CAPABILITIES OF INTRAOPERATIVE PHOTODYNAMIC THERAPY FOR TREATMENT OF LOCALLY ADVANCED BREAST CANCER

Filonenko E.V.[1], Saribekyan E.K.[1], Ivanova-Radkevich V.I.[2]
[1]National Medical Research Radiological Centre of the Ministry of Health of the Russian Federation, Moscow, Russia
[2]Peoples Friendship University of Russia, Moscow, Russia

Abstract

The original method of intraoperative photodynamic therapy for multimodality treatment of primary and recurrent breast cancer for devitalization of malifnant cells at wound surface and for prevention of further cancer dissemination was developed in P.A. Herzen Moscow Cancer Research Institute. The developed method was approved in 79 patients with locally advanced breast cancer stage IIB and IIIA,B,C with poor prognostic factors. For photodynamic therapy the photosensitizer photosens (30 min intravenous infusion at dose of 0.3 mg/kg of body weight 2 h before surgery) was used in 56 patients; alasens (solution in 100 ml of still drinking water, orally at dose of 30 mg/kg of body weight 2 h before general anesthesia) — in 23 patients. The surgical field was irradiated on a single occasion: the dose of laser irradiation on the bed of removed primary or recurrent tumor was 20–30 J/cm², in the removed regional lymph nodes area – 50 J/cm². Long-term results of the treatment were assessed in 34 patients: there were no disease progression in 50% of patients, 14.7% of patients had locoregional recurrence, distant metastases were in 35.3% of patients.

The level of photosensitizer accumulation in tissue was additionally analyzed in 26 patients by fluorescence intensity in tumor and in normal breast tissue. After injection of alasens the increase in level of alasens-induced protoporphyrin IX fluorescence was recorded in tumor (the average diagnostic parameter was 6.5 a.u.) and in intact breast tissue (an average of 0.47 a.u.), tumor/normal tissue fluorescence contrast varied from 3 to 33. The level of protoporphyrin IX accumulation was noticed to be lower in tumors with pathomorphological response after neoadjuvant therapy. For photosens value of the average diagnostic parameter in normal breast tissue was 5.6 a.u., in tumor – 34.3 a.u., tumor/normal tissue fluorescence contrast – from 2 to 9.

Keywords: intraoperative photodynamic therapy, fluorescence contrast, alasens, photosens, breast cancer.

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Contacts: Filonenko E.V., e-mail: derkul23@yandex.ru

Introduction

In breast cancer (BC) illness patterns, the share of patients with a locally advanced process reaches 30%. Almost in half of the cases, treated patients suffer from relapses, most of which fall on the first 1,5-2 years after the treatment. The disease relapses declare themselves by metastases in skeleton bones, lungs, pleura, substernal lymph glands, liver, small pelvis and other organs, as well as by loco-regional restart of growth in skin and chest wall hypoderm. In the cases of big dimensions (T4aNx), conglomerates in axillary regions (TxN2-3) and hydropic cancer types (T4b,d), the prevalence of post-surgical local progression of cancer as a relapse and continued growth reaches 40% [1].

The treatment of a locally advanced breast cancer is a huge task for onco-mammalogy, as it presupposes combination therapy including surgery with subsequent radiation- and drug treatment for prevention of a possible cancer relapse. However, in most cases, radiation treatment and chemo-hormonotherapy cannot completely destroy cancer cells. For this reason, during the months and years after the surgery, it is necessary to treat the patients to prevent the cancer progression. In this connection, treatment of a locally advanced breast cancer sometimes acquires a “chronic” character [2]. During treatment of a progressive locally advanced breast cancer, use is made of successive replacements of chemo- and hormonal drugs, bio-therapy, radiation therapy of metastases in bones and other organs, treatment by bi-phosphonates, radio-thermal ablation of liver metastases, different surgical operations aimed at cyto-reduction, photodynamic therapy (PDT) of endermic metastases, disseminations in pleura, abdominal cavity, etc. [3–6].

The article deals with possibilities of intra-operative PDT during treatment of a primary and relapsing BC. The task of intra-operative PDT is de-vitalization of wound surface cancer cells in order to prevent further advancement of the cancerous process – during surgeries aimed at removal of a primary tumor and regional metastasis zones or secondary endermic disseminates.

The PDT method is based on the ability of a photosensitizer, under local exposure to light with a certain wave-length corresponding to its absorption peak, to generate cyto-toxic agents (particularly singlet oxygen), which cause damage of tumor tissue structural elements. The effectiveness of the photodynamic damage of a sensitized cell is, in many ways, determined by the intracellular concentration (accumulation level) of a sensitizer, its localization in a cell, and a photo-chemical activity (quantum efficiency of singlet oxygen or free radicals generation) caused by a laser irradiation light dose [6].

Apart from a direct cyto-toxic influence on tumor cells, an important role in their destruction during PDT is played by:

- blood supply disturbances due to damage of tumor tissue blood vessels’ endothelium;
- cytokine reactions conditioned by stimulation of the tumor necrosis factor production, activation of macrophages, leucocytes and lymphocytes.

Synthesis and tests of the first photosensitizer – hematoporphyrin derivative (HpD) – were conducted in 1950 [7–8]. This marked the beginning of the photodynamic therapy contemporary history. During the subsequent years there were conducted multiple experimental and clinical works on diagnostics and treatment of malignant tumors with the help of hematoporphyrin derivatives. In Russia, experimental studies of PDT started in 1980, clinical tests – in 1992. The first clinical studies were carried out with the use of photogem photosensitizer. Later, such preparations as radahlorin, photoditazin, photosens and alasens were allowed for clinical use [9].

The mechanism of action of alasens differs from other photosensitizers. The active substance of this preparation is 5-aminolevulinic acid, which is a precursor of photo-active protoporphyrin IX in the human body. Its mechanism of action is based on the ability of tumor cells to increase accumulation in presence of exogenic 5-aminolevulinic acid of protoporphyrin IX. A sufficient amount of protoporphyrin IX is accumulated and preserved in a tumor during a few hours, while in normal cells and tissues its accumulation does not take place. The result of this is high selectiveness of protoporphyrin IX content in a tumor with reference to a surrounding tissue. It can reach 10-15-fold value for different tumors [10].

In P.A. Herzen Moscow Cancer Research Institute, scientists developed and tested a method of intraoperative PDT, which presupposes the use of photosens and alasens in patients with a locally advanced breast cancer of stages IIB and IIIA,B,C.

Materials and methods

There were treated 79 patients with a locally advanced breast cancer. The division of patients by the disease stages and the extent of operative intervention is presented in Table 1.

The age of the patients was from 35 to 75 years (Table 2).

The division of patients by histologic types of cancer is given in Table 3.

The primary patients with cancer of IIB, IIIA and IIIB stages were treated by a complex method, including surgery, drug therapy and, if necessary, radiation therapy. The patients with IIB and IIIA stages of the disease underwent a radical Madden mastectomy, with IIIB stage – a radical extended modified mastectomy. All the patients underwent intraoperative PDT.

During the research, 56 patients withstood intraoperative PDT with photosens preparation (registration certificate R N000199/02 of 04.03.2010, Federal State Unitary Enterprise "State Scientific Centre NIOPIK", Russia). Photosens was administered intravenously, drop wise, in the dose of 0.3 mg/kg of the patient's body weight, 2 hours before the surgery. For the irradiation of the surgical area, use was made of an optical radiation source with the wavelength of 670 nm, which corresponds to the maximum of photesens spectral absorption.

Intraoperative PDT with alasens preparation (registration certificate LP-001848 of 21.09.2012, FSUE SSC "NIOPIK", Russia) was administered to 23 patients. Dissolved immediately before use in 100 ml of still drinking water, alasens was ingested by patients in a dose of 30 mg/kg of the patient's body weight, 2 hours before the beginning of general anesthesia. To conduct a PDT session, use was made of an optical radiation source with the wavelength of 630 nm, which corresponds to the maximum spectral absorption of alasens-induced protoporphyrin IX.

Table 1.
Distribution of patients according to stage of disease and extent of surgery

Stage of disease	Radical mastectomy by Madden	Modified extended radical mastectomy	Other surgeries	Total
IIB (T2N1M0)	22 (27,8%)	-	4 (5,1%)	26 (32,9%)
IIIA (T2N2M0, T3N2M0)	27 (34,2%)	-	-	27 (34,2%)
IIIB (T4a,bN1M0, T4N2M0)	9 (11,4%)	17 (21,5%)	-	26 (32,9%)
Total	58 (73,4%)	17 (21,5%)	4 (5,1%)	79 (100%)

Table 2.
Distribution of patients according to age

Age	Number of patients
35–40	4 (5,1%)
41–50	21 (26,6%)
51–60	28 (35,4%)
61–70	21 (26,6%)
71–75	5 (6,3%)
Total	79 (100%)

Table 3.
Distribution of patients according to histological types of cancer

Histological type	Number of patients
Ductal carcinoma	42 (53,2%)
Lobular carcinoma	11 (13,9%)
Mixed ductal and lobular carcinoma	16 (20,2%)
Other types	10 (12,7%)
Total	79 (100%)

The surgical area was irradiated once, intraoperatively. One dose of laser irradiation at the zone of the removed primary or recurrent tumor was 20-30 J/cm^2, at the zones of the removed regional lymph glands – 50 J/cm^2. The intraoperative PDT was used for 3 variants of surgery: resection of a dermic-subdermic flap in case of endermic metastases, radical Madden mastectomies – at stages IIB and IIIA, radical extended mastectomies – at stage IIIB.

During the stage of the intraoperative PDT method development, the researchers additionally studied the level of photosensitizers accumulation in tissues by the intensity of fluorescence in the tumor and healthy breast tissue. These tests were conducted for 26 patients (with alasens – 23 patients, with photosens – 3 patients). The level of fluorescence of alasens-induced protoporphyrin IX or photosens was estimated by a fluorescent signal registered in tissues, using the method of locally fluorescent spectroscopy with the device LESA-01-BIOSPEC (BIOSPEC, Russia). After the surgery, the removed preparation was viewed in white light, then – in the fluorescence mode with measurement and registration of the spectra of fluorescence from the surface of tumor focal points and unaltered tissue of the breast. A diagnostic catheter was used to 3-times measure of the spectrum from every point – in order to minimize distortions; the presence and intensity of fluorescence, the limits of the fluorescent sources, correlation with tumor sources visible in white light were evaluated. A protocol was drawn up based on the results of every spectral research (see Fig.).

Fluorescence was excited in the green spectrum range (532 nm) in case of alasens use, and in the red range (630 nm) – in case of photosens use. The registration of fluorescence was performed within the range from 540 to 900 nm and from 640 to 900, respectively. The level of fluorescence was characterized by a diagnostic parameter (DP) calculated in automatic mode.

Results and discussion

Prior to administration of alasens or photosens, the DP value in normal tissue was close to zero (0,02 a.u. and 0,03 a.u., respectively), which is declarative of the absence of photosensitizers in the examined tissue.

In all 23 patients, who was administered alasens before the surgery, there was a registered increase in the level of protoporphyrin IX fluorescence in the breast tumor and unaltered tissue. In the normal breast tissue, the DP varied from 0,14 to 1,8 a.u., in average it was 0,47 a.u. In the breast tumor, the DP varied from 1,1 to 32 a.u., with 6,5 a.u. in average. In all observations, the DP level in the tumor was higher than in the normal tissue. The value of “tumor/norm” fluorescent contrast varied between 3 and 33, with 14 in average.

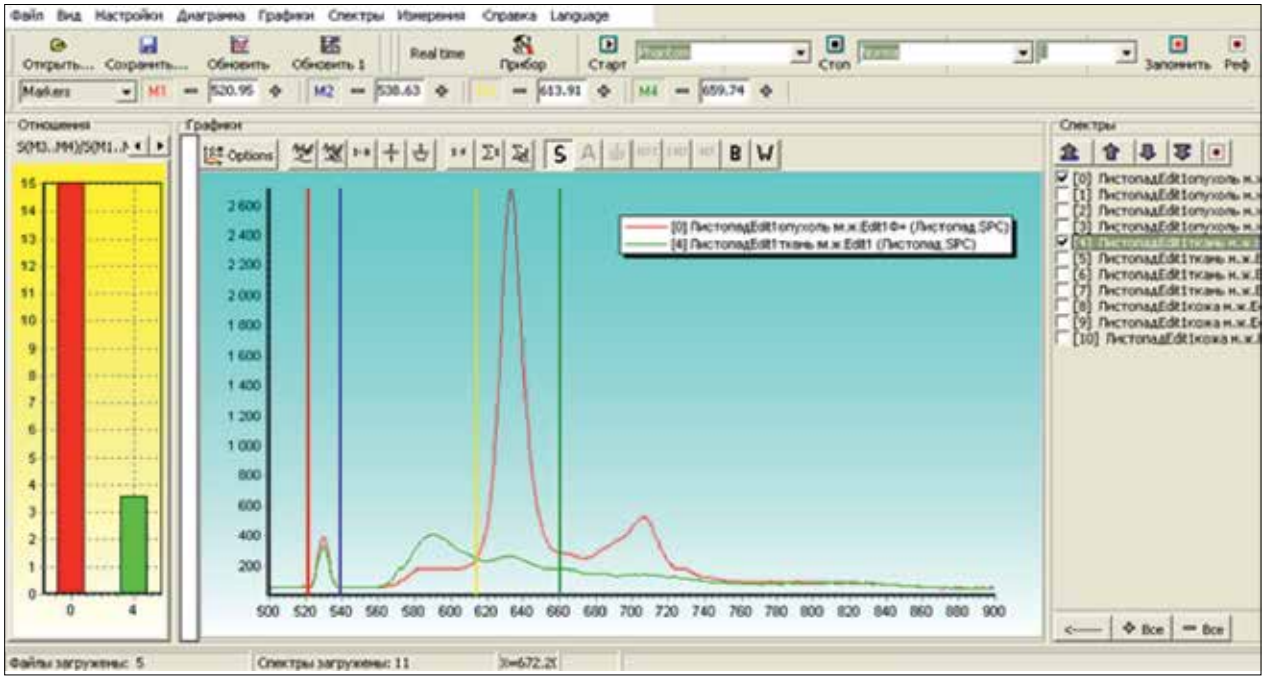

Fig. Electronic testing record

8 patients out of 23 underwent from 2 to 4 courses of neoadjuvant chemotherapy. In 2 of them, by the data of the morphological study, there was a registered medical pathomorphism of stage II, in 6 patients – of stage I. Herewith, in patients with stage II of pathomorphism, the DP in the tumor tissue was low and equal to 1,1 a.u. In 5 out of 6 patients with pathomorphism of stage I, the DP was close to average values in the group and varied from 4,3 to 5,7 a.u. One patient with stage I of pathomorphism had low registered values of DP in the tumor – 1,1 a.u.; macroscopically, in that case there were significant necrosis focal points in the tumoral nodosity. Thus, after conductance of neoadjuvant chemotherapy, the level of the photosensitizer accumulation in the tumor is lower in the patients with medical pathomorphism.

In 3 patients (those with the studied level of the photosensitizer fluorescence after administration of photosens), the DP values in the breast normal tissue was 5,6 a.u. in average, in the tumoral tissue – 34,3 a.u., while the "tumor/norm" fluorescent contrast was from 2,2 to 9,3.

The conducted research confirmed an increased accumulation of protoporphyrin IX and photosens in the breast tumor, which proves the possibility of a selective intraoperative influence of PDT with alasens and photosens preparations. It is necessary to note, that PDT was mainly used in prognostically unfavorable situations, i.e. in the cases with more aggravated factors of the disease prognosis – high-grade cancer, process dissemination, etc. The authors managed to follow remote results in 34 patients (Table 4).

During the analysis of 3-year treatment results, in 17 patients (50%), progression of the disease was not found; 5 patients (14,7%) were diagnosed a local-regional relapse, while metastases were found in 12 (35,3%) patients.

Intraoperative PDT complications and possible preventive measures

The main side effect of PDT with the use of photosens is the increased skin photosensibility conditioned by a long presence of the photosensitizer in the skin and requiring strict compliance with the light regime: it is necessary to avoid irradiation by direct sunlight from the first day after the photosensitizer administration, to treat open body surfaces with sunblock cream and antioxidant ointment, to wear sun glasses. According to the Instruction on medical use of photosens, the terms of compliance with the light regime during the preparation use are from 4 to 6 weeks. In case of the light regime violation, or in case of its compulsory extension, during 1-2 months after photosens administration, there can be sunburns in the form of hyperemia and edema of open skin surfaces with further pigmentation (suntan). In the present research, after administration of photosens, sunburns of stage I was registered in 23% of the patients; in 17%, anaplerosis was longer due to increased lymphorrhea.

According to the Instruction on medical use of alasens, the period of compliance with the light regime is 1 day. Possible complications in the case of non-compliance with the light regime are similar to those of photosens. However, they are significantly less expressed. In the conducted research, after administration of alasens, only 16% of patients noticed face skin hyperemia, which subsided during 1-3 days. Prolongation of the after-surgery wound healing was not registered.

Table 4.
Results of 3-year follow-up in patients included in the study

Stage	Recurrence-free	Locoregional recurrences	Distant metastases	Total
IIB	7 (63,6%)	1 (9,1%)	3 (27,3%)	11
IIIA	6 (50,0%)	2 (16,73%)	4 (36,3%)	12
IIIB	4 (36,4%)	2 (18,2%)	5 (45,4%)	11
Total	17 (50,0%)	5 (14,7%)	12 (35,3%)	34

Conclusion

The method of intraoperative photodynamic therapy is promising for breast cancer treatment and is aimed at devitalization of the wound surface cancer cells and prevention of after-surgery relapses. The use of two photosensitizers, namely, photosens and alasens, is possible during intraoperative PDT. Final results on the advantages of anti-tumoral influence of PDT with application of the first or second preparation have not yet been obtained. The revealed advantages of alasens compared with photosens are in the simplicity of its use and significantly less frequent complications. However, the study of alasens-induced protoporphyrin IX distribution in the tumor and normal tissue of the breast showed that the patients undergoing neoadjuvant chemotherapy demonstrated a decrease in the accumulation of the modified protoporphyrin IX upon reaching medical pathomorphism of stage II. That can be related to the development of dystrophic and necrotic changes in the tumor cells. Thus, further study, development and improvement of the intraoperative PDT method are reasonable and progressive.

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