Complete response* (for uBCC and sBCC – 3 months) = 94.9% and 100.0% *Complete response* (for T1 and T2 – 3 months) = 100.0% and 92.3% A *local recurrence* was observed in 2.3%.
Sukhova T.E. Russia 2016 [22]	ulcerative/ superficial/ nodular BCC, n=59	Photolon (solution) intravenous injection 2.0-2.5 mg/kg Photolon (solution) (intratumor injection) 1.44-2.50 mg/cm^3	The incubation times were 3 h (for i/v) and 15 min (for i/t). λ=662-665 nm ED=300 J/cm^2 rate= 0.31-0.47 W/cm^2	Pain, burning and tingling of various intensity (during several days after the PDT session). No serious adverse reactions occurred.	PDT with i/v. Photolon injection: *complete response* (for uBCC, sBCC and nBCC – 3 months) = 90.0%; 100.0%; 100.0% PDT with i/t. Photolon injection: *complete response* (for uBCC, sBCC and nBCC – 3 months) = 90.9%; 100.0%; 92.3%. *Overall relapse-free survival rate* (patients with i/v and i/t Photolon injection): 1- and 2-year rate – 93.8% vs. 96.7%.
Kapinus V.N. Russia 2017 [23]	superficial BCC, n=55 primary BCC – 41.8% recurrent BCC – 58.2%	Photolon (solution) intravenous injection 1.1-1.6 mg/kg	The incubation time was 3 h. λ=662-665 nm 1 step – intratumor irradiation: 0.2-0.4 W 2 step - ED= 50-300 J/cm^2 rate= 0.3-0.4 W/cm^2	Mild skin burning, edema, erythema or slight pain which subsequently disappeared during the next 2-4 days. No serious adverse reactions occurred.	*Complete response* (patients with primary and recurrent tumors) – 2 months = 87.0% and 65.6%, *partial response* = 13.0% and 34.4%. A *local recurrence* was observed in 4.3% (primary tumor) and 37.5% (recurrent tumor) cases in the period from 0.5-4 year after PDT.
Kapinus V.N. Russia 2021 [24]	different forms of BCC, n=532	Photodytazine (solution) 0.6-1.9 mg/kg n=72 Photolon (solution) 0.6-2.5 mg/kg n=281 Photoran (solution) 0.6-2.0 mg/kg n=179	The incubation time was 1.5-3 h. λ=662 nm ED= 100-600 J/cm^2 rate= 0.2-0.5 W/cm^2	No serious adverse reactions occurred.	A local recurrence was observed in 16.2% cases in the period from 0.5-5 year after PDT (in average). A local recurrence was observed in 19.4%; 18.9%; 10.6% cases after PDT with Photodytazine, Photolon and Photoran.

5-ALA is indicated for the treatment of the superficial form of BCC. In turn, most chlorin PS are administered intravenously. To activate these PS, lasers which generate radiation with a wavelength of 660±5 nm are used. This radiation allows you to effectively action at a great depth (up to 10 mm). Therefore, PDT with chlorins is indicated for the treatment of not only superficial, but nodular forms of BCC.

The results obtained in these studies indicate good tolerance and moderate or high antitumor efficacy of the PDT with different types PS (local forms «5-ALA» and its modifications, local and intravenous forms of chlorine-based PS – «Radachlorine», «Photodytazine», «Photoran» and «Photolon») in patients with BCC, which is confirmed by a minimal risk of adverse reactions (CTCAE, grades I-II), a high rate of complete tumor regressions (from 63.6% to 100.0%) and a various rate of disease recurrence (1.8%-37.5%).

CONCLUSION

The results obtained in this study on the use of PDT in patients with BCC are consistent with the results obtained by other authors in studies [21, 22, 23, 24]. The results obtained in our study indicate good tolerance and high antitumor efficacy of the PDT with PS «Photolon» in patients with BCC, which is confirmed by a minimal risk of adverse reactions (CTCAE, grades I-II), a high rate of complete tumor regressions (93.0%), and a low rate of disease recurrence (3.1%-6.9%).

In our opinion, the main indications for the use of PDT in the treatment of BCC are:

1. BCC: superficial, ulcerative and nodular forms, T1N0M0, I stage;
2. Primary, recurrent and residual tumors;
3. Tumors of anatomically «inconvenient» localization (auricle, angle of the eye, tip of the nose);
4. Tumors resistant to traditional methods of treatment;
5. Patient's refusal from surgery, radiation and chemotherapy;
6. Multiple and extensive tumor lesions.

In conclusion, we can summarize that PDT has a number of advantages in comparison with traditional methods of treatment of BCC, such as:

1. Minimal toxicity for the surrounding normal tissues, due to the selective accumulation of the PS in the tumor;
2. Minimal risk of pain syndrome;
3. Absence of mechanisms of primary/acquired resistance;
4. Possibility of an outpatient procedure;
5. Possibility of combination with other methods of treatment;
6. Possibility of repeated repetition of the procedure;
7. Ease of use in the multiple nature of the lesion;
8. Good cosmetic results;
9. Possibility of implementing organ-preserving methods of treatment.

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