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Polychromatic light (480–3400 nm) similar to the terrestrial solar spectrum without its UV component in post-surgical immunorehabilitation of breast cancer patients

Natalia A. Zhevago [a], Alexander A. Zimin [a], Tatyana V. Glazanova, M.D., Ph.D. [b], Natalia I. Davydova [c], Natalia V. Bychkova [c], Zhanna V. Chubukina [b], Anna I. Buinyakova [d], Marina F. Ballyuzek [e], Kira A. Samoilova [a,*]

[a] Institute of Cytology of the Russian Academy of Sciences, 4, Tikhoretsky Ave., Saint-Petersburg 194064, Russia
[b] Russian Research Institute of Hematology and Transfusiology of Federal Medico-Biological Agency, Laboratory of Immunohematology, 16, 2nd Sovetskaia, 191024 Saint-Petersburg, Russia
[c] Nikiforov All-Russian Center of Emergency and Radiation Medicine, Russian Federation Ministry of Emergency Situations, Laboratory of Clinical Immunology, 54,Optikov Street, Saint-Petersburg 197345, Russia
[d] Clinical Hospital of the Russian Academy of Sciences, Mammology Department, 72, Toreza Ave., Saint-Petersburg 194017, Russia
[e] Clinical Hospital of the Russian Academy of Sciences, Medical Administration, 72, Toreza Ave., Saint-Petersburg 194017, Russia

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ABSTRACT

To this day, two methods of phototherapy (PT) have been successfully used in post-surgical immunorehabilitation of patients with breast cancer (BC): intravenous laser irradiation of the patients' blood and reinfusion of lympholeukosuspension of BC patients after single irradiation with HeNe laser. The objective of this pilot experimental study was to verify the effectiveness of the percutaneous use of polychromatic visible light combined with polychromatic infrared (pVIS + pIR) radiation similar to the major components of natural solar spectrum in post-surgical management of BC patients. Patients with BC (adenocarcinoma) of I–II stages, n = 19 who had undergone mastectomy, were divided into 2 groups. The control group of patients (n = 8) underwent a conventional course of post-surgical rehabilitation and sham irradiation. Patients of the PT group (n = 11) additionally received 7 days of daily treatment with polychromatic light on the sacral area, D = 15 cm. The PT course began on the day after mastectomy (Bioptron-2 device; Switzerland, 480–3400 nm, 95% polarization, 40 mW/cm^2, 24 J/cm^2). Mastectomy produced many changes in cellular and humoral immunity, which was recorded on the 1st and 8th post-surgical days. The PT course resulted in a faster normalization of post-surgical leukocytosis and activation of cytotoxic CD8$^+$ T-lymphocytes (Lym), reduced the elevated concentration in blood of immune complexes and in parallel promoted cytotoxic activity of CD16$^+$/CD56$^+$ NK-cells. The PT up-regulated the number of NK-cells in patients with its decrease on the 1st post-surgical day and prevented the decrease in the amount of monocytes, CD19$^+$ B-Lym, CD3$^+$ T-Lym, CD4$^+$ T-helpers, activated CD3$^+$/HLADR$^+$ T-Lym, and the decrease of the phagocytotic capability of neutrophils. PT blocked the down-regulation of the IgM, IgA concentration and abnormally sharp increase of the proinflammatory cytokine IFN-γ content. Therefore, a 7-day course with polychromatic light prevented the development of immunosupression in the BC patients at the early post-mastectomy period.

1. Introduction

Breast cancer (BC) is the second most common cancer in the world and, by far the most frequent cancer among women with 1.67 million new cancer cases diagnosed in 2012 (25% of all cancers) [1]. Postoperative morbidity from breast or axillary procedures for breast cancer is reported to be as high as 30% [2]. Most commonly, early postoperative problems include wound issues such as cellulitis, flap necrosis, abscess, dehiscence, hematoma and seroma. It is necessary to avoid delay in wound healing which may increase the risk of long-term morbidity. It is well known, that the immune system and microcirculation play a crucial role in regenerative processes. Therefore, appropriate and timely rehabilitation is vital in the recovery from breast cancer surgeries, including breast-conserving surgery, mastectomy, axillary lymph node dissection and breast reconstruction [3].

Conventional BC treatment methods (surgery, chemo- and radiotherapy) may cause immunodepression. The immunorehabilitation of BC patients is considered to be an important part of the treatment and recovery: the cellular and humoral components of the immune system play a critical role in tumor growth and metastasis, as well as greatly influence the outcome of the treatment [4,5]. In the monograph

* Corresponding author.
E-mail address: samoilova3@yandex.ru (K.A. Samoilova).

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"Immunotherapy of malignant tumors" written by V. Karandashov et al. [6] the antitumor efficiency of various phototherapeutic methods is discussed. Reinfusion of suspension of autologous lymphocytes and leukocytes after their laser irradiation [7], as well as intravenous laser irradiation of blood [8,9] were used for immune rehabilitation treatments in cancer clinics of Moscow and Kiev in the 1980s. It was concluded that invasive methods of phototherapy (PT) have anti-inflammatory, immunomodulatory, and wound-healing effects. Concurrently, reports of other authors [10–15] and our own studies [16–19] indicate, that similar effects can also be achieved by application of non-invasive phototherapeutic sessions. In our studies the PT course included the repeated irradiations of small area of body surface with polychromatic visible and polychromatic infrared light (pVIS + pIR, 480–3400 nm). This is close to natural solar radiation by spectral content and power density without the UV component. It should be noted, that pVIS + pIR light constitutes 97% of the terrestrial solar radiation energy and thereby is an important environmental factor. From the evolutionary aspect, in human and animal organisms, pVIS + pIR light could have been a major factor in promoting the development of adaptive mechanisms of its absorption and utilization, and specifically, in the development of the mechanisms to decrease the immunosuppressive and carcinogenic effects of solar UV radiation.

The aim of the present work was to verify the effectiveness of the percutaneous irradiations with pVIS + pIR light for post-surgical immunorehabilitation of BC patients, which is in good compliance with distinct contemporary tendency of using the physical medicine methods for rehabilitation of oncological patients [20].

2. Material and Methods

2.1. Patients

The work was carried out at the Mammology Department of the Clinical Hospital of the Russian Academy of Sciences in St. Petersburg. The Ethical Committee of the Hospital approved the design of the study. The inclusion of patients in the study was voluntary, with the provision of rights and protection of the patient. Nineteen women with BC (adenocarcinoma) of I–II stages participated in the study, their mean age was 54,0 ± 4,28 years.

2.1.1. Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study enrollment.

1. Patients are female 18 years of age or older;
2. Patients who have histologically confirmed and newly diagnosed breast cancer;
3. Patients who have Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1;
4. Patients who have clinical I or II operable breast cancer according to the American Joint Committee on Cancer (AJCC) Breast Cancer Staging, 7th Edition;
5. Patients who have adequate bone marrow function, defined as: absolute neutrophil count ≥1.5 × 10^9/l; hemoglobin ≥100 g/l; platelets 100 × 10^9/l;
6. Patients who have adequate hepatic and renal function, defined as: aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase ≤2.5 × upper limit of normal (ULN); total bilirubin ≤1.5 × ULN; serum creatinine ˜120 μmol/l;
7. Subjects are able to understand the study objectives and procedures and willing to show consent by signing the informed consent documents.

2.1.2. Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study. Patients who: 1. have bilateral breast cancer; 2. are pregnant or lactating; 3. have had prior treatment for breast cancer, including chemotherapy, biologic therapy, hormone therapy, immunotherapy, radiation; 4. have other active malignancy or history of malignancy in the past 5 years; 5. have New York Association Stage 3 or 4 cardiac disease; 6. have autoimmune diseases including rheumatoid arthritis, type I diabetes mellitus or any other autoimmune disease that, in the opinion of the investigator, would compromise the subject's safety; 7. have immune deficiency diseases or immunosuppressive therapy that might interfere with appreciate immune response; and 8. have positive test for HIV, or hepatitis B (HBsAg) or hepatitis C.

All patients were divided into two groups and then underwent mastectomy. Allocation of patients into each group was by the discretion of the hospital medical doctors. They based their choice of patients according to the following inclusion criteria: similarity of diagnosis (adenocarcinoma), newly diagnosed after mammographic, ultrasonic and histological studies; comparability of patient age (in control (PT^-) group — 57,6 ± 2,99 years and PT^+ group — 54,3 ± 3,87 years); similarity of surgical protocols.

All patients received a course of conventional post-surgical rehabilitation. Patients of the PT^+ group (n = 11) additionally received daily treatment with pVIS + pIR light, while control group of patients (n = 8) received sham irradiation. The PT started on the day after mastectomy and consisted of 7 daily sessions. The low number of patients in each group is explained by the fact that fibroadenoma was the dominant diagnosis in patients treated at the Mammological Department, and the number of BC patients was limited. Additionally some of the BC patients declined the offer to participate in the trial with photoirradiation and repeated blood test or dropped out of post-surgical treatment.

2.2. Phototherapy

A Bioptron-2 phototherapeutic device (Bioptron AG, Wollerau, Switzerland) was used for irradiation of the lumbar-sacral area, 15 cm in diameter (480–3400 nm, polarization level 95%, power density 40 mW/cm^2, energy density 24 J/cm^2, duration of irradiation — 10 min). The irradiation procedure was developed based on studies on photoimmunomodulation in healthy volunteers [16–19] and in accordance with guidance from the Russian Oncological Scientific Centre not to treat with low level laser light the skin projections of tumors [21].

2.3. Immunological Parameters

Immunological parameters were analyzed before surgery and PT, 1 and 8 days after mastectomy and PT. The amount of leukocytes in peripheral blood was counted on a Cell-Dyn device (Abbott, USA). To determine the subsets' composition of lymphocytes (Lym), they were labeled by monoclonal antibodies to CD markers of human leukocytes (Beckman Coulter, USA) and studied on an FC-500 flow cytometer (Beckman Coulter, USA). This part of the study was performed in the Laboratory of Immunohematology of Russian Research Institute of Hematology and Transfusiology in St. Petersburg, providing the control group values obtained in this laboratory from healthy donors using the same methods and reagents [22].

In the same laboratory with a capability of neutrophils to phagocytize bacteria (*Staphylococcus aureus*) was studied on smears with the aid of a light microscope, using the standard procedure [23]. The norm values obtained in this laboratory were published in the paper [24]. Cytolytic activity of natural killers (NKs) was evaluated by the DNA-cytometry method with an Epics XL flow cytofluorometer (Beckman Coulter, USA) [25]. The method is based on calculating the difference (1.47-fold) between the modal number of chromosomes in human Lym and that in human malignant K-562 cells, used as the effector and target cells, respectively. MultiCycle AV ver. 3 programme (Beckman Coulter, USA) was used for evaluation of histograms in control and irradiated samples. In each sample 10,000 events were