PHOTODYNAMIC THERAPY OF INTRADERMAL METASTATIC BREAST CANCER (LITERATURE REVIEW)

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Abstract

In recent years, an increase in the incidence of breast cancer has been observed throughout the world, and in 20% of cases, with the development of intradermal metastases. The possibilities of surgical and radiation treatment of intradermal breast metastases are quite limited, and the effectiveness of polychemotherapy using standard regimens does not exceed 22–27%, while the period of remission, in general, is only 2–3 months. Photodynamic therapy (PDT) is a promising treatment for intradermal metastases of breast cancer. The experience of using PDT in this nosology is quite limited, but the results show its high efficiency and safety. Thus, several Russian studies are devoted to assessing the effectiveness of PDT of intradermal breast metastases with Photolon, a chlorin series photosensitizer. According to the authors, the therapeutic effect was achieved in 85–97% of patients (the percentage of patients with full and partial effect was 73–85%). Studies on the effectiveness of PDT in patients with the same nosology using the Photosens photosensitizer show a slightly lower effectiveness – the therapeutic effect was achieved in 81.8% of cases, while the proportion of patients with full and partial effect was only about 50%. Several studies have been carried out abroad on models of metastatic breast cancer using new photosensitizers (e.g. sodium sinoporphyrin) and new combined PDT regimens (e.g. adjuvant PDT with fluorouracil or Capecitabine). The obtained results demonstrate the promise of new approaches: PDT with sodium sinoporphyrin inhibited the growth of both the tumor itself and its metastases; the use of adjuvant regimens led to an increase in the tumor cells differentiation in the animal model, the cessation of tumor and metastatic foci growth.

Keywords: breast cancer, skin metastases, photodynamic therapy, photosensitizer, photochemical reaction.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ ВНУТРИКОЖНЫХ МЕТАСТАЗОВ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ (ОБЗОР ЛИТЕРАТУРЫ)

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Резюме

В последние годы во всем мире наблюдается рост заболеваемости раком молочной железы (РМЖ), причем в 20% случаев при РМЖ происходит развитие внутрикожных метастазов. Возможности хирургического и лучевого лечения внутрикожных метастазов РМЖ достаточно ограничены, а эффективность полихимиотерапии с применением стандартных схем не превышает 22–27%, при этом срок ремиссии, как правило, составляет лишь 2–3 мес. Фотодинамическая терапия (ФДТ) является перспективным методом лечения внутрикожных метастазов РМЖ. Опыт применения ФДТ при данной нозологии достаточно ограничен, но полученные результаты демонстрируют его высокую эффективность и безопасность. Так, несколько российских исследований посвящены оценке эффективности ФДТ внутрикожных метастазов РМЖ с фотосенсибилизатором хлоринового ряда фотолон. По данным авторов, лечебный эффект был достигнут у 85–97% пациенток (доля пациенток с полным и частичным эффектом составляла 73–85%). Исследования эффективности ФДТ у пациенток с такой же нозологией с использованием фотосенсибилизатора фотосенс демонстрируют несколько меньшую эффективность – лечебный эффект был достигнут в 81,8% наблюдений, при этом доля пациенток с полным и частичным эффектом составляла только около 50%. За рубежом проведен ряд исследований на моделях метастазирующего РМЖ с использованием новых фотосенсибилизаторов (например, синопорфирина натрия) и новых комбинированных схем ФДТ (например, адъювантная ФДТ с 5-фторурацилом или капецитабином). Полученные результаты демонстрируют перспективность новых подходов: ФДТ с синопорфирином натрия ингибировала рост как самой опухоли, так и ее метастазов; применение адъювантных схем привело к повышению дифференцировки опухолевых клеток у животной модели, прекращению роста опухоли, а также метастатических очагов.

Ключевые слова: рак молочной железы, кожные метастазы, фотодинамическая терапия, фотосенсибилизатор, фотохимическая реакция.

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Breast cancer, which affects about 1.2 million women in the world every year, over 52,000 in the Russian Federation and more than 4,000 in Kazakhstan, attracts focused attention of specialists because of its increasing prevalence and high mortality rate of the patients. Thus, according to official statistics, the incidence rate of malignant tumors of this localization in the Russian Federation in the period from 2008 to 2017 increased from 67.95 to 89.60 per 100,000 people, i.e., a 33.8% increase had place [1]. In the Republic of Kazakhstan, only from 2012 to 2017, the incidence of breast cancer increased from 21.3 to 24.5 per 100,000 population. Moreover, according to the forecasts of specialists of the International Agency for Research on Cancer, over the next two decades, the number of patients diagnosed with breast cancer will almost double [2].

Surgery still remains the main treatment against breast cancer: in accordance with the modern concept of surgery development, the scope of operations on the mammary gland is increasingly reduced to organ-preserving treatment, including limited removal of clinically negative axillary lymph nodes. In addition, an increase in survival and a decrease in mortality from malignant neoplasms of the mammary gland is associated with the appropriate use of systemic therapies [3].

However, the proportion of patients with stage III–IV of breast cancer is still high, reaching 45%, according to some reports [4]. In this context, in 20% of observed cases, the development of intradermal metastases is noted, mainly after surgical treatment. As a rule, the treatment of metastatic breast cancer includes systemic therapy (chemotherapy, hormone therapy) used in combination with radiation therapy and excision of the metastatic focus. However, it should be noted that surgical treatment in such cases is not always possible due to the multiple nature of the pathologic process and its high extent. In addition, the somatic state of patients after combined treatment often does not make it possible to perform an optimal volume of surgery. In turn, the possibilities of radiation treatment of breast metastases are often limited by the multiple nature of the metastasis process. The effectiveness of polychemotherapy with breast metastases in the skin, in case of standard regimens, does not exceed 22–27%, while the period of remission, as a rule, is only 2–3 months [5]. To achieve longer remission periods, it is necessary to administer multi-course polychemotherapy. It must be noted that radiation therapy and chemotherapy have an immunosuppressive effect, which is exacerbated in case of repeated courses. Other methods of treating skin metastases of breast cancer include electrochemotherapy, local chemotherapy (MILTEX), laser destruction, brachytherapy, hyperthermia, cryotherapy, etc.; however, the data on their effectiveness remains highly controversial [6]. Thus, the dissatisfaction with the results of treatment of breast cancer patients with skin metastases stimulates the search for new methods of therapy.

One of the current trends in modern oncology is the treatment of patients with intradermal metastases of breast cancer with the use of photodynamic therapy (PDT), which is now considered to be one of the most effective methods for malignancies treatment [7]. PDT is a non-systemic therapeutic procedure that begins to function in the presence of a combination of three separate components: a photoactivated photosensitizer, a specific light source and molecular oxygen [8–11]. This method is based on the fact that tumor cells are able to selectively accumulate certain photosensitizers in larger quantities than healthy tissues do [12, 13]. Subsequently, when irradiated with light the spectrum of which corresponds to the spectral composition of the absorption of the photosensitizer, a photochemical reaction takes place in the tumor cells. As a result, substances with cytotoxic activity are formed, and their action leads to tumor necrosis [14, 15].

The PDT method can be used independently or in combination with surgical and radiation treatment, as well as for palliative purposes [16]. The advantages of PDT are the high selectivity of tumor cell damage, the absence of serious side effects, the possibility of repeated courses of treatment, and the combination of diagnostic and treatment options in the same procedure. An additional advantage of PDT is its relative painlessness and the possibility of repeated courses.

However, the PDT method also has some drawbacks, including the following:

- a limited depth of penetration of light exposure into the tumor (from 2 to 15 mm, depending on the applied wavelength according to some data, and from 4 to 8 mm according to other data). The penetration depth is determined by the choice of the photosensitizer for the therapy [17];
- the dependence of treatment effect on the degree of oxygenation and blood supply to the tumor;

- the absence of morphological control after the treatment;
- the high cost of some photosensitizers [18].

General indications for PDT for exposure in accordance with the radical program are tumors that can selectively accumulate a photosensitizer and are accessible for laser radiation exposure, with an indolent exophytic and/or infiltrative component that does not exceed the depth of radiation penetration into the tissue. In cases where the tumor does not meet the above criteria, palliative PDT or the use of PDT in combination with other methods of exposure is possible [19].

Absolute contraindications for the procedure include respiratory and cardiovascular failure, decompensated diseases of the liver and kidneys, cachexia, intolerance to the drug. Among relative contraindications, allergic diseases can be mentioned [20].

A PDT procedure consists of introducing a photosensitizer (PS) in a way that is optimal for its accumulation in the tumor, and its activation under the influence of laser radiation at a certain wavelength. Therefore, the choice of PS has a significant impact on the efficiency of PDT of malignant tumors of various localization and on the radiation parameters, since the depth of the therapeutic effect on the neoplasm is determined by the spectral range of the PS. Thus, the maximum exposure depth is provided by sensitizers with a wavelength of spectral maximum exceeding 770 nm. Accordingly, the fluorescent properties of the sensitizer play an important role in the development of treatment tactics, evaluation of the drug biodistribution, and monitoring of the results [21].

An analysis of the literature data allows us to conclude that the use of PS of different classes significantly affects the effectiveness of PDT of neoplasms. Thus, the best results with respect to intradermal metastases of breast cancer were obtained with the use of tetramethahydroxyphenyl chlorin (Foscan, $\lambda = 652$ nm), sulfonated aluminum phthalocyanine (Photosens, $\lambda = 670$ nm), chlorine e_6 trisodium salt (Photolon, $\lambda = 661 \pm 5$ nm) [5, 22, 23].

According to some authors, the indications for the use of PDT in breast cancer are the following:

- Paget's desease T1–2N0M0;
- breast cancer relapse on the chest wall after surgical treatment;
- intradermal metastases after surgical, combined and complex treatment;
- primary breast cancer T1–2N0M0 (nodular form) with the patient's emphatic refusal from surgical treatment and the presence of severe concomitant diseases [24].

As for the effectiveness of PDT in patients with breast cancer, E.V. Goranskaya and M.A. Kaplan in his study demonstrated that PDT of skin metastases in breast cancer with a chlorine-type photosensitizer (Photolon) allows achieving a therapeutic effect in 85% of cases. In this context, complete regression was noted in 46%, and partial, in 39% of cases. Based on these data, the authors came to the conclusion that photodynamic therapy can be seen as a method that can achieve a good result with the least number of side effects, which makes it possible to recommend PDT for use in medical institutions [5]. In another study concerning the treatment of intradermal metastases of breast cancer, PDT demonstrated higher clinical efficacy: therapeutic effect was achieved in 97% of cases. At the same time, the authors note the high selectivity of the method in relation to the tumor tissue destruction, as well as the absence of severe local and systemic complications and the possibility of repeating the treatment. In addition, researchers mention the use of PDT for palliative purposes, as it will lead to tumor volume reduction and improve the quality of life of patients with breast cancer and its intradermal metastases [25].

The work by M.A. Kaplan et al. evaluated the effectiveness of PDT for intradermal metastases of breast cancer with the use of photolon. According to the results of treatment of 46 patients, 54.3% of which were found to have only intradermal metastases, and the rest also had organ metastases (in lymph nodes, bones, liver, lung tissue, and the second mammary gland), complete regression was noted in 33.6% of cases, partial regression in 39.4%, stabilization in 22.6% and progression only in 4.4%. An objective response was obtained in 73.0% of cases, and therapeutic response in 95.6% of cases [26].

Completely different results were obtained in the study by S.V. Evstifeev et al. for the evaluation of the effectiveness of PDT against intradermal metastases of breast cancer: full effect was achieved only in 22.7% of patients, partial in 27.3%, stabilization of the process was recorded in 31.8% of cases, and the rate of disease progression characterized by the appearance of new metastatic foci reached 18.2% [27]. It should be noted that in this study we used Photosens, a domestically produced synthetic porphyrin photosensitizer of the second generation. It is possible that the use of photosens as a photosensitizer in this study adversely affected the effectiveness of PDT compared to the study mentioned earlier.

Foreign researchers are constantly searching for new photosensitizers that ensure both high efficacy and safety in the treatment breast cancer and its metastases. In this regard, the results obtained by X. Wang et al. are of interest. The researchers evaluated the effect of PDT with sodium synoporphyrin on the proliferation and metastasis of tumor cells in the highly metastatic 4T1 cell line on a mouse xenograft model. As a result, it was found that the selected treatment tactic significantly increased the life expectancy of mice with breast cancer, and also inhibited the growth of both the tumor and its metastases, which is consistent with the results of *in vitro* experiments. In addition, the authors noted that PDT with this pharmaceutical product was more effective than therapy with

Photofrin, the PS which had already been registered. Preliminary toxicological results suggest that sodium synoporphyrin is a relatively safe medication. These data can be regarded as evidence of the promising prospects related to the use of this photosensitizer, which, however, requires further study [28].

In turn, S. Anand et al. suggested, in order to increase the effectiveness of PDT in breast cancer, that a neoadjuvant (5-fluorouracil) be used before PDT with aminolevulinic acid ester. This approach did increase the efficacy of PDT; however, a serious toxic effect of 5-fluorouracil was noted. In order to reduce it, the researchers proposed the use of the non-toxic precursor of 5-fluorouracil capecitabine in combination PDT mode. As a result, a significant increase in the differentiation of tumor cells in the animal model was demonstrated, as well as their death, which exceeded the level in the control group by 5 times. As a result, the authors noted that tumor growth stopped, as well as metastatic foci growth [29].

Foreign researchers devoted a lot of works to the assessment of the clinical efficacy of PDT in patients with skin metastases of breast cancer. For instance, P. Wyss et al. provide the results of the use of two different PDT protocols in the treatment of skin metastases. The first protocol included the administration of PS meta-tetra (hydroxyphenyl) chlorin at a dose of 0.10 mg/kg followed by irradiation at a dose of 5 J/cm^2, while in the second protocol the dose of PS was 0.15 mg/kg and the exposure was 10 J/cm^2. As a result, a complete clinical effect was observed in all patients, regardless of the PS dose or irradiation dose. The authors note that the healing rate mainly depended on the irradiated area of the site [30].

The authors of an extensive literature review on the use of PDT for the treatment of breast cancer provide numerous evidence of its clinical efficacy; the PS administered in the cases under consideration were various, and combined approaches were also used (a combination of PDT and immune therapy). However, it is emphasized that further research is necessary since the experience accumulated to date is still insufficient [31].

A number of authors provide data on the use of a matrix emitter on semiconductor diodes with a variable geometry of the radiating surface. Its advantages are the following:

- the possibility of simultaneous exposure of large metastatic lesions areas in the skin of the chest wall;
- shorter treatment sessions, more comfortable for the patient;
- the reduction of the incidence of severe necrotic phototoxic reactions of irradiated tissues due to the low power density of the light energy;
- the opportunity for prompt administration of a repeated PDT session in the presence of clinical indications, on an outpatient basis;
- accurate dosimetry;
- insignificant divergence of radiation over bright diodes, since the radiating surface of the device is congruently adjacent to the irradiated surface of the chest wall;
- optimal formation of irradiation fields by the use of the photosensitizer fluorescence method;
- the opportunity to control the local process without systemic treatment, which significantly improves the quality of life of patients [32].

In the study by M. L. Gelfond et al., a case study of 8 patients with regional breast cancer at stage III and more advanced, it was found that in three cases PDT with the use of a matrix emitter led to a complete regression of metastatic formations in the skin. Partial regression was achieved in 4 patients, which had required repeated sessions, and in 1 woman, vast necrosis areas developed in place of the affected areas of the chest wall tissue, after which the patient was excluded from the observation. The relapse-free survival median was 14 months. According to the authors, this experience testifies to the advantages of this technique over irradiation of each metastasis in the skin using a fiber with a focusing nozzle. This technology makes it possible to simultaneously irradiate relatively large areas of affected tissue and deliver the planned dose of light energy per unit time at a power density sufficient to excite the photochemical reaction. On the one hand, this can significantly reduce the total exposure time, and on the other, it creates more comfortable conditions for patients without reducing the effectiveness of the method [33].

Nevertheless, insufficient satisfaction with the effectiveness of the existing PDT protocols for skin metastases in patients with breast cancer leads to the search for new approaches to the procedure. Also, further development of the method will be associated with the synthesis of new photosensitizers characterized by more selective accumulation in the tumor, greater activity for the induction of singlet oxygen, and excitation at a longer wavelength. Of great importance is the development and implementation of methods for early monitoring of the procedure effectiveness and the identification of predictors of response to photodynamic therapy in order to individualize the exposure parameters [34].

A promising feature is the increased selectivity of PS accumulation in tumor tissue cells, which helps to minimize the effect on healthy tissues. In addition, this makes it possible to implement the principles of theranostics, when the same procedure includes both diagnostic and therapeutic options.

Currently, studies are underway on the use of antibody-directed delivery of PS to antigens of target cells. This method is essentially based on the use of viral particles incapable of reproduction which have PS in their composition, which ensures phototoxicity in PDT. The surface of these particles features specific antibodies

to antigens that are present on the plasma membrane of only cancer cells, which ensures targeted action [35]. However, it should be noted that at present, specific antigens have not been discovered for every specific form of cancer, and antigen verification attempts involve serious difficulties. Nevertheless, this method seems to be very promising, although it requires considerable efforts for its follow-up enhancement before being introduced into wide clinical practice.

Thus, breast cancer is one of the most pressing problems of modern oncology. This is largely due to the large number of patients with advanced stages of the tumor process and the difficulties involved in the treatment of metastases. Indeed, the currently used surgical, radiation and pharmaceutical methods are not always effective. In this regard, the method of photodynamic therapy, which has proven its effectiveness in the treatment of malignant tumors of various localizations, seems to be very promising. However, despite the active study of this method in the recent years, many issues remain unclear. Nevertheless, considerable experience has already been gained in its use for the treatment of skin metastases in patients with breast cancer. In this connection, the study of the possibilities of the photodynamic therapy method for the treatment of intradermal breast cancer metastases continues.

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