

Photodynamic therapy for classic (idiopathic) type of Kaposi's sarcoma (case report)

ABSTRACT (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

The author presented a description of the clinic case of the successful application of photodynamic therapy in the treatment of the classic (idiopathic) type of Kaposi's sarcoma of the third toe of the foot in a patient aged 59 years. Photosensitizer «Photolon» (RUE «Belmedpreparaty», Republic of Belarus) was injected intravenously at a dose of 2 mg/kg body weight. Photoirradiation session was carried out 3 hour after the injection of photosensitizer with the use of a semiconductor laser «UPL PDT laser» («Lemt», Republic of Belarus, $\lambda=660\pm5\text{nm}$). The exposure dose was 100 J/cm^2 with power density of laser radiation was 0.38 W/cm^2 and time was 10 min. The effectiveness of treatment was assessed based on an analysis of clinical data. During the follow-up period of 3 and 6 months, no clinical signs of local recurrence in the photoirradiation area were detected.

Keywords: Kaposi sarcoma, photosensitizer, photodynamic therapy

1. INTRODUCTION (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

Kaposi's sarcoma (KS) was first described in 1872 by Moritz Kaposi, a Vienna-based Hungarian dermatologist, as a rare multifocal angioproliferative tumor involving blood and lymphatic vessels in elderly men of Jewish origin (Kaposi, 1872).

In 1994, in the laboratory of Columbia University (New York, USA) Chang Y. and colleagues using a polymerase chain reaction, human type 8 herpes virus (HHV-8, subgroup of γ -herpes virus) was identified in patients with various types of KS [1]. HHV-8 is a risk factor for the development of KS, but infection with this virus does not necessarily lead to the development of KS.

Diagnosis is established based on clinical examination, histological examination of affected skin and mucous membranes, as well as detection of antibodies to HHV type 8. On the basis of the factors that cause the disease, and its clinical symptoms, Braun-Falko O. in 1991 proposed the allocation of 4 types of KS:

- idiopathic (classical);
- endemic (African);
- AIDS-associated (epidemic);
- immunosuppressive.

Cutaneous lesions are the most frequent symptoms, but lesions in internal organs have also been observed. The initial stages of the disease is characterized by the appearance of spots or plaques with clear, irregular contours on the skin of the feet, shins, mucous membranes without subjective sensations. Later, itching, burning and aching in the area of rashes, intensifying in the evening and night. Eruptions have clear boundaries, increase in size, darken and turn into nodules of various sizes, thickened plaques or nodes with vascular crimson nodules, which can be located on the upper limbs, trunk, face, mucous membrane

34 of the tongue and scrotum area. The defeat of internal organs occurs quite often, but, as a
35 rule, proceeds asymptotically and is detected during autopsy [2].

36 At the moment, the development of new effective methods for treating patients with KS is
37 very relevant. Existing methods do not lead to a complete cure, but contribute to the
38 temporary stabilization of the pathological process and do not allow preventing the
39 occurrence of relapses and the further development of the disease. The choice of the
40 method of therapy for KS depends on its prevalence and the intensity of changes in the
41 immune status.

42 In a common process, patients with KS are given cytostatic therapy: herbal medicines
43 (vinblastine, vincristine), alkylating compounds (cyclophosphamide, fotretamine),
44 antimetabolites (methotrexate, pumite), liposomal (doxorubicin and daunorubicin). The
45 maximum effect from its application comes in 5 months, and the average duration of
46 remission is 4 months. The above chemotherapeutic agents affect skin and visceral
47 manifestations of KS, inhibit cell growth and proliferation. Some progress has been made in
48 the administration of chloride propidium, especially in combination with IFN- α 2 (Viferon) and
49 IFN- α (Leukinferon) [3, 4].

50 As reported by M.G. Kartashova and colleagues, with localized forms of the disease,
51 methods aimed at local destruction of lesions (cryotherapy with liquid nitrogen, electron
52 radiation and close-focus X-ray therapy) are applied. The authors note that the curative
53 effectiveness of the proposed methods reaches 80%, however, in the early observation
54 periods of 3 to 6 months, the development of recurrence of the disease remains high.
55 The use of remote gamma therapy and a high-energy electron beam makes it possible to
56 improve the results of treatment [4].

57 Today, the search for new and effective methods of treatment of skin forms of KS with high
58 efficacy, minimal amount of adverse reactions and complications, and good cosmetic effect
59 is topical. One of the promising directions in the treatment of this pathology is the
60 photodynamic therapy (PDT), which a treatment method is based on the significant increase
61 of the cytotoxicity of drugs with photo irradiation of the tumor tissue. According to numerous
62 studies of photochemical reactions include a direct interaction of excited molecules with the
63 help of photo irradiation the photosensitizer (PS) on the substrate and forming transient
64 radicals that react with oxygen. Interaction initiates a complex cascade of free radicals, such
65 as singlet oxygen ($^1\text{O}_2$), hydroxyl radical ($\cdot\text{OH}$), hydrogen peroxide (H_2O_2) and superoxide
66 anion radical ($\cdot\text{O}_2^-$), causing the development of oxidative stress syndrome. As a result, PDT
67 effectively induced tumor-cell apoptosis and necrosis. The two possible mechanisms might
68 be:

- 69 • promoting mitochondria to release Cyto-C and activate Caspase-3, then to initiate
70 apoptosis;
- 71 • the destroying of microvessels, inhibition of angiogenesis and the induction of
72 ischemia and anoxia of tumor cells, resulting in ischemic necrosis [5, 6].

73 The **aim** of this case report is to evaluate a safety and antitumor efficacy of PDT with
74 chlorine-based PS photolon for treatment patient skin form of KS].

2. MATERIAL AND METHODS / EXPERIMENTAL DETAILS / METHODOLOGY (ARIAL, BOLD, 11 FONT, LEFT ALIGNED, CAPS)

[Case report

Patient B., born in 1954, in April 2013, appealed to the Department of hyperthermia and photodynamic therapy (N.N. Alexandrov National Cancer Center, Republic of Belarus) for medical advice with the purpose of counseling and establishing an accurate diagnosis.

According to the patient, he considers himself ill about 1 year. At the time of the examination, the patient complained of the presence of tumor-like formations on the plantar part and the second toe of the right foot. At 432 Minsk Military Hospital, a nodule biopsy was performed on the right foot skin, a preliminary diagnosis was made – Kaposi sarcoma (in doubt). Morphological conclusion (№ 12959-960/3 dated May 15, 2013): the morphological pattern corresponds to the Kaposi sarcoma.

Status localis: on the skin of the lateral surface of the right foot there are two nodules of dark blue color, 0.7 cm in diameter.

The patient was recommended to receive treatment with the use of PDT. The study was approved by local ethic committee. Patient signed informed consent to procedure in compliance with Helsinki declaration of 1964 (revised 2013).

PDT session: PS «Photolon» (RUE «Belmedpreparaty», Republic of Belarus), which is a complex of chlorin e6 trisodium salt with polyvinylpyrrolidone, was injected intravenously at a dose of 2 mg/kg body weight, in a darkened room. The tumor photoirradiation (PI) session was carried out 3 hour after the injection of PS with the use of a semiconductor laser «UPL PDT laser» («Lemt», Republic of Belarus, $\lambda=660\pm5\text{nm}$). The exposure dose was 100 J/cm^2 , power density of laser radiation was 0.38 W/cm^2 and PI time was 10 min. The area of irradiation included a section of healthy tissue, retreating from the edge of the tumor to 5 mm.

Immediately after the PDT session, we detected the appearance of signs of hemorrhagic necrosis: the color of the pathological focus became black-brown, and insignificant exudation was revealed. The final formation of a necrotic scab with a clear border and the correct form in the zone of PI occurred 1 week after the treatment. The tolerability and safety of the PDT session was assessed based on the criteria CTCAE (Version 4.03).

The effectiveness of treatment was assessed based on an analysis of clinical data. Performance criteria were as follows (according to WHO, 1979):

- complete regression (CR): absence of all signs of the disease, 100% resorption of pathological foci in 3 months after PDT;
- partial regression (PR): reduction of the total tumor size by 50% or more with subsequent stabilization established 3 months after the PDT session;
- 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;

- progression of the process: an increase in the total size of the tumor node by 25% or more, or the development of new foci.

3. RESULTS AND DISCUSSION

[The PDT session was accompanied by a mildly expressed pain syndrome (grade I). There were no other complications and adverse reactions. The skin phototoxicity was not observed. At the control observation in 3 months in the zone of PI, we noticed the formation of a connective-tissue scar (Figure 1).



A

B

Fig. 1. Patient B., 60 years old.

Clinical diagnosis: Kaposi's sarcoma of the third toe of the right foot, classic (idiopathic) type:
A – state before PDT; B – state 3 months after PDT (exposure dose – 100 J/cm²)

During the follow-up period of 3 and 6 months, no clinical signs of local recurrence in the PI zone were detected.

KS is a lympho-angioproliferative disease, having four variants: idiopathic (classical), endemic (African), AIDS-associated (epidemic) and immunosuppressive. Classical KS is characterized by single or multiple pea-sized bluishred macules on the distal portions of the lower extremities. The treatment of KS depends on the extent and the localization of lesions as well as on the clinical type of the disease. Modalities include surgical excision, chemotherapy, ionizing radiation, cryotherapy, laser irradiation, IFN- α 2 (Viferon) + IFN- α (Leukinferon) and PDT.

At the moment, in the literature there are few research data on the use of the method of PDT in the treatment of skin symptoms of KS.

Prokofiev A.A. et al. reported the effective use of PDT with local administration of PS «Photoditazine» in 16 patients with KS. There were no local recurrences at the time of observation up to 6 months [7]. The same authors described the case of the successful use of PDT in the treatment of the classic type of KS in the region of the glans penis in a patient of 60 years [8].

147 Kartashova M.G. et al. presented the experience of treating 5 patients with a chronic form
148 of idiopathic type of KS with PDT using local application of PS «Radachlorin». The drug was
149 injected into the tumor in a volume of 0.5-1 ml/cm² at an angle of 45°C to the surface of the
150 tumor, which corresponded to a dose of 1.75-3.5 mg/cm². As a source of laser radiation, a
151 medical laser magnetic pulse apparatus «LAMI» ($\lambda = 662 \pm 3$ nm) was used. The exposure
152 doses was 200-300 J/cm², the power density was 0.141-0.56 W/cm², and the irradiation field
153 diameter was 1.5-3 cm. During the entire follow-up period (9 months), local recurrences of
154 KS in the PI zone were not revealed [4].

155 Gelfond M.L. et al. reported on their own experience of treatment of a patient with KS by
156 the method of PDT with PS «Photoditazine» at a dose of 1.2 mg/kg. PI was carried out
157 3 hours after the administration of the drug with an exposure dose of light of at least 400
158 J/cm². At control observation in 3 months the authors noted stable clinical stabilization of the
159 process [9].

160 Park M.Y. et al. published results of treatment of a patient with 6 foci of KS in the region
161 of the lower limb. 20% methyl 5-ALA («Metvix») was injected directly into the tumor focus.
162 PI was carried out at an exposure dose of 100 J/cm² at a radiation power density of 100
163 mW/cm² ($\lambda = 580$ and 740 nm). The authors note that after 4 treatment sessions a partial
164 regression of pathological foci was noted [10].

165 Tardivo J.P. et al. studied the effectiveness of PDT (18 J/cm²) with local administration of
166 methylene blue and toluidine blue in the combined treatment of patients with KS. The author
167 noted a good therapeutic and cosmetic result of the treatment [11].

168 Szeimies R.M. et al. reported on the successful experience of treatment of 6 patients with
169 30 skin lesions of KS by PDT with photosensitizing agent indocyanine green at a dose of
170 2.2 mg/kg. PI was produced by a diode laser ($\lambda=805$ nm, the exposure dose was 100 J/cm²,
171 and the radiation intensity was 3 W/cm²). The authors noted the fact that the complete clinical
172 regression of pathological foci (n = 27) was noted in all patients with the initial stages of the
173 disease, in the case of the nodal form, only in 1 case out of 3 observations [12].

174 Thus, the PDT method has demonstrated its clinical effectiveness and can be
175 recommended for the treatment of patients with KS restricted and common forms against a
176 background of complex cytostatic therapy.

177

178 **4. CONCLUSION**

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180 [In our opinion, based on the available contradictory data on the insufficient effectiveness of
181 the use of the PDT method with local administration of PS and a small number of patients
182 included in the protocols, further studies of this method of treatment of KS with systemic
183 administration of PS photolon are very relevant].

184

185 **CONSENT (WHERE EVER APPLICABLE)**

186

187 Author declare that 'written informed consent was obtained from the patient (or other
188 approved parties) for publication of this paper and accompanying images.

189

190 **ETHICAL APPROVAL (WHERE EVER APPLICABLE)**

191

192 Author hereby declare that all medical and diagnostic issues have been examined and
193 approved by the appropriate ethics committee (N.N. Alexandrov National Cancer Center,

194 Republic Belarus) and have therefore been performed in accordance with the ethical
195 standards laid down in the 1964 Declaration of Helsinki.

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228 DEFINITIONS, ACRONYMS, ABBREVIATIONS

229 Here is the Definitions section. This is an optional section.

230 **Term:** Definition for the term

231

232 **APPENDIX**

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