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Photodynamic therapy with chlorin e_6 for skin metastases of melanoma

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Background: Photodynamic therapy (PDT) has been successfully applied in clinical settings to destroy neoplasms, but the efficacy of such a treatment is dependent on the type of neoplasm and the photosynthesizer used. Here, we perform a clinical assessment of PDT for skin metastases of pigmented melanoma using chlorin e_6.

Study design/Materials and methods: PDT with chlorin e_6 photosensitizer was administered to 14 patients with skin metastases from melanoma (10 females, four males, mean age 49.6 years). Chlorin e_6 at a dose of 5 mg/kg of patient's weight was intravenously injected. The treatment course consisted of two courses of PDT exposure 1 h after intravenous chlorin e_6 injection and 24 h post-injection. The light energy density for each skin tumor was 80–120 J/cm^2 per treatment, with a light power density of 250–300 mW/cm^2.

Results: All skin melanoma metastases that received PDT showed complete regression with no recurrence during the study period. The complete response of all skin metastases from melanoma occurred in eight cases after one PDT treatment. In the remaining six individuals, tumors required multiple PDT courses prior to complete regression. No cases of photodermatitis were registered. The Karnofsky performance scale score of the patients with skin metastases from melanoma showed no significant difference before and after PDT. No patients had significant changes in blood cell counts that would indicate chlorin e_6 systemic toxic effect. Blood chemistry and urinalysis did not show any evidence of chlorin e_6 renal and hepatic injury.

Conclusions: PDT with chlorin e_6 for skin metastases from melanoma is effective and well tolerated. Further clinical investigation of PDT with chlorin e_6 is warranted.

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Photodynamic therapy (PDT) is essentially a new approach to the diagnosis and

treatment of patients with malignant tumors (1, 2). At present, 5-aminolaevulinic acid (ALA) and some hematoporphyrin derivatives (HPDs, photofrin 2) are being widely used as PDT photosensitizers (2–4). PDT is implemented by injecting various photosensitizer dyes capable of selective accumulation in malignant tumors, followed by exposure to laser radiation (in the range of active absorption) that triggers the destruction of tumor cells in the presence of oxygen. The employment of laser equipment and a special guided light has made it possible to administer PDT in the treatment of pulmonary, esophageal, and gastric cancer (5–10). The advantages of PDT over conventional methods of malignant neoplasm treatment are that it allows selectivity of tumor destruction and repeated courses of treatment if necessary.

The efficacy of PDT was demonstrated in the treatment of basal cell carcinoma of the skin and metastases to the skin from breast cancer (2, 11). However, PDT for skin metastases from melanoma produced a clinical effect only in 20–30% of the patients (12, 13). The researchers hypothesized that this deficit might be due to the presence of a large amount of melanin pigment in tumor cells of pigmented melanoma, which intensively absorb optical radiation, resulting in only a shallow light penetration into the tumor tissue. This has led to recent efforts by researchers in the search for new and more effective photosensitizers, chlorin derivatives in particular (14, 15).

Chlorin e_6 was synthesized at the Laboratory of Photochemistry, National Academy of Sciences of the Republic of Belarus (16). PDT techniques were developed in experiments on animals with inoculated tumors and necrobiotic changes were demonstrated to occur in the tumor tissue exposed to PDT with chlorin e_6, followed by subsequent regression of the transplanted tumors in rats (17–19).

During the course of phase I clinical trials of PDT with chlorin e_6, we established that effective treatment with PDT is achieved at a chlorin e_6 dose of 5 mg/kg or higher, with the maximum tolerance dose of the drug being 18 mg/kg (20). The major side effects of chlorin e_6 are rigor, pain in the photoradiation area during the course of PDT procedure, and an increase in body temperature.

Methods

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Chlorin e_6 photosensitizer

Chlorin e_6 medical preparation produced by Dialek, Ltd (Minsk, Belarus) was used in all trials. Chlorin e_6 at a dose of 5 mg/kg of patient's weight was dissolved in 200 ml of 0.9% sodium chloride solution and intravenously injected during a 30-min period. One hour and 24 h post-injection, laser therapy was administered at tumor sites. After the photosensitizer administration, all the patients spent a week in a shaded ward. Two weeks after the treatment, patients were discharged and advised to wear dark glasses and avoid exposing the skin to bright sunshine.

Patients

For 24 months beginning in January of 2000, PDT was given to 14 patients with skin metastases from melanoma (10 females, four males, age mean 49.6 years). The Karnofsky performance scale (KPS) score of the patients was at least 80 at the time of enrollment (21). Pathologic examinations of one or two excised melanoma skin metastases were performed in all cases of multiple melanoma skin metastases before starting PDT.

Thirteen patients presented with melanoma progression after previous multi-modal treatment. All these patients had prolongation of skin metastases despite multiple courses of chemotherapy. No distant metastases into internal organs were observed. A female patient (case 13, Table 1) had an initial diagnosis of melanoma of the pedal skin with multiple metastases to the pedal skin. Another female patient (case 7, Table 1) had multiple (150) metastases to the skin of the

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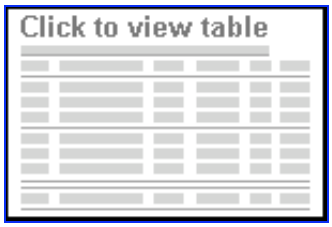

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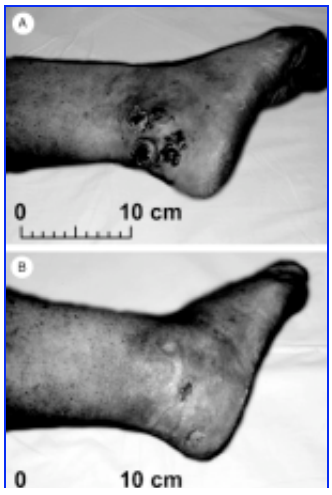
Table 1. Clinical results in 14 cases of skin metastases of melanoma



right inferior limb. Eight patients received one PDT course, three patients received two courses, and three patients received between three and five PDT courses. The clinical details of the 14 patients with melanoma skin metastases are summarized in Table 1. The Scientific and Ethic Committees of N.N. Alexandrov Research Institute of Oncology and Medical Radiology approved the protocol in January 1997, and all patients gave informed consent.

Immediately after the PDT treatment, the exposed area became pale gray with bright skin hyperemia surrounding it. Three days later, the tumor and up to 5 mm of the adjacent skin grew dark violet. Ten to fifteen days after photo-irradiation, a dry crust appeared in the area, which was rejected 1—1.5 months later. The wound completely healed 2.5—3 months after the treatment (Fig. 1). After crust rejection, in all cases we performed non-invasive imprint cytologic examinations from the bottom of the wound. No melanoma cells were seen in 13 cases after post-treatment examination. Only one patient (case 13) still showed the presence of melanoma cells after two courses of PDT, with additional treatment leading to complete regression. After the third PDT course, we did not find melanoma cells in the wound.

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Fig. 1. Complete response of intracutaneous metastases of pigmented melanoma after PDT: (A) before th...

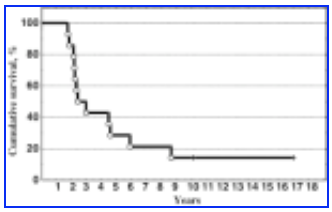

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Fig. 2. Overall survival of all patients.

Parameters of PDT with chlorin e_6

To administer PDT treatments, we used an LD 680—2000 laser unit (BioSpec, Ltd, Moscow, Russia) complete set including fiber-optic guides for external application with a microlens. The LD 680—2000 laser unit is based on a semiconductor laser diode (the wavelength of the generated laser radiation 670 nm), and is intended for PDT using photosensitizers with absorption in the spectral range of 660—690 nm. Before the PDT treatment, the light spot diameter was established so as to insure sufficient exposure of the peripheral part of the tumor. To achieve this goal, the size of the irradiated area should be at least 20% larger than the tumor size. We treated the lesions from one point of photo-irradiation only if their size was not more than 1 cm in diameter. In case of a large lesion (diameter of lesion more than 1 cm), we administered PDT treatment from several focal points. The treatment course consisted of two PDT exposures — 1 and 24 h after intravenous chlorin e_6 injection. The light energy density for each skin tumor per treatment was 80—120 J/cm^2, with a light power density of 250—300 mW/cm^2.

Statistical methods

We used the method described by Glass et al. (22) to determine the tumor surface area before and after PDT courses. The survival rate of all patients was also evaluated as of January 1, 2003. Survival curves for the patients were estimated by the Kaplan—Meier technique (23).

Results

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Clinical efficacy of PDT with chlorin e_6

All skin melanoma metastases treated with PDT showed complete regression during the study without recurrence during the follow-up period. Complete response (complete disappearance of all treated tumors) after one course of PDT was seen in eight cases. A female patient with pedal skin melanoma and multiple metastases to the pedal skin (case 13) receiving light radiation on a 3 cm thick tumor presented with only a partial response after the first PDT course, and that required three more courses of treatment separated by 2-month intervals to treat additional melanomas. Another female patient (case 3) received five courses (with 1.5-month intervals) of PDT because of excessive number of skin metastases of melanoma (120 tumors). All the irradiated lesions in this case were cured after one course of photo-irradiation. A complete response was seen in both cases following the administration of additional therapy, and no new skin melanoma metastases were seen during the course of follow up. In the remaining patients, the treatment of all individual lesions yielded complete regression after one course of PDT and

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newly appearing lesions were treated after additional courses, but PDT therapy was terminated due to the advanced progression of melanoma. Despite complete tumor destruction in these individuals, too many new metastases were seen post-treatment to consider continuing PDT on new tumors.

No new tumor growth occurred in the photo-irradiation area in the cases of complete response in the follow-up period of 6—24 months. The median overall survival time for the patients (since the time surgery was performed) was 883 days (Fig. 2). Eleven patients died due to the progression of melanoma (pulmonary, cerebral, and hepatic metastases).

Side effects of PDT with chlorin e_6

Chlorin e_6 administration caused rigor and temperature rise up to 38temp1.txttemp1.txt°C in two patients. No cases of severe pain during PDT were registered, but eight patients complained of pain for 2—5 days after PDT. They were administered MST-Continuous 60 mg *per os* daily, for 3—5 days. No cases of photodermatitis were noted. An increase of granulocytes was seen in all cases (average granulocyte counts 1 week before PDT were 2.8±0.2×1000/μl compared with 13.5±0.5×1000/μl 1 week after PDT). Three weeks after treatment, the neutrophil levels returned to a normal range. Additional blood chemistry and urinalysis did not show any evidence of chlorin e_6 renal and hepatic injury. The evaluation of the KPS score in the patients with skin metastases from melanoma showed no significant difference before and after PDT (Table 1).

Discussion

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At present, PDT photosensitizers, HPD (photofrin) and photofrin 2 (a purified form of HPD) in particular, are being widely used in clinical applications. However, these preparations have a number of disadvantages restraining application of the method:

(1) As the light energy absorption maximum of those photosensitizers falls at about 630 nm, the light sources of this wavelength provide a low penetrability of photo-irradiation, which make it impossible to employ PDT for deep-seated tumors.

(2) Slow excretion of HPDs from the skin significantly increases the probability of photodermatitis.

(3) Low selectivity of the photosensitizer accumulation in malignant neoplasms reduces penetrance of the malignancy.

For this reason, a keen interest is being displayed in identifying new sensitizers that localize more effectively in tumors, absorb more intensely at longer wavelengths, and can be prepared with high purity. Much of this interest has been directed towards chlorins (reduced porphyrins), whose typical absorption is strong in red light (14).

Chlorin e_6 belongs to the chlorin compounds, which contain a number of photophysical properties superior to those of HPD and photofrin 2. It possesses a higher photodynamic activity under *in vitro* and *in vivo* conditions (17—19). In contrast to photofrin, chlorin e_6 absorption peak is in the long-wave spectral area (660 nm), and this results in improved light penetrability in biological tissues.

Despite the available experience in the clinical application of chlorin derivatives (tetrahydroxyphenyl chlorin (mTHPC, Foscan), mono-L-aspartyl chlorin e_6 (Npe_6)) in PDT for malignant tumors (oral cancer, basal cell carcinoma, early carcinomas of the upper aerodigestive tract, mesothelioma, etc.), no reports can be found in

the literature on their use in the treatment of skin metastases from melanoma (24–29). Koderhold et al. (30) reported about their experience with PDT in dermatology. They cured 15 patients with skin tumors (12 with basalioma, one with mesothelioma of scrotum, one with Queyrat's erythroplasia, and one with skin metastases of melanoma) using PDT with Photosan III. All patients were treated by a dye argon laser system. The light dose was 50–80 J/cm^2. The patient with skin metastases of melanoma gave no response.

We used a power density of 250–300 mW/cm^2 on the basis of the experimental *in vivo* data of Michailov et al. (31). The authors used a total light dose of 360 J/cm^2, which was delivered at the rates of 260, 320, 380, 440, and 500 mW/cm^2. Complete tumor response was obtained with mice in 40% of cases following 380 mW/cm^2.

PDT of malignancies at a power density of 250 and greater mW/cm^2 can cause the local tumor hyperthermic effect. According to the data of Kimel et al. (32), damage to the chick chorioallantoic membrane vasculature due to combined PDT+hyperthermia was compared with the outcome of the individual modalities, and a synergistic effect of about 40% was observed. Leunig et al. (33) in their research of evaluation of photodynamic therapy-induced heating of melanoma *in vivo* also concluded that a combination of PDT and hyperthermia might act in an additive, synergistic manner. We suppose that this possible synergistic effect of local hyperthermia during photo-irradiation may be of great importance for good antitumor effect of PDT with chlorin e_6 on melanoma skin metastases.

In the treatment of numerous malignant tumors of the skin, PDT procedures may be repeated to achieve the desired effect. For instance, Robinson et al. (34) described the treatment of two patients with Bowen's disease with an overall number of tumors of more than 500. Five treatments provided complete cure (6-month follow up). We had a case of PDT for a female patient with skin metastases from pigmented melanoma, 150 metastases in total. The patient received five PDT courses during a year and a half. No new skin metastases from melanoma were detected in the patient within 2 years after the treatment.

It is noteworthy that our study is limited with only 14 cases because of the relatively low incidence of isolated melanoma skin metastases without distant metastases into internal organs. The median survival for patients with melanoma may vary between 218 days and 1977 days (35, 36). The median survival of our patients was 883 days. In this situation, it is difficult to determine the PDT influence on the general survival of the patients, with only skin melanoma metastases as most of the patients' mortality was attributable to metastatic tumors in other organs.

Akimov et al. (37) achieved the total response only in 56% cases after chemotherapy (dacarbazine+cisplatin+BCNU+tamoxifen) in combination with laser coagulation for disseminated skin melanoma (16 patients). Using only PDT, we saw a complete response in eight cases of disseminated skin melanoma after one PDT course and in another six cases after two to five PDT courses without severe toxic side effects.

In conclusion, PDT with chlorin e_6 for skin metastases from pigmented melanoma is well tolerated and effective, especially in cases of isolated melanoma skin metastases. Further clinical investigation of PDT with chlorin e_6 is warranted to define the place of PDT in the treatment of skin metastases of melanoma.

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