Photodynamic Therapy of Breast Cancer with Photosense

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ABSTRACT

Photodynamic Therapy (PDT) using second-generation photosensitizer Aluminium Phthalocyanine (NIOPIC, Russia) (PS) in dose 0.5-0.8 mg per kg of body weight have been provided in 15 patients with breast cancer. In 5 patients with T2-T3N0M0 primary tumor was treated as the preoperarive treatment, radical mastectomy has been fulfilled after PDT with subsequent histological examination. 10 patients had local recurrences of breast cancer after combined treatment, chemotherapy and radiotherapy. Fluorescent diagnostics of tumor, accumulation of PS in tumor, adjacent tissue before and during PDT was fulfilled. For PDT semiconductive laser - \( \lambda = 672 \pm 2 \text{nm} \), \( P = 1.5 \text{ W} \) was used. Treating primary tumor interstitial irradiation has been done in light dose 150 J/cm\(^2\). In patients with skin metastases multiple surface irradiations were provided with interval 24-72 hours and total light dose 400-900 J/cm\(^2\). In cases of preoperative PDT pathomorphosis of different degree has been found in all cases. In patients with advanced skin recurrences of breast cancer partial regression of tumor has been got in 2 months after PDT or progression with lung or bone metastasis. In 5 patients with early skin metastases in 80% complete response’ve been got 2 months after treatment with recurrences in 6 months in 60% patients. Our experience show pronounced efficacy of PDT for treating breast cancer.

Keywords: photodynamic therapy, breast cancer, metastases, photosense

1. INTRODUCTION

In Europe, 135000 new breast cancer cases are diagnosed each year and 58000 deaths from this disease are annually registered. This disease is well-known for its early metastatic spread and therefore innovative treatments are badly needed. Even after apparently curative surgery, where all local disease has been eradicated and the axillary nodes show no evidence of histological involvement by tumour, approximately 30% of women relapse with metastasis within 5 years, thus different variants of combined treatment, adjuvant chemotherapy, hormonal therapy are used for these patients. During last years a lot of attention is paid to angiogenesis of tumour\(^1,2\), which is a nesessary step in the cascade of events leading to metastasis, so inhibition of neovascularisation may represent a new potential approach to prevent the development of metastasis. Photodynamic therapy (PDT) having well-marked effect both on tumour parenchima and on vessels could has the potential to reduce the biological aggressiveness of solid tumor and possibly arrest tumor spread during subsequent operation. This paper deals with the results of clinical trials for Sulfated aluminium Phthalocyanine (PS) (Photosense, Russia) approved by Pharmacology Committee for stage 3 clinical trials in Russia in patients with primary breast cancer and skin recurrences after 24, combined treatment. PDT in patients with breast cancer have been provided earlier in clinic mostly with dihematoporphyrine ether for subcutaneous metastases\(^3,4\) and adequate local control was reached mostly in cases with tumor sites less then 0.5 cm in diameter.

2. MATERIALS AND METHODS

Photodynamic therapy (PDT) using second-generation photosensitizer Aluminium Phthalocyanine (NIOPIC, Russia) (PS) have been provided in 15 patients with breast cancer (histology - infiltrating ductus carcinoma or adenocarcinoma), 36-72 years old in frames of 2 protocols for 3 stage of clinical trials. They were treated as in patients at Cancer Research Cancer AMS of Russia and observed daily for at least a week after PDT. Whole clinical examination have been provided in all patients, including chest X-ray, mammography, radioisotope scintigraphy of bones, clinical ultrasonography of mammae, lymph nodes
and liver, biopsy proven tumor type. In 5 patients with T2-T3N0M0 primary tumor was treated as the preoperarive treatment (1 protocol), modified radical mastectomy with preservation of both major and minor pectoralis muscles has been fulfilled 7 days after PDT with subsequent detailed histological examination with estimation of pathomorphoses. 10 patients had recurrences of breast cancer T1-2N0-1MO after combined treatment (modified radical mastectomy or breast-conserving surgery plus breast irradiation), chemotherapy and radiotherapy (2 protocol): 9 pts - skin metastases and in 1 case skin metastases and subsequently progression of process to contlateral cancer. In all patients of these group skin metastases to chest wall were the only sig of disease. The interval between finishing of combined treatment and recurrence was from 6 months till 5 years. Previous conventional treatment took place in 10 patients and included combined therapy (all patients), multiple courses of chemotherapy (3-12 courses: CMF, taxotere or CAF – 7 patients (70%), radiotherapy (40 – 80 Gy, 8 patients (80%), hormonal therapy (all patients). The interval between chemotherapy and PDT was at least 1,5 months, between radiotherapy and PDT - at least 3 months. So it was heavily pretrained group of patients. All of them signed informed consents stating the investigational nature of treatment, alternate treatment available and the side effects to be expected (especially the increased solar photosensitivity). Multiple lesions were treated in all patients with skin metastases of breast cancer (minimal number of 3 tumor sites).

During 3 stage of clinical trials the same PS dose were used in two protocols for patients with breast cancer. PS dissolved in 0,9 % NaCl was injected intravenously in dose 0.5 mg per kg of body weight. Fluorescent diagnostics of tumor, accumulation of PS in tumor, adjacent tissue, skin before and during PDT was fulfilled with the help of Spectral-fluorescent Video Complex (He-Ne-laser, λ=633 nm) and spectranalyser LESA-6. Individual spectrometric control measurements were done before and after every PDT for evaluation of PS level and its photobleaching during PDT session. First PDT was provided 24 hours after infusion in all patients. As a source of light we used semiconductive laser - λ=672±2nm, P=1,5 W ("Biospec"). As preoperative PDT one session with interstitial irradiation has been done , light dose 150J/cm3. Metallised catheters were injected into tumor through standart needles under ultrasound control in 2 dimensions. In patients with subcutaneous metastases multiple PDT sessions have been done (3-10) with at least 3 irradiated fields with interval 24-72 hours, quartz fibers 0.4 -1.8 mm in diameter with microlense have been used. All surface treatments were done to cover an area extending at least 1 cm beyond the fluorescent borders of the tumor. The rest of the patients exposed areas were covered with few layers of drapes. The desired power density was 100 -300 mW/cm², regardless of spot side, light dose - 150 - 200 J/cm² during first PDT session, total light dose till 900 J/cm². In patient with progression and second breast involment 3 PDT courses have been performed with reduction of PS dose till 0.3 mg per kg of body weight and combination of surface and interstitial irradiation has been provided during third course and identical light regime (24-hour interval between injection and first laser irradiation, 24 -48 hours interval between irradiations, 3 sessions). Because of pain intervenous or potentiated anesthesia were required, especially during treating of primary tumor. Biopsies were done in all patients before treatment, 1 and 2 months after PDT, then every month during first year after treatment. Whole clinical examination have been provided in all patients 2 months after PDT, including chest X-ray, mammograghy, radioisotope scintigraphy of bones, clinical ultrasound of mammea, lymph nodes and liver. In case when biopsies were positive 2 months after PDT or lung or bone metastasis have been found chemotherapy or immunotherapy were provided subsequently.

Tumor response (WHO) was evaluated as: complete response (CR) if there were no evidence of tumor determined by two observations not less than 4 weeks apart; partial response (PR) was more then a 50% decrease in total tumor load of the lesions that have been measured to determine the effect of therapy by two observations not less than 4 weeks apart with no appearance of new lesions or progression of any lesion; no change (NC) - was a reduction less then 50% in total tumor size and the increase not more then 25% been demonstrated, progressive disease – 25% or more increase in size of one or more measurable lesions or appearance of new lesions. After discharge, patients were seen at least every month during first year and periodically after. The longevity of observation is from 6 till 36 months. All have been followed to the time of this report or their demise

2. RESULTS AND DISCUSSION

The reaction to the infusion of PS was seen in 1 patient: arterial blood pressure falled down. Usually the concentration ratio of PHS between tumor and adjacent normal skin appeared to be 2,5 : 1 to 1,5 : 1. In cases when spread tumors more then 3 cm in diameter were visualized after PS infusion nongomogeneity of accumulation of the drug have been seen. During PDT session the “photobleaching” of sensitizer was seen in all patients by means of Video Complex and spectranalyser. In all patients increase of fluorescence could be seen during the first 2 minutes with subsequent decrease after 10 minutes of laser irradiation with intensity 150-200mW/cm2. Because of a therapeutical residual concentration of PS in tumor after first PDT, we had provided next sessions in day or two. We think that fractionated doses give additive effect to the tumor, may be partly
because of improvement of oxygenation of irradiated tissues between PDT sessions and reduce the alteration of adjacent tissue. We didn’t see any specific direct reactions of adjacent skin in patients with previous radiotherapy and chemotherapy. In cases of preoperative PDT visual areas of necrosis of tumor have developed, even the regression was near or less then 50%. In all patients histology examination after operation showed infiltrating ductus carcinoma with areas of necrosis and expressed hemorrhages of tumor, pathomorphosis of different degree (2-4) has been found in all cases. We have considered it as therapy-induced changes. No changes in postoperation period were found in patients. They are followed up without sighs of recurrence for 6-12 months.

In second group the direct efficacy of treatment (2 weeks after PDT) was more than 50% regression of tumor or complete responce in all cases with the exception of 1 patient with wide spread skin recurrence and multiple drug and radio-resistance. This woman earlier was progressing in skin metastasis even during courses of modern high-dose taxotere combinations. PDT was an attempt of salvage therapy for her and stabilisation have been reached. In 2 months after PDT in group of 5 patients with advanced skin metastases partial regression of tumor has been got in 2 patients (40%), progression with local progression (2 patients) and lung metastasis (1 patient) in 60% of cases. In 5 patients with early skin metastases in 80% it was complete responce (CR) 2 months after treatment with recurrences in 6 months in 3 patients (local recurrence near the previous PDT field in one patient and bone metastases found out in dynamics by x-ray and radioisotope scintigraphy in 2 cases with no sign of local recurrences).

Concerning adverse effects we must emphasize that only once we had the inflammation of the treated area with raising of temperature a month after PDT with subsequent deep necrose formation in patient with previous radiotherapy (70Gy). The possibility of such late complications is especially high in patients with high-dose radiotherapy in anamnesis. In such patients total light dose mustn’t preseed 500J/cm2. In some patients with concomittant arterial hypertension we saw transitory increase of blood pressure during treatment. The traditional side effect in PDT is increased solar sensitivity of skin. In all patients it was lasting at least 1 month after injection of PS because of it’s retention in normal skin, thus leading to changes in usual social activity of patients, but there were no serious sunburns or hyperpigmentation of skin of open parts of body. Hyperpigmentation of irradiated skin was seen only in patient with three PDT courses.

The combination of PDT with systemic therapy such as chemotherapy may enchance the degree of control achieved and its duration. Previous radiotherapy, especially in high therapeutical doses more then 60 Gy, is the factor exacerbating the possibility of adverse local reactions. Even patients with advanced skin metastasis could benefit from PDT and reach short-term (2-5 weeks) stabilization of process, but treatment is palliative in these cases and is to be followed by chemotherapy or courses of PDT. The best results could be reached in patients with few skin metastases where long-term local control could be achieved with PDT.

3. CONCLUSIONS

Preliminary results of our study show the pronounced efficacy of PDT with Photosense for subcutaneous metastases of breast cancer and possibility of providing preoperative PDT for breast cancer. PDT for patients with subcutaneous metastases of breast cancer after combined treatment without other signs of generalisation of process could be a possibility of effective treatment and reaching long-term local control. Having now the experience of long-term follow up of patients of breast cancer after PDT we see a serious problem of tumour progression with development of bone or lung metastasis with no sign of local recurrences during first 6 months after successful PDT. That’s why these patients need dynamic follow-up during first year after PDT. The combination of PDT with systemic therapy such as chemotherapy may enchance the degree of control achieved and its duration, that is the field of our future investigation.

REFERENCES