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THE DIRECT EFFICIENCY OF THE DIFFERENT MODES OF SCHEME "PACLITAXEL +CAELYX " IN THE TREATMENT OF THE PATIENTS HAVING INFLAMMATORY BREAST CANCER

Inflammatory breast cancer (IBC) with a poor prognosis occurs in 1-5% of patients with breast cancer. Combination of Paclitaxel and Caelyx were applied for 42 patients with IBC with the use of 2 regimens. Paclitaxel - 135 mg/m² 1 day, Caelyx 40 mg/m² 1day within a cycle of 3 weeks (21 sick women); the weekly regimen has a scheme: 60 mg/m² on 1st, 8th and15th days and Caelyx - 25 mg/m² on 1st, 8th days within a cycle of 4 weeks (21 sick women). The final analysis of the effectiveness of 2 chemotherapy regimens showed that an objective impact was reached in 85.7% (18/21) in the group of weekly insertion of the drugs by the end of the research; and in the group of routine chemotherapy it was 52.4% (11/21). Though general results are satisfactory in both 2 regimens of the chemotherapy, the weekly insertion of the drugs let to decrease a hematologic toxicity of 3-4 degree in 2.5-3 times and a frequency of LPS in 10 times.

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Introduction

Edematous inflammatory breast cancer refers to diffuse forms of tumor and occurs in 1-5% of patients with inflammatory breast cancer (IBC) (Somlo et al., 2004; Tai et al., 2005). According to data of different authors, IBC is one of the most malignant forms of tumor, it has unfavorable prognosis - total five-year survival rate in average does not exceed 12-50% (Liauw et al., 2004; Cristofanilli et al., 2006). At present time the study of clinic course peculiarity and development optimal methods of edematous inflammatory breast cancer therapy is one of the topical problems of clinical oncology; it is conditioned by the growth of inflammatory breast cancer sickness rate in whole and growth of edematous inflammatory breast cancer sickness rate particularly.

It is known that inflammatory breast cancer is sensitive tumor to drug therapy. Appreciable progress in therapy of metaplastic breast cancer (MBC) patients was achieved in 90s of the last century using phytogenic drugs - taxane, vinorelbine, and also modern pyrimidine antagonist - capecitabine.

Interest to study of taxanes, haparticularly Paclitaxel, in chemotherapy of disseminated IBC has not decreased in recent years; primarily it is explained by uniqueness of its action mechanism. From the middle of 90s, the interest of researchers has considerably increased to short infusions of taxol received with 1 week interval. There were a number of theoretical prerequisites: taxol being a phase-specific cytostatic stimulating collection of microtubules and depressing their depolymerization, blocks tumor cells in G2/M phases of cell cycle. Weekly administration of the drug promotes increasing of the number of cells located in G2/M phases, this process brings to loss of big number of tumor cells. Such intensification of dose mode can strengthen cytostatic effect more than simply increase of single dose of the drug. In addition, more continuous exposition of cytostatic strengthens antiangiogenic effect and invokes p53-independent apoptosis (Seidman et al., 1999; Perevodchikova, 2001; Hindenburgl et al., 2003).

In spite of accessibility of many new antitumor drugs, anthracyclines remain an important therapeutic drugs to MBC patients. However, application of doxorubicin is limited by its toxic effects and first of all by development of cumulative cardiotoxicity. New antitumor drug Caelyx - pegylated liposomal doxorubicin - demonstrated reliable efficiency in multi center randomized research in phase III at MBC patients. Unique characteristic of Caelyx is the fact that risk of development of cardiological complications on its prescription is reliably lower than on prescription of traditional doxorubicin ($p<0.01$) (Kurpeshev et al., 2003; O'Brein et al., 2004).

Failure of chemotherapy of malignant tumors is associated not only with the toxicities of the latter, but also with resistance of tumor cells to cytostatics. And therein Caelyx is very interesting, because one of the way to overcome the chemoresistance of tumor is increase of cytostatic lipophilicity that brings to decreasing of affinity to Pgp170 (Kurpeshev et al., 2003).

In our research for the treatment patients with IBC the combination on the basis of Paclitaxel and Caelyx was chosen, considering that taxanes and anthracyclines are basic drugs of first line of chemotherapy of IBC patients.

Materials and methods

There were 42 patients with IBC involved into research. Criteria of involvement: edematous-infiltrative form of cancer, nodular form with cutaneous edema located on more than a half of gland surface; presence of distant metastasis in other organs was not an exception considering primacy of disease and edematous form of tumor. Allocation of IBC patients on TNM was the following: T4N0-2M0 - 33 (78.6±6.3)%; T4N0-2M1 - 9 (21.4±6.3)%.

Patients were randomized on 2 subgroups. 1a subgroup consisted of 21 patients received a treatment according to the scheme: Paclitaxel - 135 mg/m^2 1 day, Caelyx - 40 mg/m^2 1 day of 3 weeks cycle. 2a subgroup consisted of 21 patients received a treatment on every week mode according to the scheme: Paclitaxel 60 mg/m^2 1, 8, 15 days and Caelyx 25 mg/m^2 1, 8 days of 4 weeks cycle.

On hyperexpression of Her-2/neu the target drug Herceptin was additionally introduced in standard mode of chemotherapy (5 patients) in mode: 8mg/kg of weight load dose, then on 6 mg/kg of weight 1 time in 3 weeks. In every week mode (4 patients) - 4 mg/kg load dose, then 2 mg/kg every week.

The composition of researched groups on age, degree of prevalence and receptor status of tumor were approximately similar (Table 1).

According to design of research, patients with IBC received 4 course of chemotherapy on scheme Paclitaxel+Caelyx in different modes. The result of conducted treatment was assessed on the basis of objective clinical and radiographic data, including MMG, KT/MRT, USD and, when necessary, scintigraphic data. Assessment of efficiency of chemotherapy was conducted after 4th course; when the effect was positive the chemotherapy was continued till 4-8 courses, then patients with locally extensive process (T4N0-2M0) proceeded operative treatment followed by adjuvant, chemical and ray therapy. If there was no effect or stabilization with negative dynamics (increase of tumor on 25%), patients were conducted a ray therapy on radical program till SOD 60gr with following operative treatment on positive dynamics.

In case of progressing of process on the background of conducted chemical and/or chemo-radiotherapy, patients went to the second line of cytostatic treatment.

TABLE 1. DISTRIBUTION OF IBC PATIENTS ON AGE, RECEPTOR STATUS AND STAGE OF DISEASE

Clinical-anamnestic, molecular biological data	Groups of patients	
	Paclitaxel 135 mg/m² + Caelyx 40 mg/m² 1 time per 3 weeks (n=21)	Paclitaxel 60 mg/m² 1,8,15 days and Caelyx 25 mg/m² 1,8 days of 4 weeks cycle. (n=21)
Middle age (years)	49.1 (25-75)	50.1 (31-75)
Receptor status (%)		
RE/RP (+), Her(-)	23.8	23.8
RE/RP (+), Her(+)	9.5	9.5
RE/RP (-), Her(-)	28.6	28.6
RE/RP (-), Her(+)	14.3	9.5
T4N0-2M1 (%)	19.0	23.8

Results of treatment

Results of the treatment after 4 courses of chemotherapy showed that not in one case a full answer of tumor was not achieved, partial regression were registered in 26 (61.9%) of patients, stabilization - in 12 (28.6%) and progression on the background of treatment - in 4 (9.5%). Objective effect in patients of subgroup 2a with every week therapy mode was 71.4% (15/21), and in patients with the standard drugs administration - 52.4% (11/21). Stabilization was noted in 33.3% (7/21) in subgroup 1a and in 23.8% (4/21) in 2a subgroup. Progression was 3 times more frequent in patients with standard mode of chemotherapy (Table 2).

TABLE 2. ASSESSMENT OF TREATMENT EFFICIENCY IN IBC PATIENTS AFTER 4 COURSES OF CHEMOTHERAPY

Scheme of treatment	Quantity of patients (n)	Degree of tumor regression			
		100 %	≥ 50 %	Stabilization	Progression
1a subgroup: Paclitaxel + Caelyx (standard)	21	-	11 (52.4±10.9)%	7 (33.3±10.3)%	3 (14.3±7.6)%
2a subgroup: Paclitaxel + Caelyx (every week)	21	-	15 (71.4±9.9)%	5 (23.8±9.3)%	1 (4.8±4.7)%
TOTAL	42	-	26 (61.9±7.5)%	12 (28.6±7.0)%	4 (9.5±4.5)%

Primary spreading IBC with remote metastases in different organs had a place in 9 patients. In group, who received a treatment by standard mode, only stabilization of process was recorded while drugs administration by every week mode brought to partial regression in 60%. In whole, partial regression was recorded in 3 (33.3%) patients, stabilization - in 4 (44.5%) and progression - in 2 (22.2%) patients (Table 3).

Clinical effect in patients with primary spread IBC, which is with stage of disease T4N0-2M1, was 77.8%. Firstly, as we can see in Table 3, every week mode of chemotherapy was found more effective in patients with metastatic IBC. However, application of accurate Fisher criteria, considering low number of observations, showed invalidity of these differences (P=0.167).

Hereby, based on results of assessment of first stage of chemotherapy, 4 (9.5%) patients with process progression were transmitted into 2nd line of chemotherapy; two of them had primary spread IBC. Considering that IBC in the most cases refers to resistant forms

of cancer, it was decided to continue the treatment on the same program at patients with positive effect (partial regression + stabilization).

Treatment according to protocol of research was continued to 38 IBC patients, 7 of which were with primary-disseminated process. Conducting of additional 2-3 chemotherapy courses in group with weekly mode drugs introduction brought to regression of decease on 50% and more in 3 patients. In other cases stable remission remained. Progression of the process was not observed (Table 4).

TABLE 3. ASSESSMENT OF EFFICIENCY OF CHEMOTHERAPY IN IBC PATIENTS (T4N0-2M1) AFTER 4 COURSES OF CHEMOTHERAPY

Scheme of treatment	Quantity of patients (n)	Degree of tumor regression			
		100 %	≥ 50 %	Stabilization	Progression
1a subgroup: Paclitaxel + Caelyx (standard)	4	-	-	2 50.0%	2 50.0%
2a subgroup: Paclitaxel + Caelyx (every week)	5	-	3 60.0%	2 40.0%	-
TOTAL	9	-	3 33.3%	4 44.5%	2 22.2%

TABLE 4. ASSESSMENT OF TREATMENT EFFICIENCY AT IBC PATIENTS AFTER 6-7TH COURSES OF CHEMOTHERAPY

Scheme of treatment	Quantity of patients (n)	Degree of tumor regression			
		100 %	≥ 50 %	Stabilization	Progression
1a subgroup: Paclitaxel + Caelyx (standard)	18	-	11 (61.1±11.5)%	7 (38.9±11.2)%	-
2a subgroup: Paclitaxel + Caelyx (every week)	20	-	18 (90.0±6.7)%	2 (10.0±6.7)%	-
TOTAL	38	-	29 (76.3±6.9)%	9 (23.7±6.9)%	-

Final analysis of efficiency of two modes of chemotherapy, used for treatment of IBC patients, showed that in 69% of cases the objective effect was achieved, while the ratio made 85.7% (18/21) in the group with weekly drugs administration, and 52.4% (11/21) in the group of routine chemotherapy (Table 5).

TABLE 5. ASSESSMENT OF CHEMOTHERAPY EFFICIENCY IN IBC PATIENTS AFTER CHEMOTHERAPY COMPLETION

Scheme of treatment	Quantity of patients (n)	Degree of tumor regression			
		100 %	≥ 50 %	Stabilization	Progression
1a subgroup: Paclitaxel + Caelyx (standard)	21	-	11* (52.4±10.8)%	7 (33.3±10.3)%	3 (14.3±7.6)%
2a subgroup: Paclitaxel + Caelyx (every week)	21	-	18* (85.7±7.6)%	2 (9.5±6.4)%	1 (4.8±4.7)%
TOTAL	42	-	29 (69.0±7.1)%	9 (21.4±6.3)%	4 (9.5±4.5)%

Note: *P<0.001

In group of patients with locally spread IBC, 26 (61.9%) patients underwent the radical operation after chemotherapy with consecutive adjuvant treatment; 5 (7.1%) patients with stabilization of the process by the second stage underwent the ray therapy. However, managing operative treatment after irradiation was provided only to 3 patients. Totally, of 42 IBC patients involved into research the radical treatment was held to 29 (69%) patients; the chemo-radiotherapy was made to 2 (4.8%) patients with locally spread process. 4 (9.5%) patients were transferred on the second line of chemotherapy in connection with cancer progression, 2 (4.8%) of which had primary spread process.

The problem of toxicity of anti-tumor therapy, that often limits its possibilities and therefore decreases its general effect, remains as the one of the most topical in clinic oncology. Consequently, one of the tasks of our research was study of side effects of used modes of chemotherapy. Toxicity of the treatment was assessed on WHO criteria.

As said above, assessment of efficiency was held after 4 courses of chemotherapy. Depending on results of the treatment, patients either went to the second line of chemotherapy (4 patients with progression) or continued to receive the same mode till 6-7 courses. For that reason, frequency of side reactions was analyzed towards general number of courses. General number of courses of chemotherapy in group 1a was 106, patients received from 4 till 7 cycles of chemotherapy (median - 5.9) in group 2a (every week mode) patients received also from 4 till 7 courses of cytostatic therapy (median - 6.2), totally 112 cycles of treatment were conducted.

Spectrum of toxic effects of "Paclitaxel + Caelyx " combination, observed in this research, corresponded to that what typical to mentioned cytostatics.

Of hematological complications the leucopenia was met mainly. General frequency of leucopenia in both groups was the same: 62.4% under standard introduction of cytostatics and 64.3% - under weekly administration. While the decrease of leukocytes, assessed by 3-4 degree of toxicity, was two times more frequent in groups of patients received a treatment by standard mode. Cases of neutropenic fever were also authentically observed on introduction of drugs 1 time per 3 weeks. However, preventive application of KSF (colony-stimulating factors) and/or antibiotics decreased the frequency of this complication during the following cycles of chemotherapy; that allowed conducting the treatment to all patients involved into research. Frequency of anaemia did not exceed 16% under standard mode of treatment, deep anaemia was observed only in single cases in both groups. Thrombocytopenia was temperate; thrombocytopenia of 3-4 degree of toxicity was not recorded in any case. Hematological toxicity did not become a reason to stop a chemotherapy in any case (Table 6).

TABLE 6. ASSESSMENT OF HEMATOLOGICAL TOXICITY ON CHEMOTHERAPY IN PATIENTS WITH EDEMATOUS INFILTRATIVE IBC

Side effect	Paclitaxel + Caelyx (standard mode of introduction) - 106 courses (n=21)			Paclitaxel + Caelyx (every week mode of introduction) - 112 courses (n=21)		
	Toxicicty					
	Total	1-2 degree	3-4 degree	Total	1-2 degree	3-4 degree
Leucopenia	66 (62.3±4.7)%	47 (44.3±4.8)%	19* (17.9±3.7)%	72 (64.3±4.5)%	63 (56.3±4.7)%	9* (8.0±2.6)%
Hypogranulocytosis	59 (55.7±4.8)%	37 (34.9±4.6)%	22** (20.8±3.9)%	54 (48.2±4.7)%	47 (42.0±4.7)%	7** (6.3±2.3)%
Anemia	17 (16.0±3.6)%	15 (14.2±3.4)%	2 (1.9±1.3)%	14 (12.5±3.1)%	11 (9.8±2.8)%	3 (2.7±1.5)%
Thrombocytopenia	6 (5.7±2.2)%	6 (5.7±2.2)%	-	2 (1.8±1.3)%	2 (1.8±1.3)%	-

Note: Absolute numbers - quantity of courses of chemotherapy when the side effects were observed; *P<0.01; **P<0.001

Of non-hematological effects for patients of both groups the more typical were the symptoms connected with mucositis - stomatitis and diarrhea which were observed in 83 and 40.2% of cases accordingly in groups 1a and 2a, more often on the background of hypogranulocytosis development. Symptoms of asthenia, muscle and/or articular pains were also typical for the patients. Nausea accompanied about half of courses of chemotherapy "Paclitaxel + Caelyx", but it was under control and only during 16 (15.1%) cycles of standard mode was assessed by 3-4 degree of toxicity; this required additional conducting anti emetic and desintoxication therapy. Episodes of emesis were rare. Palmoplantar syndrome (PS), being a side effect and dose limiting in chemotherapy by Caelyx, requires particular interest. In group of patients with standard mode of treatment this syndrome was developed in patients after 4-5 courses. In 3 cases it was assessed by 3-4 degree of toxicity that totally brought to termination of treatment at 3 patients. While introduction of drugs in every week mode allowed decreasing PS frequency in 10 times, decreasing the degree of toxicity as well (Table 7).

TABLE 7. ASSESSMENT OF NON-HEMATOLOGICAL TOXICITY ON CHEMOTHERAPY IN PATIENTS WITH EDEMATOUS INFILTRATIVE IBC

Side effect	Paclitaxel + Caelyx (standard mode of introduction) - 106 courses (n=21)			Paclitaxel + Caelyx (every week mode of introduction) - 112 courses (n=21)		
	Toxicity					
	Total	1-2 degree	3-4 degree	Total	1-2 degree	3-4 degree
Nausea	73* (68.9±4.5)%	57 (53.8±4.8)%	16 (15.1±3.5)%	48* (42.9±4.7)%	48 (42.9±4.7)%	-
Emesis	11 (10.4±3.0)%	11 (10.4±3.0)%	-	4 (3.6±1.8)%	4 (3.6±1.8)%	-
Diarrhea	34** (32.1±4.5)%	28 (26.4±4.3)%	6 (5.7±2.2)%	11** (9.8±2.8)%	11 (9.8±2.8)%	-
Stomatitis	54 (50.9±4.9)%	32 (30.2±4.5)%	12 (11.3±3.1)%	34 (30.4±4.3)%	30 (26.8±4.2)%	4 (3.6±1.8)%
Neurotoxicity	27 (25.5±4.1)%	27 (25.5±4.1)%	-	19 (17.0±3.5)%	19 (17.0±3.5)%	-
Asthenia	78*** (73.6±4.3)%	76 (71.7±4.4)%	2 (1.9±1.3)%	54*** (48.2±4.7)%	54 (48.2±4.7)%	-
Myalgia/arthralgia	25 (23.6±4.1)%	25 (23.6±4.1)%	-	15 (13.4±3.2)%	15 (13.4±3.2)%	-
Lipopolysaccharide	20**** (18.9±3.7)%	17 (16.0±3.5)%	3 (2.8±1.6)%	2**** (1.8±1.3)%	2 (1.8±1.3)%	-

Note: Absolute numbers - quantity of courses of chemotherapy when the side effects were observed; *;**;***;****P<0.001

It is known, that Herceptin, being a standard cure for patients with hyperexpression of receptors Her-2/neu, has a temperate cardio-toxicity (2.6%), but in combination with anthracyclines (doxorubicine, epirubicin) increases a risk of cardio-toxicity development to 28%. In the other side, peculiarities of pharmacokinetics of Caelyx, which also refers to group of anthracyclines, ensure low system toxicity including and cardio-toxicity. In the group of patients with hyperexpression Her2/neu function of myocardium was a subject to regular monitoring during the whole period of treatment. Inclusion into scheme of treatment of target drug Herceptin in 9 patients during the observation time did not bring to changing from the myocardium side in any case.

Thereby, every week introduction of cytostatics (Paclitaxel and Caelyx) in lower doses to IBC patients allowed reaching objective effect in 85.7% cases against 52.4% on standard modes, difference is authentic ($p<0.001$). It provided to decrease reliably the hematological toxicity of 3-4 degree, particularly leucopenia and hypogranulocytosis, from 17.9% to 8% and from 20.8% to 6.3%, accordingly. It also led to decreasing of other kinds of toxicity: nausea, diarrhea, asthenic and palmoplantar syndromes, in average on 22.7%.

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