Efficacy and safety of cisplatin and paclitaxel (PlaTax regimen) in the neoadjuvant treatment of patients with stage II–III triple-negative breast cancer

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Background. *Treatment results for the patients with stage II–III triple negative breast cancer (TNBC) have to be improved. Not only the new treatment regimens, but new predictive and prognostic factors should to be developed.*
Materials and methods. *We included 98 patients with stage II–III TNBC in our study. We studied efficacy and safety of PlaTax regimen (cisplatin 75 mg/m^2 day 1 + paclitaxel 80 mg/m^2 days 1, 8, 15, course every 4 weeks) in this cohort of patients. We assessed pathologic response, survival and factors, which were relevant for predicting response and prognose survival.*
Results. *PlaTax regimen is characterized by high efficacy and tolerable toxicity. Clinical efficacy was 85.8 %, pCR achievement was 60.5 %, tpCR achievement was 58.1 %. The regimen has low haematological toxicity (neutropenia III–IV grades – 4.1 %); the most frequent adverse events were polyneuropathy (18.5 %) and decreased renal function (24.5 %). 3-year progression-free survival was 68.4 %, most of the relapses (92 %) occurred during first 2 years. 3 year overall survival was 77.6 %. The most relevant predictive factor was level of Ki-67≥50 % (pCR 38.5 % vs. 68.7 %, p = 0.038). pCR achievement was the most important prognostic factor, resulting in improved 3-year progression-free survival (44.3 % vs. 89.1 %, p <0.0001), and 3-year overall survival (61.5 % vs. 91.6 %, p = 0.001). Not only the residual disease, but also the size of residual tumor was important from prognostic point of view. Other important prognostic factors were size of the tumor, status of regional lymph nodes, grade. Delay in surgical treatment more than a month leads to decreased 3-year progression-free survival: 87.1 % vs. 62.5 % (p = 0.047).*
Conclusions. *Our data suggest that studied regimen could be an option for patients with stage II–III TNBC. The assessment of the predictive and prognostic factors will help improve the treatment results for patients with stage II–III TNBC.*

Key words: *triple negative breast cancer, neoadjuvant chemotherapy, pCR, predictors of pCR, prognostic factors*

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Background

Breast cancer (BC) is still the leading cause of morbidity and mortality among women in Russia [1]. Triple negative breast cancer (TNBC) is still the most aggressive subtype among all types of BC. Thus, new treatment regimen and options are constantly being developed [2]. For early and locally advanced BC the timing and schedule of the treatment play a pivotal role [3–5]. Neoadjuvant therapy administration even for early BC has a multiple advantage. Close interaction between modern surgical technologies and effective cytostatic regimens is a basis for achievement good treatment result [6–12].

Pathological complete response (pCR) achievement (absence of invasive component both in primary tumor and regional lymph nodes) is one of the most important goals of neoadjuvant chemotherapy (NACT). It was shown to correlate with both progression-free survival (PFS) and overall survival (OS) [4]. That is why pCR is chosen by FDA as a primary end point for studies of new NACT regimens [13]. Possible way to improve pCR rates in TNBC is an addition of platinum to the standard regimen [5, 14–18]. These platinum-based regimens lead to improved results and minor toxicity increase.

Prediction of achieving pCR is very important as it allows to change treatment strategy. For example, taking into account patient's or tumor's unfavorable characteristics, treatment intensification could be discussed and vice versa [6, 7].

Thus, not only new treatment regimens but also different predictive and prognostic markers should be studied. This includes patient's, tumor's characteristics, treatment type and schedule. This comprehensive analysis could lead to the development of the most effective strategy and improve survival.

Objective: assess efficacy and safety of PlaTax regimen in patients with stage II–III TNBC.

Materials and methods

Since 2014 we included 98 patients with stage II–III TNBC in our study, who were treated in N.N. Blokhin Russian Cancer Research Center, Ministry of Health of Russia. All patients received PlaTax regimen as NACT followed by surgery and adjuvant therapy (if indicated). All patients were examined according to the local protocol (mammograpy + regional ultrasound, breast magnetic resonance imaging was performed in patients with high breast density), distant metastases were excluded.

TNBC was verified using core needle biopsy followed by histological examination and immunohistochemistry. Fine needle biopsy ($n = 27$) or core biopsy ($n = 14$) of regional lymph nodes was performed in those patients with suspicion for local dissemination. In 47 patients tumor infiltrating lymphocytes (TILs) level was assessed according to guidelines of TILs-working group (2014).

Clinical and morphological characteristics. All patients were women; median age was 50.5 years (22–77). *BRCA1/2* testing was performed in 68 (69.4 %) patients, significant germ-line mutations were detected in 23 (33.8 %) patients, most of them – 12/23 (42.2 %) – had 5382insC mutation.

Upon presentation 41 (41.8 %) patients had T4 tumor, 11 (11.2 %) – T3, 40 (40.8 %) – T2. 23 (23.5 %) didn't have nodal involvement, 36 (36.7 %) had N1 status, 15 (15.2 %) – N2, 24 (24.5 %) – N3. Thus, early BC (T1–3N0–1) was diagnosed in 41 (41.8 %) patients and locally advanced (T4/N2–3) – in 57 (58.1 %) patients. The most common histology was invasive ductal carcinoma: 89 (90.8 %), G_2 and G_3 was documented in 37 (37.8 %) and 50 (51.0 %), respectively. Ki-67 varied from 22 % to 90 % (median – 78.5 %), Ki-67 <50 % was registered in 16 (16.3 %), ≥50 % – in 82 (83.7 %). TILs varied from 4 to 65 %, median 15 %; TILs <5 % noted in 15 (31.9 %) patients, ≥5 % – in 32 (68.1 %) patients (table 1).

Before treatment administration tumor of 29 (29.6 %) patients was clipped, in 13 (13.3 %) patients lymph node was also marked (fig. 1).

Median time from biopsy to NACT was 21 days (7–118 days), mean – 25.9 days (less than 3 weeks – 51 %, more than 3 weeks – 49 %).

All patients started with systemic NACT which included cisplatin 75 mg/m^2 (day 1) and paclitaxel 80 mg/m^2 (days 1, 8, 15), cycles every 4 weeks, up to 6 cycles (PlaTax). Mean number of administered cycles in planned regimen was 5, median – 6. The whole volume of planned treatment was administered to 73 (74.4 %) patients. If treatment efficacy was unsatisfying (disease progression or stable disease) treatment regimen was changed for AC (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2, q3w). This change was made in 8 (8.1 %) patients. We measured kidney function before each cycle. If nephrotoxicity was registered, we switched to carboplatin AUC6. If peripheral neuropathy was registered it was allowed to stop NACT after 5th cycle. Median time between biopsy and treatment initiation was 21 days (7–118 days), mean – 25.9 days (<3 weeks – 51 %, ≥3 weeks – 49 %).

Table 1. *Main characteristics of patients included in the analysis (n = 98)*

Parameter	Value
Age, years, *n* (%):	
<40	23 (23,5)
41–50	27 (27,5)
51–59	24 (24,5)
>60	24 (24,5)
Mean age, years	49,9
Median age, years	50,5
BRCA mutations, *n* (%):	
not detected	45 (45,9)
detected	23 (23,5)
unknown	30 (30,6)
Status, *n* (%):	
primary operable breast cancer	41 (41,8)
locally advanced breast cancer	57 (58,1)
Histological variant of invasive breast cancer, *n* (%):	
ductal (non-specific)	89 (90,8)
lobular	3 (3,0)
papillary trabecular	1 (1,0)
metaplastic	5 (5,1)
Tumor grade (G), *n* (%):	
2	37 (37,8)
3	50 (51,0)
unknown	11 (11,2)
Proliferation index (Ki-67), *n* (%):	
low (<20 %)	–
high (≥20 %)	98 (100)
Mean proliferation index, %	69,3
Median proliferation index, %	78,5
TILs count*, *n* (%):	
<5 %	15 (31,9)
<5 %	32 (68,1)

Note. *TILs – tumor infiltrating lymphocytes.*
**TILs count was assessed in 47 patients.*

After NACT we assessed efficacy with mammography. Complete response was documented if there was only fibrosis without any tumor nodule, partial response – if tumor shrank more than 20 %, disease progression – if tumor increased.

If patient achieved operable condition, we performed radical surgery, followed by pCR achievement in primary tumor and regional lymph nodes. If patient did not achieve operable condition, she continues with systemic treatment (± radiotherapy). Median time between NACT completion and radical surgery was 36 days (12–181 days), mean – 44,5 days, <4 weeks – 36.1 %, ≥4 weeks – 63.9 %.

Radical surgery was performed in 86 (87.8 %) patients. Radical mastectomy without reconstruction was performed in 57 (66.3 %), radical resection in 15 (17.4 %), subcutaneous mastectomy – in 14 (16.3 %) patients. Quantity of removed lymph nodes varied from 1 to 35, mean 11.2, median – 11. Median time from end of NACT to surgery was 36 days (12–181 days), mean – 44.5 days, less than 1 month – 36.1 %, more than 1 month – 63.9 %.

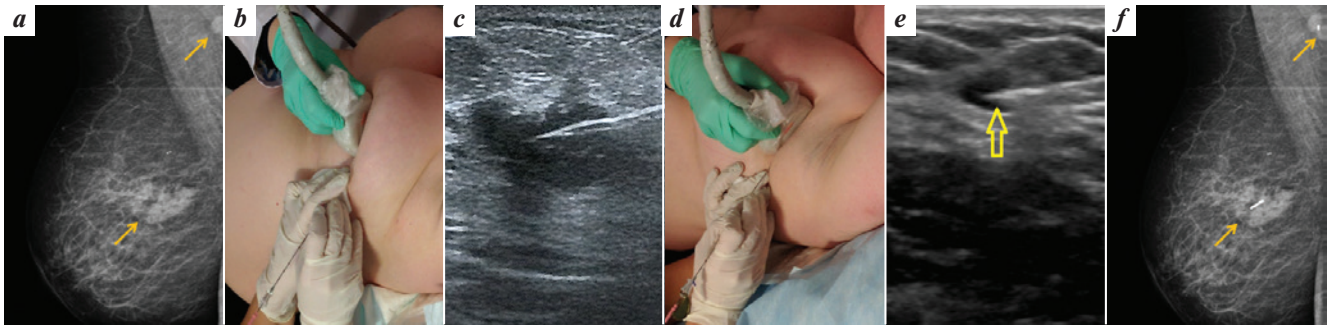

Fig. 1. *Mapping of the primary breast tumor and an axillary lymph node affected by metastasis: a – mammography scan before mapping (arrows indicate the primary tumor and axillary lymph node with verified metastasis); b – ultrasound-guided insertion of the clip into the primary tumor; c – ultrasound control of clip installation in the tumor; d – ultrasound-guided insertion of the clip into the metastatic lymph node; e – ultrasound control of clip installation in the lymph node; f – radiological control after mapping (arrows indicate clips in the primary tumor and lymph node)*

Adjuvant radiation therapy was performed upon indication. Adjuvant chemotherapy was performed in 14 patients, anthracycline-based – in 9 cases (64.3 %), capecitabine – in 5 cases (35.7 %). In 7 (7.1 %) patients, whose residual tumor had hormonal expression, adjuvant hormonal therapy was initiated.

According to study design (fig. 2) we assessed clinical efficacy and safety of PlaTax regimen, pathological response both in primary tumor and lymph nodes (tpCR). We also identified predictive factors of achieving complete pathological response. 3-year PFS and OS rates were assessed, prognostic factors were determined.

Statistical analysis was performed using SPSS (v. 22.0), non-parametric data was analyzed using χ^2 and Fisher criteria, survival was assessed using Kaplan–Meier method, differences were assessed with *log-rank*-test. Cox regression analysis was used in order to determine predictive and prognostic factors, level of significance was chosen as $p < 0.05$.

Results

Clinical efficacy of PlaTax regimen in the whole group was 85.8 %. In 37 (37.8 %) patients complete clinical response was achieved (examination and radiological assessment), in 47 (48 %) – partial clinical response, progression was registered in 7 (7.1 %) patients, 1 (1 %) patient denied to continue the treatment, so the clinical efficacy was not assessed.

Surgery was performed in 86 (87.8 %) patients. Among them 71 (82.5 %) patients received radical mastectomy ± reconstruction, 15 (17.4 %) – radical resection. Median time from end of chemotherapy till surgery was 39.5 days. In all patients, who experienced breast-sparing surgery, tumor was marked before the surgery with anchor needles. In case of complete clinical response, we used a marker, which was placed in tumor before the treatment as a guide (fig. 3). Pathological response was assessed in primary tumor and regional lymph nodes using Lavnikova score. Complete pathological response (tpCR) was registered in 58.1 % patients, there were no difference between early and locally advanced stages (61.1 % vs. 56 %, $p > 0.05$).

Predictors of pCR in stage II–III TNBC. We did not find any clinical (age, body mass index, metabolic syndrome, *BRCA* mutation), morphological (histology subtype, grade, tumor size, stage) or treatment factor to be correlated with pCR achievement ($p > 0.05$). The highest predictive value had level of Ki-67, pCR was 68.7 % (Ki-67 ≥50 %) vs. 38.5 % (Ki-67 <50 %), $p = 0.038$. TILs level also had a high predictive value: 69.8 % (TILs ≥5 %) vs. 38.5 % (TILs <5 %),

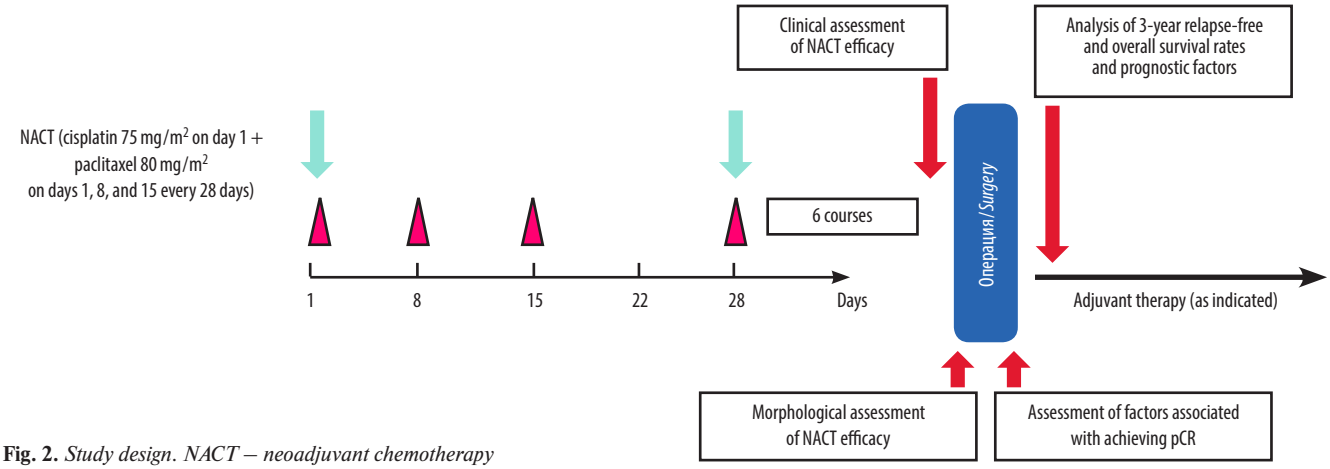

Fig. 2. *Study design. NACT – neoadjuvant chemotherapy*

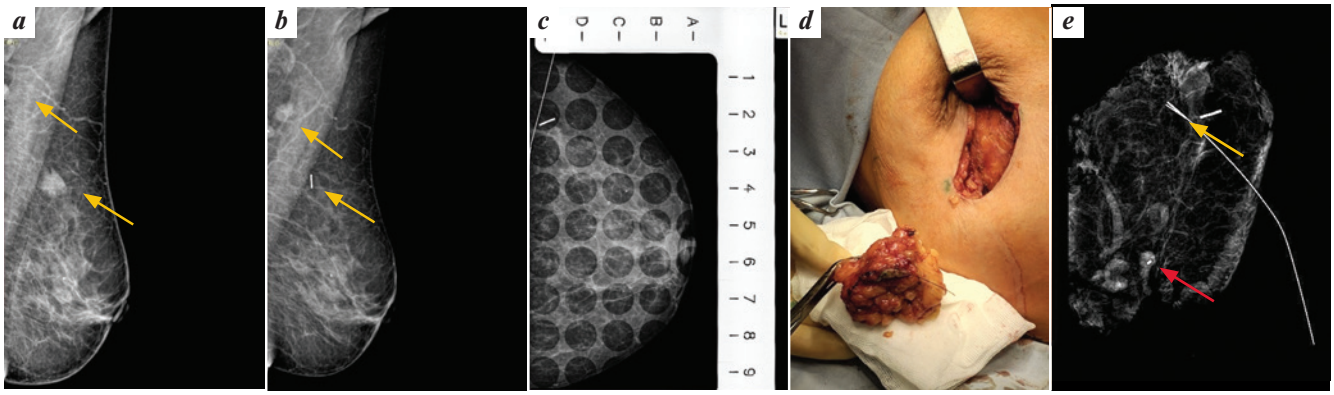

Fig. 3. *Mapping of the primary tumor and axillary lymph node before neoadjuvant chemotherapy for subsequent preoperative mapping and organ-sparing surgery: a – mammography scan before the initiation of neoadjuvant chemotherapy; arrows indicate the breast tumor and an axillary lymph node; b – mammography scan after neoadjuvant chemotherapy; arrows indicate the clip in the breast (complete radiological response) and the lymph node; c – radiologically-guided mapping; a hook-wire needle is attached to the clip; d – stage of radical resection; breast sector with regional lymph nodes have been removed; e – radiological control of the removed sector: hook-wire needle attached to the clip in the primary tumor (yellow arrow) and the clip in the lymph node (red arrow)*

$p = 0.05$. In patients with both high Ki-67 and high TILs pCR was achieved in 75 % of cases (table 2).

Survival and prognostic factors. The median follow-up was 23.1 months. Progression was registered in 26 (26.5 %) patients. 17 patients (65.4 % of patients with progression, 17.3 % of all patients) died, all of them because of the progression. 3-year PFS was 68.4 %, most of the events (92 %) occurred during first 2 years of follow up (fig. 4). 3-year OS was 77.6 %. The main sites of first progression were central nervous system – 10 (39 %), liver – 4 (15 %), local recurrence – 6 (23 %), lungs – 5 (19 %) (fig. 5).

Progression was registered in 14 (42.4 %) patients without achievement of pCR, and in 4 (7.5 %) patients with pCR ($p < 0.0001$). This confirms high prognostic value of pCR for patients with TNBC.

In patients with marked tumor locoregional progression was registered only in 1/29 (3.4 %) cases, and in 5/69 (7.2 %) cases without clipping. 3-year survival without local recurrence had a tendency to be better in group of patients with clipped tumor, 96.1 % vs. 88.2 %, $p = 0,087$. Even though this difference was not statistically significant, clipping of primary tumor allows to plan surgery more precise and, as a consequence, leads to better survival (fig. 6). Clipping of regional lymph node also did not result in better survival, which can be explained by adjuvant radiation therapy, which was performed if indicated.

We found that following factors were prognostic: age (PFS), tumor size, N-status, grade, stage (PFS and OS) (table 3). PFS was significantly lower in elderly patients (52.7 %), patients with locally advanced disease (60.7 %), and patients with G_2 tumors (54.1 %).

The most important factor for prolonging PFS was timing: gaps between biopsy and start of NACT and between end of NACT and operation (fig. 7, 8). If treatment start was delayed more than 3 weeks after biopsy, 3-year PFS decreased from 77.6 % to 59 %, $p < 0.05$. If surgery was delayed more than 1 month after end of NACT, 3-year PFS decreased from 87.1 % to 62.5 %, $p = 0,047$. Type of surgery was not a significant factor (table 4).

Clinical efficacy had a great prognostic value, all patients, who experienced a progression during NACT, died

Table 2. *Predictive value of TILs count and combination of TILs count and Ki-67*

Factor	bpCR		tpCR	
	Not achieved	Achieved	Not achieved	Achieved
TILs count, *n* (%): <5 % ≥5 %	8 (61,5) 10 (31,2)	5 (38,5) 22 (69,8)	7 (58,3) 12 (37,5)	5 (41,7) 20 (62,5)
Significance (*p*)	0,05		0,049	
TILs >5 % + Ki-67 ≥50 %, *n* (%) TILs <5 % or TILs ≥5 % + Ki-67 <50 %, *n* (%)	6 (25,0) 12 (57,1)	18 (75,0) 9 (42,9)	6 (25,0) 13 (65,0)	18 (75,0) 7 (35,0)
Significance (*p*)	0,028		0,008	

Note. *bpCR – breast pathologic complete response (primary tumor); tpCR – total pathologic complete response (primary tumor and lymph nodes); TILs – tumor infiltrating lymphocytes.*

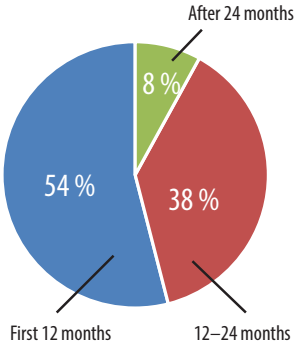

Fig. 4. *Time to progression*

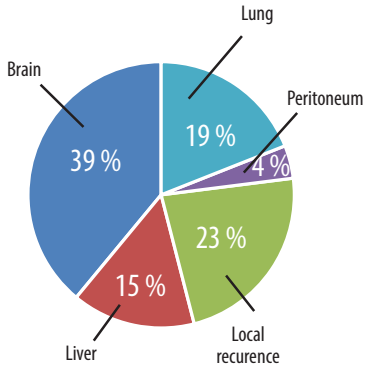

Fig. 5. *Location of metastases*

during 28 months. pCR and tpCR achievement also played a crucial role for increasing of survival. Interestingly, not only a presence residual tumor, but also its size had a prognostic value (table 5).

Among all patients 25 (25.5 %) did not received all planned (5–6 cycles) therapy and switched to another regimen. In was caused by progression (12 %) and toxicity (88 %). The most significant adverse events were nephrotoxicity (creatinine clearance <60 ml/min) and polyneuropathy grade ≥II grade (table 6).

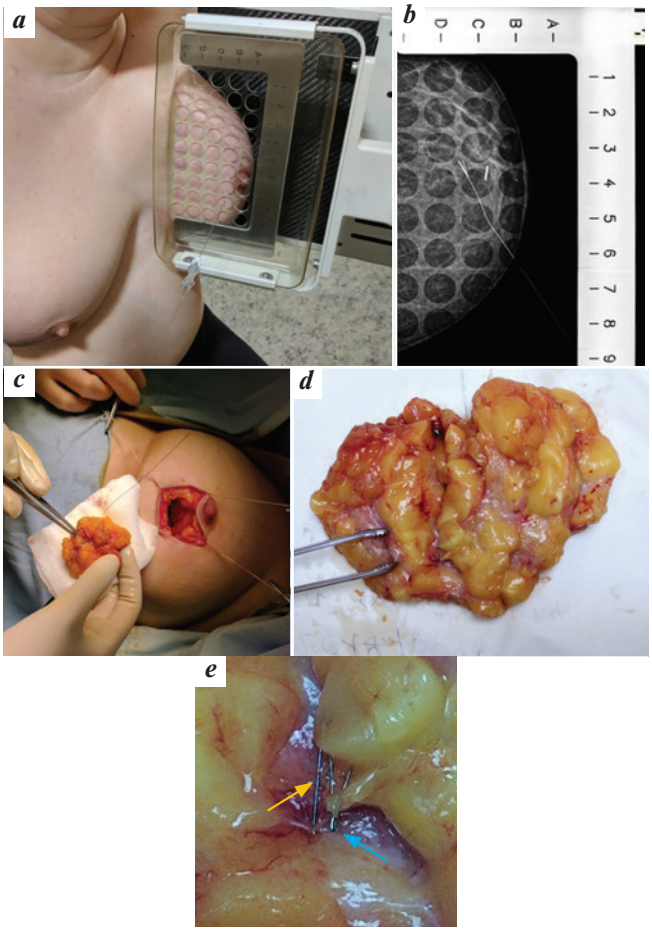

Fig. 6. *The following characteristics of surgical treatment in patients who demonstrated complete response to neoadjuvant chemotherapy ensure effective locoregional control: a – mapping of the resection area (mammography-controlled attachment of the hook-wire needle to the marked area); b – radiological control of hook-wire needle placement (mammography scan shows a titanium marker and the hook-wire needle near it); c – stage of radical resection (breast sector with the hook-wire needle has been removed); d – gross specimen of the removed sector dissected along the hook-wire needle; e – titanium marker (yellow arrow) and the end of the hook-wire needle (blue arrow) can be seen in this section*

Table 3. *Prognostic value of clinical and morphological factors*

Factor	Relapse-free survival		Overall survival	
	3-year, %	*p*	3-year, %	*p*
Age, years: <60 ≥60	 74,0 52,7	0,049	 82,0 63,3	0,057
Status: primary operable breast cancer locally advanced breast cancer	 84,3 60,7	0,036	 93,8 69,5	0,01
Tumor grade (G): 2 3	 54,1 79,4	0,008	 65,9 88,0	0,009
Proliferation index (Ki-67): <50 % >50 %	 71,1 67,5	0,705	 65,6 80,0	0,4
BRCA mutations: not detected *BRCA1/2* mutation	 65,8 72,4	0,353	 75,2 74,6	0,813

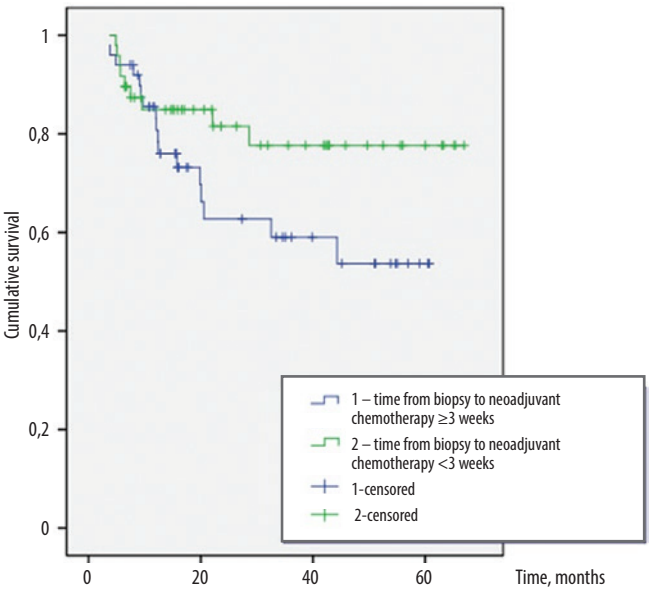

Fig. 7. *Relapse-free survival depending on the time of the biopsy*

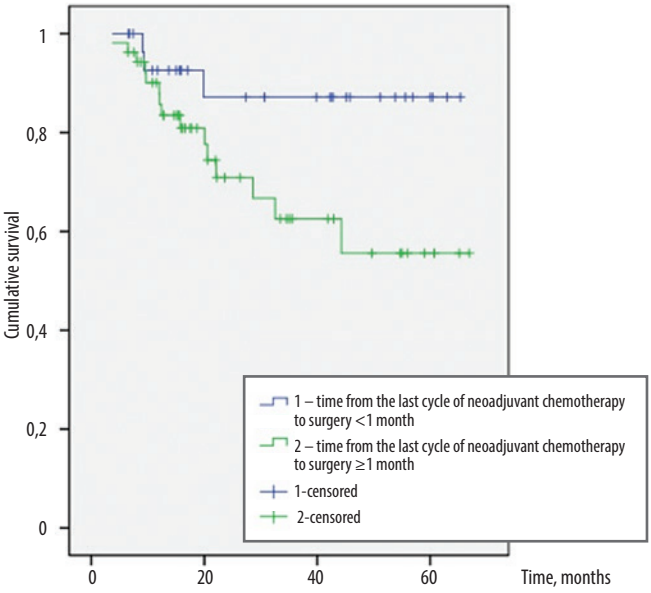

Fig. 8. *Relapse-free survival depending on the time to surgery*

Table 4. *Prognostic value of treatment scheme used*

Factor	Relapse-free survival		Overall survival	
	3-year, %	*p*	3-year, %	*p*
Number of NACT cycles: ≤4 5–6	 59,7 71,4	0,462	 76,3 77,8	0,974
Time from biopsy to NACT, weeks: <3 ≥3	 77,6 59,0	0,08	 73,9 80,8	0,426
Time from the last NACT cycle to surgery, months: <1 ≥1	 87,1 62,5	0,047	 90,6 74,6	0,063
Tumor mapping before NACT: no yes	 68,5 77,8	0,798	 76,6 91,7	0,465
Surgery: radical mastectomy ± reconstruction radical resection	 73,2 69,2	0,723	 79,3 91,3	0,231

Note. *NACT – neoadjuvant chemotherapy.*

Discussion and conclusions

PlaTax regimen as a NACT has shown its high efficacy: clinical complete response was achieved in 37.8 % of all cases, pathologic complete response both in primary tumor and lymph nodes – in 58.1 % of all cases. The highest predictive value was observed for patients with both high Ki-67 (≥50 %) and high TILs (≥5 %); pCR for this group was 75 %.

Survival data in this study corresponds with data from other studies in patients with stage II–III TNBC [14, 15, 19–22]. The highest prognostic value had age, tumor size, regional lymph node involvement and stage upon presentation. Timing is crucial for survival in this group of patients; best results were achieved in patients, who were operated less that one month after NACT completion.

Clipping of primary tumor and involved regional lymph nodes should be mandatory before treatment initiation in patients with stage II–III TNBC, as it allows to plan surgery optimally and provide a local control, which was demon-

Table 5. *Prognostic value of treatment efficacy and characteristics of residual tumor*

Factor	Relapse-free survival		Overall survival	
	3-year, %	*p*	3-year, %	*p*
Clinical response: complete response partial response stable disease progressive disease	 84,3 71,1 50,0 0	<0,0001	 82,9 83,0 75,0 0	<0,0001
bpCR: not achieved achieved	 44,3 89,1	<0,0001	 61,5 91,6	0,001
tpCR: not achieved achieved	 58,5 83,7	0,023	 61,1 93,3	0,042
Residual tumor in the breast: none (pCR) yes, <2 cm (ypT1) yes, 2–5 cm (ypT2) yes, >5 cm (ypT3)	 89,0 45,7 55,2 0	<0,0001	 91,5 62,5 65,5 37,5	<0,0001
Lymph node status after neoadjuvant chemotherapy: cN0 → ypN0 cN^+ → ypN0 cN^+ → ypN^+	 66,6 79,4 59,1	0,085	 76,7 85,9 65,2	0,249

Note. *pCR – pathologic complete response; bpCR – breast pathologic complete response (primary tumor); tpCR – total pathologic complete response (primary tumor and lymph nodes).*

Table 6. *Incidence of significant adverse events in patients receiving the PlaTax regimen (n = 98)*

Toxicity	Number of patients, *n* (%)
Anemia	5 (5,1)
Neutropenia	4 (4,1)
Febrile neutropenia	1 (1,0)
Thrombocytopenia	2 (2,1)
Hypersensitivity reaction	2 (2,1)
Mucositis	1 (1,0)
Vomiting	3 (3,1)
Diarrhea	1 (1,0)
Peripheral polyneuropathy	18 (18,4)
Nephrotoxicity	24 (24,5)
Elevated transaminases	7 (7,1)
Ototoxicity (all grades)	2 (2,0)

strated in our study [8, 10, 22, 23]. Moreover, it leads to a precise morphological assessment and detection of residual disease, which helps to plan following treatment. Survival also correlated with pCR and tpCR achievement. Moreover, not only the presence of residual disease, but also its size correlated played an important role.

PlaTax regimen had a low hematological toxicity. The most common adverse events were nephrotoxicity, polyneuropathy, transaminase elevation and anemia. Other adverse events were observed less that in 5 % of patients.

In conclusion, this data could be a basis for following studies of new treatment regimens, predictive and prognostic factors, which would lead to better treatment results in patients with stage II–III TNBC.

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I.V. Kolyadina: obtaining data for analysis, analysis of the obtained data, developing the research design, article writing, scientific editing of the article;
L.G. Zhukova, I.P. Ganshina: obtaining data for analysis, developing the research design, scientific editing of the article;
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