Immediate results of complex treatment of patients with locally advanced breast cancer.

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Summary.

The analysis of the immediate results of treatment of 105 patients with locally advanced breast cancer was done. The method of complex treatment of patients with locally advanced breast cancer with use of neoadjuvant chemotherapy scheme CAP intraarterial was worked out. During neoadjuvant chemotherapy the hematological parameters of patients with breast cancer were estimated. The increasing of percentage of radically operated patients, was analyzed. Application of the developed technique in patients with locally advanced breast cancer does not impair hematopoiesis and feeling sick, reduces toxic manifestations of chemotherapy, and increase of 14.6% the number of surgical interventions compared with controls.

Keywords: locally advanced breast cancer, complex treatment, neoadjuvant therapy, intraarterial chemotherapy, conservative surgery, immediate results.

Introduction.

Breast cancer (BC) in almost all countries is the main cancer pathology in women. Every year nearly 1 million new cases of BC are recorded. Every year in Ukraine, about 16 000 women infected with this pathology [1].

It's difficult to overestimate the role of neoadjuvant chemotherapy (NPHT) in the treatment of patients with locally distributed (LD) BC, because the objective clinical effect in all existing schemes and NPHT modes, according to different authors, range from 60 to 80% [3, 8]. Benefits of NPHT at LDBC are evident, but the problem of the development of optimal schemes and modes of neoadjuvant treatment still remains actual.

Special urgency NPHT use in patients with LDBC from the perspective of organsaving surgery in younger women, which significantly affects the quality of life and social rehabilitation of patients is especially important[1,6].

Standards for NPHT in patients with LDBC is considered to be systemic (intravenous) drug therapy. Today there exist 30 different schemes of chemotherapy. At present multischemes of NPHT which showed higher efficiency, compared with monotherapy, namely AC, FACVP, CMFA, CMFAV, AVCF, VAM, VCAF, CAMP, CAF, CAP, AT, TAC are used[2, 5, 9] . It is important at the initial stage of treatment to use the whole arsenal of existing facilities to the maximum intensification of the treatment process of carrying out at least 3-6 cycles of chemotherapy - to get the maximum response of the primary tumor and affected metastatic lymph nodes (LN).

With a significant increase in efficacy important drawback of the system NPHT is high proportion of complications. Overall toxicity on the body in a whole, the negative impact on the

functional activity of the liver and kidneys, cardiotoxic effect myelosuppressive effect, inhibition of immune status do not always allow apply comprehensive treatment, in full and in due time [3]. Moreover, the systemic NPHT causes a partial inactivation of chemotherapy, which affects the immediate results of treatment [6,10].

To prevent the above mentioned effects of chemotherapy and to increase its efficiency in recent years using selective intraarterial polychemotherapy (IAPCT) is used[7].

Research Methods and treatment characteristics of patients

A new method of combined treatment with LDBC NPHT with intraarterial administration of cytostatics scheme CP and systemic administration anthracyclines has been worked out. Analysis of the immediate results of treatment 68 patients on the LDBC IIB-IIIb stage were investigated. Age of patients studied ranged from 38 to 63 years. The main group consisted of 36 patients who underwent LDBC NPHT scheme CAP with intraarterial administration of carboplatin and cyclophosphamide and anthracycline systemic administration, 32 patients with LDBC in the control group who underwent systemic NPHT scheme by CAP standards. Each patient performed a standard clinical and laboratory examination, radiographic studies - mammography (MMG) in direct and lateral projections, axillography, comprehensive ultrasonography (USG) of the breast and the regional LN [4], computed tomography of the chest and abdomen, pelvis, ECG.

Distribution of patients on the LDBC conducted in accordance with the center of randomisation: Depending on the stage of disease and age was homogeneous in both groups (seeTable.. 1, 2).

Table 1 Distribution of patients on the LDBC depending on age

Age	Study group n (%)	Control group n (%)	P
30-39	3 (8,33 ± 4,61)	4 (12,50 ± 5,85)	p>0,05
40-49	10 (27,78 ± 7,47)	8 (25,00 ± 7,65)	p>0,05
50-59	18 (50,00 ± 8,33)	13 (40,63 ± 8,68)	p>0,05
60-69	5 (13,89 ± 5,76)	7 (21,88 ± 7,31)	p>0,05
All	36 (100,00)	32 (100,00)	

Table 2 Distribution of patients on the LDBC depending on the stage of the disease

Stage of the disease	Study group n, (%)	Control group n, (%)	P
IIБ (T2-3N0-1M0)	8 (22,22 ± 6,93)	11 (34,38 ± 8,40)	p>0,05
IIIA (T2-3N1-2M0)	12 (33,33 ± 7,86	9 (28,13 ± 7,95)	p>0,05

IIIБ (T4N0-2M0)	16 (44,44 ± 8,28)	12 (37,50 ± 8,56)	p>0,05
All	36 (100,0)	32 (100,0)	

In all patients the diagnosis was verified by fine-needle biopsy or trepan-biopsy.

For histological structure most often met was particle infiltrating carcinoma: a study group - 17 patients (47,22 ± 8,32)%, in control - in 15 (46,88 ± 8,82)%, (P> 0.05). Infiltrating ductal carcinoma in the study group were diagnosed in 13 patients (36,11 ± 8,01)%, in control - in 12

(37,50 ± 8,56)%, (P> 0.05). Medullary carcinoma noted in 2 (5,56 ± 3,82)% patients with primary and in 3 (6,25 ± 4,28)% patients in the control group (P> 0.05), mucous carcinoma - in 1 (2, 78 ± 2,74)% patients with primary and 2 (6,25 ± 4,28)% patients in the control group (P> 0.05). In 3 patients of group (8,33 ± 4,61)% and 1 control group (3,13 ± 3,08)%, histological structure of the tumor in the breast remained not determined due to the almost complete regression after a to surgery treatment. Difference percent of patients with different morphological types of tumors in both study groups was not reliable (see Table 3).

Table 3 Distribution of patients on the depending on the histological structure of the tumor

Гістологічна структура пухлини	Основна група n, (%)	Контрольна група n, (%)	P
Infiltrating particle carcinoma	17 (47,22 ± 8,32)	15 (46,88 ± 8,82)	p>0,05
Infiltrating ductal carcinoma	13 (36,11 ± 8,01)	12 (37,50 ± 8,56)	p>0,05
Mucous carcinoma	1 (2,78 ± 2,74)	2 (6,25 ± 4,28)	p>0,05
Medullary carcinoma	2 (5,56 ± 3,82)	3 (6,25 ± 4,28)	p>0,05
Uncertain tumor structure	3 (8,33 ± 4,61)	1 (3,13 ± 3,08)	p>0,05
Total	36 (100,0)	32 (100,0)	

Study group received three courses NPHT scheme CAP: 1 day, injected intraarterial cyclophosphamide dose of 600 mg/m2 and itravenously doxorubicin 50 mg/m2 system, 2 day intraarterial carboplatin 300 mg/m2. Patients of the control group was carried out by the CAP, but all drugs administered systemically (intravenously).

The grounds for intravenous anthracycline is prevention threatening complications IAPCT such as dermato- and steatonekroza breast tissue, due to the aggressive action of anthracycline chemotherapy row to the skin and subcutaneous tissue. The emergence of this complication affects the aesthetic appearance of breast, reduces the possibility of organ or reconstructive surgery.

Selective angiographic studies was LDBC performed in special X-ray operating room, equipped with television monitors and digital image device registration, automatic injector radiopaque substance. Catheters used for IAPCT are reinforced throughout, different types and

caliber, specially modeled for catheterization of blood vessels breast cancer. Thus, there is always the possibility of changing catheter to solve therapeutic problems.

Angiography and installation of intraarterial catheter was performed under the supervision of hagiographical install Philips BV Pulsera (see Fig. 1, 2).

Picture 1. Angiographic unit Philips BV Pulsera

Picture 2. Angiographic unit Philips BV Pulsera

As the treatment of Stage 1 LDBC treatment modern technology of neoadjuvant intraarterial catheter selective chemotherapy has been developed. By way Seldinger: a special catheter was installed in afferent vessel tumor and left it for the long-term infusion of anticancer drugs. Guided delivery of cytostatics enhances their local concentration more than 10 times in comparison with systemic chemotherapy.

Intraarterial chemotherapy is designed for the selective destruction of tumor, to bring to flu state of clinical remission as a reduction in weight and volume of tumors and regional LN, lower the disease stage, to convert unresectable tumors to resectable status [10].

Results.

Evaluation criteria of NPHT was conducted by RECIST (Response evaluation criteria in solid tumor) by MMG in the frontal and sagittal projections and ultrasound, depending on the percentage of tumor regression evaluated options - full, partial regression, stabilization or progression process.

According to the clinical and radiographic study in patients with stage IIb LDBC full regression (CR) tumors detected in 2 (25,00 ± 15,31)% patients of the main group and in 1 (9,09 ± 8,67)% patients in the control groups (p> 0,05).

Partial regression (PR) tumors was detected in 4 (50,00 ± 17,68)% patients of group and in 4 (36,36 ± 14,50)% - control (p> 0.05). Stabilization process was found in 2 (25,00 ± 15,31)% patients of the main group and in 4 (36,36 ± 14,50)% of control (p <0.05). Progression of tumor in the study group is not found, and the control group was 2 (18,18 ± 11,63)% of patients. (See Table 4).

Table 4 The immediate results of treatment of patients with LDBC (stage IIb) according to the criteria RECIST.

Tumor response to treatment (according to the criteria RECIST)	Main group n (%)	Control group n (%)	P
Complete regression	2 (25,00 ± 15,31)	1 (9,09 ± 8,67)	p>0,05
Partial regression	4 (50,00 ± 17,68)	4 (36,36 ± 14,50)	p>0,05
Stabilization of process	2 (25,00 ± 15,31)	4 (36,36 ± 14,50)	p>0,05
Progression of process	0 (0,00)	2 (18,18 ± 11,63)	p>0,05
Total	8 (100%)	11 (100%)	

In Fig. 3 the results of treatment of patients with LDBC are also shown.

Picture 3. Immediate results of treatment of patients with LDBC (stage IIb) according to the criteria RECIST.

According to the clinical and radiographic study in patients with stage IIIA LDBC CR tumors was detected in 1 (8,33 ± 7,98)% patients of the main group and was not found in the control group (p> 0,05). PR tumors detected in 6 (50,00 ± 14,43)% patients of group and in 3 (33,33 ± 15,71)% - control (p> 0.05). Stabilization process found in 4 (33,33 ± 13,61)% patients of the main group and in 4 (44,44 ± 16,56)% of control (p> 0.05). Progression of tumor in the study group found in 1 patient (8,33 ± 7,98)%, while the control group was 2 (22,22 ± 13,86) patients. (See Table. 5, Fig. 4).

Table 5 The immediate results of treatment of patients with LDBC (stage IIIA) by RECIST criteria

Tumor response to treatment(according to the criteria RECIST)	Main group n (%)	Control group n (%)	P
Complete regression	1 (8,33 ± 7,98)	0(0,00)	p>0,05
Partial regression	6 (50,00 ± 14,43)	3 (33,33 ± 15,71)	p>0,05

The stabilization process	4 (33,33 ± 13,61)	4 (44,44 ± 16,56)	p>0,05
Progression process	1 (8,33 ± 7,98)	2 (22,22 ± 13,86)	p>0,05
Total	12 (100 %)	9 (100 %)	

In Fig. 4. also shows the results of treatment of patients with LDBC.

Fig.4. Immediate results of treatment of patients with LDBC (stage IIIA) by RECIST criteria

According to the clinical and radiographic study in patients with stage IIIB LDBC CR tumors detected in 2 (12,50 ± 8,27)% patients of the main group and was not detected in patients in the control group. PR tumors detected in 6 (37,50 ± 12,10)% patients of group and in 4 (33,33 ± 13,61)% - control (p> 0.05). Stabilization process was found in 7 (43,75 ± 12,40)% patients of the main group and in 6 (50,43 ± 14,43)% of control (p> 0.05). Progression of tumor in the study group found in 1 patient (6,25 ± 6,05)%, while the control group was 2 (16,67 ± 10,76)% of patients. (See Table. 6, Fig. 5).

Table 6 immediate results of treatment of patients with LDBC (stage IIIB) by RECIST criteria

Tumor response to treatment(according to the criteria RECIST)	Main group n (%)	Control group n (%)	P
Complete regression	2 (12,50± 8,27)	0 (0,00)	p>0,05
Partial regression	6 (37,50± 12,10)	4 (33,33± 13,61)	p>0,05
The stabilization process	7 (43,75± 12,40)	6 (50,43± 14,43)	p>0,05
Progression process	1 (6,25± 6,05)	2 (16,67 ± 10,76)	p>0,05
Total	16 (100%)	12 (100%)	

In Fig. 5 the results of treatment of patients with LDBC are also shown.

Fig.5. Immediate results of treatment of patients with LDBC (stage IIIB) according to the criteria RECIST.

According to the clinical and radiological studies in patients with LDBC CR tumors detected in 5 (13,89 ± 5,76)% patients of the main group and was detected in 1 (3,13 ± 3,08) patients in the control group (p <0 , 05). PR tumors detected in 16 (44,44 ± 8,28)% patients of group and in 11 (34,38 ± 8,4)% - control (p> 0.05). Stabilization process found in 13 (36,11 ± 8,01)% patients of the main group and in 14 (46,88 ± 8,82)% of control (p> 0.05). Progression of tumor in the study group found in 2 patients (5,56 ± 3,82)%, while the control group was 6 (18,75 ± 6,9)% of patients (p <0.05) (see Table. 7, 6).

Table 7 Immediate results of treatment of patients with LDBC (all stages) by RECIST criteria

Tumor response to treatment(according to the criteria RECIST)	Main group n (%)	Control group n (%)	P
Complete regression	5(13,89 ± 5,76)	1 (3,13 ± 3,08)	p□ 0,05
Partial regression	16(44,44 ± 8,28)	11(34,38 ± 8,4)	p>0,05
The stabilization process	13(36,11 ± 8,01)	14(46,88 ± 8,82)	p>0,05
Progression process	2(5,56 ± 3,82)	6(18,75 ± 6,9)	p□ 0,05
Total	36 (100%)	32 (100%)	

Fig. 6 also shows the results of treatment of patients with LDBC.

Fig.6. Immediate results of treatment of patients with LDBC (all stages) by RECIST criteria

After analyzing the responses to neoadjuvant treatment surgery was carried out. With the positive effect of the treatment was possible organsaving operations, at stabilization process - mainly conducted mastectomy by Maden, at the progression - a more extensive surgery.

Assessment of toxicity of treatment was performed according to Common Toxicity Criteria NCIC.When analyzing changes in indicators of hematopoiesis and functional changes it should be noted that:

- the 1 stage of severity severity manifested in 11.1% of patients with primary and 15.6% of the control group, anemia II degree was observed in 16.7% of patients in the main group and 9.9% in control anemia in the third degree was determined in 2.8 % of patients in the control.

- Leukopenia 1 stage of severity were observed in the study group in 16.7%, of patients in the control group were 37.5%, leukopenia of second degree in 8.3% of patients in the main group and 9.4% in controls.

- Investigation of changes in indicators of hematopoiesis, liver and kidneys revealed the possibility of courses of chemotherapy using circuit CAP without significant violations of laboratory parameters. Nausea, vomiting and II degree was observed in 47.2% of patients with primary and 75% - the control group for 1-3 days after a course of chemotherapy. All patients, as the drugs accompaniment, had to use antiemetics. Diarrhea I- II degree was observed in 16.7% of patients in the study group and 46.9% in controls. Alopecia of II-IV degree was observed in 93.5% of the main group and in 93.8% of patients in the control. All patients of main group took courses NPHT in appointed term, interruptions in the treatment is not observed and in 2 patients in the control NPHT postponed for 2 weeks. Organsaving operations were performed in 11 patients (30,60 ± 7,68)% core group, the control group - in 7 patients (21,90 ± 7,31)%, (p> 0.05). Mastectomy by Maden was performed in 19 (52,80 ± 8,32)% patients of group and in 15 (46,90 ± 8,820)% in control patients (p> 0,05). There were operated 6 (16,70 ± 6,21)% patients of group and 10 (31,30 ± 8,19)% patients of the control group (p <0.05) (see Table. 8).

Table 8 List of surgeries performed on patients with LDBC.

Groups of patients		Quadrantectomy n (%)	Mastectomy n (%)	Not operated n (%)
Main group	IIБ (T2-3N0-1M0)	6 (75,00 ± 16,30)	2 (25,00 ± 15,3)	0 (0,00)
	IIIA (T2-3N1-2M0)	5 (41,70 ± 14,20)	7 (58,30 ± 14,2)	0 (0,00)
	IIIБ (T4N0-2M0)	0 (0,00)	10 (62,50 ± 12,10)	6 (37,50 ± 12,1)
	Всього	11 (30,60 ± 7,68)	19 (52,80 ± 8,32)	6 (16,70 ± 6,21)*
Control group	IIБ (T2-3N0-1M0)	5 (45,50 ± 15,01)	6 (54,60 ± 15,01)	0 (0,00)
	IIIA (T2-3N1-2M0)	2 (22,20 ± 13,90)	5 (55,60 ± 16,60)	2 (22,20 ± 13,90)
	IIIБ (T4N0-2M0)	0 (0,00)	4 (33,30 ± 13,60)	8 (66,70 ± 13,60)
	Total	7 (21,90 ± 7,31)	15 (46,90 ± 8,820)	10 (31,30 ± 8,19)*

Note: - p <0.05

Thus, a method of combined treatment using LDBC IAPCT proved its effectiveness, feasibility study and subsequent use.

References

1. The technique of combined treatment using LDBC IAPCT with intraarterial administration of cytostatics scheme CP and systemic administration anthracyclines, which is based on catheterization of the internal thoracic artery or subscapular artery was worked out.

2. Using IAPCT in complex treatment of patients with LDBC improves the number of CR tumors by 10.8% (p <0.05) and the PR tumors - 10.1% (p> 0.05) observed growth of tumor progression in patients in the control group to 13.19% (p <0.05).

3 Application IAPCT in patients with LDBC leads to significant reduction of toxic manifestations of chemotherapy in the treatment process that allows a NPHT in full.

4 Application of IAPCT in patients with LDBC core group can hold a 14.6% increase radical surgery compared with the control group (p <0.05).

List of references:

1. GV Bondar, Sedakova IE, Shlopov VG Primary-inoperable breast cancer. - "Chestnut." - Donetsk. - 2005. - 347 p.

2. Gorbunova VA, Artamonova EV, Bagrov SG and others Этyudы chemotherapy (five years to come down.) - Moscow - Lytterra. - 2006. - p.154-173.

3. Dobrovolskaya NY Lekarstvennaya and luchevaya therapy in the treatment of disseminated cancer mestnorasprostranennoho and breast cancer. / / Abstract. diss. dock. honey. Science. - M., 2007. - P.15.

4. Luchevaya diagnosis diseases molochnыh glands / / Guide for doctors under Prof. editors. Trufanova GE - ЭLBY. - St. Petersburg. - 2006. - S. 143-199.

5. Translators NI Guide to chemotherapy opuholevыh diseases. - Moscow - Practical medicine. - 2005. - S.254-267.

6. Semiglazov VF Manyhas AG, Semiglazov TY, Bessonov AA, VV Semiglazov Neoadyuvantnaya systemnaya cancer therapy breast gland / / Agraf +. - St. Petersburg. - 2012. - 109 p.

7. Tarazov PG, Korытova LI, EG Shachynov Vnutryarteryalnaya cancer therapy breast gland / / Questions oncology. - 2011. - T.57, № 1. -126,131 P.

8. Bonnefoi H., Diebold-Berger S., Therasse P. et al. Locally advanced / inflammatory breast cancers treated with intensive epirubicin-based neoadjuvant chemotherapy: are there molecular markers in the primary tumour that predict for 5-year clinical outcome? / / Annals of Oncology. - 2003. - V.14. - P.406 -413.

9. Kim T., Lau J., Erban J. Lack of uniform diagnostic criteria for inflammatory breast cancer limits interpretation of treatment outcomes: a systematic review / / Clin Breast Cancer. - 2006. - V.7 (5).-P.386-395.

10. Kitagava K., Yamakado K., Nakatsuka A. et al. Preoperative transcatheter arterial infusion chemotherapy for locally advanced breast cancer (stage IIIb) for dowing-staging and increase of reshecnability / / Eorop.J.Radiol. - 2002. - Vol.43. - P.31-36.

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