

THE METHOD OF TREATMENT OF PATIENTS WITH LOCALLY-ADVANCED BREAST CANCER

Igor Sedakov

*Head of Donetsk Regional Antitumoral Center
2a Polotsk str., Donetsk, Ukraine, 83092
sedakov@interdon.net*

Vladlena Dubinina

*Head of oncology department
Odessa Medical University
2 Valihovsky per., Odessa, Ukraine, 65082
Vladlena.od@gmail.com*

Oleksandr Bondar

*Surgery department
Odessa University Clinic
8 Tenistaia str., Odessa, Ukraine, 65062
bondar86@mail.ru*

Oleg Lukianchuk

*Head of cancer hospital
32 Negdanovoi str., Odessa, Ukraine, 65055*

Abstract

A method of care of patients with locally-advanced breast cancer consisting of using regional selective intraarterial chemotherapy in the schedule of the complex (palliative) treatment is presented. Results of treatment showed an advantage in comparison with the application of traditional methods of the breast cancer treatment. The methodology on intra-arterial introduction of chemotherapeutic agents developed at Donetsk Regional Antitumoral Center and University clinic of Odessa showed its undisputable contribution into development of modern oncology through decrease of primary tumoral locus, transition from inoperable state into the state at which it is possible to perform the radical volume of surgical interference to patient. The special attention is paid to development of new methods of treating BC patients (regional forms of disease) with unfavorable factors for forecast of tumor growth.

Keywords: locally-advanced breast cancer, complex and palliative treatment.

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1. Introduction

The urgency of developing the new methods of treatment for patients with breast cancer (BC) is undoubtful now. Unfortunately statistics shows a steady increase in the incidence of breast cancer in the past 20 years, with no tendency to stabilization [1, 2]. Morbidity (72.8 cases per 100,000 female population in 2014) and mortality (32.0 %) in Ukraine is approaching the level of the European Union.

Particular attention is paid to the development of new methods of treatment of breast cancer patients with locally advanced forms of the disease or the presence of significant comorbidities which does not allow perform the radical surgery.

2. The purpose of the work

To improve the immediate and long-term results of treatment of patients with locally-advanced forms of BC, to improve their life quality.

3. Materials and methods

The present study was based on the data of 136 patients with locally-advanced and metastatic forms of BC, with the stages T4N0-2M0-1 treated in 1997–2013.

During the research for an adequate analysis of the results of treatment by the technique under study there were formed two groups of patients. The first study group included 92 patients who had complex treatment program: two or three cycles of selective intra-arterial polychemotherapy (PCT) with an interval of 21 days, evaluation of the effect, the interval, radiation therapy (RT) of the breast and areas of the regional lymph outflow in the static mode SFD – 2–2.5 Gy, CFD – 40 Gy, the interval, evaluation of the effect, the second phase of RT with SFD 2–2.5 Gy with elevation of the dose up to – CFD 60 Gy against the background of the third course of PCT, evaluation of the effect, the interval of three weeks, the fourth course of palliative chemotherapy in adequate functioning of the catheter. Catheterization of the internal thoracic artery was made through the upper epigastric cone (a patent № 29318 of Ukraine of 01.07.2000, a patent № 2169014 of the Russian Federation of 20.06.2001). Mastectomy in the patients of the group under investigation was performed only at presence of bleeding from the tumor (16 of 92 patients at different stages of treatment). When performing mastectomy some of these patients were catheterized the perforating branch of the internal thoracic artery (ITA) – for further IAPHT – worked out in Donetsk regional antitumor center by the original method (a patent № 29318 of Ukraine of 01.07.2000). Courses of intraarterial PCT were given by the scheme CMF, CAF or CAMF. The number of courses is determined based on the evaluation of the effectiveness of treatment, general condition of the patients and presence and severity of local and systemic complications. Usually 2–3 cycles were sufficient to achieve the effect of neoadjuvant mode. If no effect was observed, the scheme of PCT included anthracyclines (1–2 cycles) [3–5].

The control group comprised 44 patients who were given 4–6 cycles of systemic PCT schemes of CMF, CAF or CAMF at the first stage of treatment, then mastectomy was performed. Further on the patients consulted a radiologist to decide on the appropriateness of radiotherapy.

At examination during primary visit 7 (7.6 ± 3.4 %) patients of the investigated group were revealed distant metastases.

In this case the patients in this group were most frequently detected bone metastases as it was noted in 4 (4.3 ± 2.6 %) cases there were detected liver metastases, metastatic mediastinal and contralateral pleural effusion – 1 (1.08 ± 1.08 %) cases respectively with the same frequency. Pulmonary metastases in patients of the group under investigation were not marked [6–10].

Histological examination of trephine biopsy materials in the investigated group of the patients revealed tumors of the following morphological structure: noninfiltrating: intraductal cancer – 1 (1.08 ± 1.08 %); lobular carcinoma – 1 (1.08 ± 1.08 %); infiltrating: infiltrating ductal carcinoma – 49 (53.3 ± 5.8 %); infiltrating ductal carcinoma with a predominance of intraductal component 9 (9.8 ± 3.8 %); infiltrating lobular carcinoma 30 (32.6 ± 5.3 %); medullar cancer 1 (1.08 ± 1.08 %); papillary carcinoma 1 (1.08 ± 1.08 %).

In 59 (64.1 ± 5.5 %) patients of the investigated group there was revealed overexpression of estrogen and progesterone receptors ($ER \pm PR \pm$), 5 (5.4 ± 2.9 %) were revealed to have overexpression of estrogen receptors at the absence of expression of progesterone receptors ($ER \pm PR -$) which was an indication for the use of two-way tubovariectomy or releasing hormone agonists in the patients in pre-menopause. On the basis of immunohistochemical data the postmenopausal patients were administered corresponding conservative hormonal therapy. In 20 (21.7 ± 5.1 %) patients of the investigated group the tumor did not express estrogen and progesterone receptors ($ER - PR -$), and 3 (3.2 ± 2.3 %) patients showed no expression of estrogen receptors at the presence of the progesterone receptor expression ($ER - PR \pm$). There were found no statistically significant differences in the immunohistochemical status of the patients in the control group. The immunohistochemical status of the tumor has not been studied in 5 patients of the investigated group.

At examination during the primary visit 5 (11.4 ± 4.8 %) patients in the control group were revealed distant metastases.

Bone metastases were the most frequently reported in the patients of the control group as well as in the patients of the group under study; it was noted in 3 (6.8 ± 3.8 %) cases. Equally common metastases were encountered in the liver and lungs – 1 (2.3 ± 2.3 %) cases respectively. Metastatic pleural effusion and mediastinal involvement has been identified in the patients of this group during the primary visit. In case of metastatic affections of the bones bisphosphonates were added in the scheme of complex treatment of patients in the control and investigated groups.

In the control group of patients histological identification of tumors were represented by the following morphological variants: noninfiltrative: lobular carcinoma – 1 (2.3 ± 2.3 %); infiltrating: infiltrating ductal carcinoma – 25 (56.8 ± 7.5 %); infiltrating ductal carcinoma with a predominance of intraductal component 7 (15.9 ± 5.5 %); infiltrative lobular carcinoma – 10 (22.7 ± 6.3 %); medullar cancer 1 (2.3 ± 2.3 %). Statistically significant differences in the frequency of different morphological variants between patients of the control and investigated groups were not found ($p=0.87$).

Also there was no statistically significant difference in the distribution of staging in category N patients in the controls and the group under the investigation ($p=0.06$).

The analysis of the age, prevalence of tumor, presence of comorbidity of the patients showed that they were homogeneous in the control and investigated groups.

All patients were informed in detail with the objectives of the study, the programs of therapeutic and diagnostic procedures and gave their written informed consent for this type of treatment.

In accordance with the protocol of this study, the scheme of complex treatment of all patients included radiation therapy that was given at the radiological department of Donetsk regional anti-tumor center. Irradiation of the primary lesion and regional areas was performed by gamma – therapeutic devices “Rokus” and “Agat” in the classical modes of dose fractionation.

In carrying out small fraction radiotherapy single focal dose to the mammary gland was 2–2.5 Gray, to the zones of the regional lymph outflow – 2 Gray. The cumulative tumor dose to the breast was 47–60 Gray, zones of the regional lymph outflow – 47–60 Gray [11–14].

Hormone therapy was given in accordance with modern views and approaches to this problem. Pharmacological or surgical ablation was performed in the patients with preserved menstrual function and presence of the steroid hormone receptors in the tumor after which the anti-estrogen drugs were administered for 2–3 years, followed by administration of aromatase inhibitors or anti-estrogens extension up to 5 years [15–20]. Anti-estrogens or aromatase inhibitors were prescribed for all patients in postmenopause that had not been studied hormonal status of the tumor or the hormonal status of the tumor was positive. At the absence of steroid hormone receptors tumor hormone therapy was not given [21, 22].

4. Results and discussion.

Immediate results of palliative treatment of patients

Evaluation of the effect of the treatment was made in the period after neoadjuvant chemotherapy.

Traditionally to assess the objective effect of chemotherapy there were used the well-known criteria of the WHO Expert Committee. The evaluation of the tumor size and metastases was used as a derivative of the two largest perpendicular sizes. It should be noted that the instrumental tests were made in the same hospital (DRATC) in compliance with the principles of continuity (one apparatus and the same specialists). For linear measurements of breast tumors there was used a medical caliper of McGhan company with divisions of 0.1 mm.

In the course of evaluating the effectiveness of the method in therapy of solid tumors the scale RECIST (Response Evaluation Criteria in Solid Tumors) was used. In all cases tumors were assessed as measurable. The maximum size of all lesions was determined, total size before treatment was considered as the baseline and compared with that after treatment.

In evaluating the therapeutic effect there were taken into consideration dynamics of the objective state of patients and results of clinical and laboratory examinations, and dynamic trephine biopsy was made (evaluation of tumor pathomorphism after PCT)

Long-term efficacy of the treatment

The clinical course of the disease and long-term results of treatment were assessed by the following parameters:

- life expectancy without recurrences and new metastases;
- frequency of lymphatic and hematogenous metastasis;
- corrected five-year survival rate.

These indices were calculated in all investigated contingent of the patients and separately for the control and investigated groups depending on the variants of palliative treatment.

Calculation of long-term results was made from the beginning of treatment.

Evaluation of the effectiveness of treatment of the investigated patients revealed: the total effect was observed in 6 (6.5 ± 3.1 %) patients, partial response – in 59 (64.1 ± 5.5 %) women, stabilization of the process was detected in 21 (22.8 ± 4.5 %) cases, the disease advance – in 6 (6.5 ± 3.1 %) cases.

In the control group of patients the following effectiveness of the palliative treatment was revealed: the total effect was detected in 3 (6.8 ± 3.8 %) patients, partial response – in 19 (43.2 ± 7.5 %) cases, stabilization of the process was found in 10 (22.7 ± 6.3 %) patients, the disease advance was observed in 12 (27.3 ± 6.7 %) patients. Differences in distributions of effectiveness evaluation of treatment for the patients in the control and investigated groups by the RECIST scale is statistically significant ($p=0.02$) (Table 1).

Table 1

The effectiveness of treatment of the patients

Effect by the scale RECIST	Investigated group %±		Control group %±	
Total	6	6.5 ± 3.1	3	6.8 ± 3.8
Partial	59	64.1 ± 5.5	19	43.2 ± 7.5
Stabilization	21	22.8 ± 4.5	10	22.7 ± 6.3
Advance	6	6.5 ± 3.1	12	27.3 ± 6.7

Assessing the risk ratio one can conclude that the risk of the disease advance for the patients of the investigated group compared with the controls decreases in $RR=3.4$ (CI 1.4–8.4) times (the difference is statistically significant, $p=0.01$).

The effect of the treatment was evaluated by mammography.

Long-term results of palliative treatment of the patients

During the follow-up the investigated patients were revealed the following variants for advance of the disease after treatment: totally the advance of the disease was observed in 28 (30.4 ± 5.6 %) patients, four of them had metastatic pleuritis, the average interval before continuation of the disease was 5.1 ± 0.8 months. Pulmonary metastases were detected in the 1st patient in 13.5 months. Liver metastases were detected in 1 patient at the control examination in 31.5 months. New skeletal lesions were diagnosed in 10 (10.8 ± 3.9 %) patients on an average in 10.2 ± 3.3 months. Intradermal metastases were detected in 2 patients; the average interval was 13.5 months. Continued growth of the tumor was found in 7 (7.6 ± 3.4 %) patients; on an average in 10.2 ± 3.4 months. A supraclavicular lymph node metastatic lesion was found in 1 case in 39 months. Brain metastases were detected in 1 patient after 6 months after completion of treatment. Combination of pleurisy and metastatic liver metastases was diagnosed in 1 case in 13 months after the end of chemoradiation and surgery.

The patients in the control group were obtained the following results during the dynamic follow-up: 21 (47.7 ± 7.5 %) patients showed a continuation of the disease. 2 patients were diagnosed metastatic pleurisy, the average interval was 21 months. Pulmonary metastases were detected in one patient in 18 months. Bone metastases were diagnosed in 4 (9.1 ± 4.3 %) patients on an average in 16.1 ± 4.9 months. Intradermal metastases were detected in 6 (13.6 ± 5.2 %) patients on an average in the interval of 15.6 ± 4.5 months. Continued growth of the tumor was found in 4 (9.1 ± 4.3 %) patients, on an average in 24.3 ± 11.5 months. Brain metastases were detected in 1 patient in 2.5 months after completion of treatment. Supraclavicular lymph node metastatic lesions were detected in 3 (6.8 ± 3.8 %) cases in an interval of 12.9 ± 5.0 months.

All patients diagnosed with the disease continuation received palliative symptomatic treatment.

Consideration of cases of the disease continuation revealed the following results: in the control group a minimum period of metastasis was 4.6 months, maximum – 23.2 months; while in the investigated group of patients the minimum and maximum period of metastasis made 4.7 months and 54.1 months, correspondingly. The average time till metastases (median rate) in the control group was 7.9 ± 2.4 months, whereas in the instigated one it was 14.5 ± 3.5 months (the difference is not statistically significant, $p>0.05$).

Median survival rate for the investigated patients was 35.5 months while it was 13.9 months for the patients in the control group.

5. Discussion of the results

The comparison of the survival curves for both groups of the patients showed a statistically significant difference ($p < 0.001$ at using log-rank test with Yates correction). It was found that the patients who achieved a complete or partial effect of treatment by the RECIST scale live longer after selective intra-arterial chemotherapy. Complete or partial response by the RECIST scale ($p = 0.02$) was recorded more often in the patients in the investigated group that was resulted in their best survival rates.

All patients diagnosed with a continuation of the disease received palliative chemo- and hormone treatment. The average life expectancy in these patients was 11.4 months. The greatest number of patients with a continuation of the disease (26 women) died within 12 months after the end of the palliative treatment. The next peak registration of deaths is observed in the third year of the follow-up.

The average life expectancy of the patients of the investigated group was 50.52 ± 14.4 months, significantly exceeding the statistical data of domestic and foreign authors. Indices of total 3-year survival rate of the patients of the investigated group made up $77.7 \% \pm 12.1$ months, and 5-year – 63.0 ± 14.5 months.

In the control group index of 3- and 5-year survival rates were significantly lower – $62.4 \pm 19.3 \%$ and $44.7 \% \pm 22.4$ months respectively.

6. Conclusion

Results of complex treatment of locally- advanced breast cancer by the developed technique using selective intra-arterial chemotherapy in the pool of the internal thoracic artery in combination with radiation and hormonal therapy exceed the results of standard treatment programs for patients with the locally-advanced forms of breast cancer with the performance of mastectomy and systemic chemotherapy. The technique developed by the authors can be recommended for wide use in such patients.

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