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PREDICTIVE AND PROGNOSTIC POTENTIAL OF CD44 AND CD24 EXPRESSION IN PRIMARY TUMOUR AND AFTER CHEMOTHERAPY IN PATIENTS WITH BREAST CANCER

Aim: *to evaluate prognostic and predictive value of surface-cells markers — CD44 and CD24 in the primary tumour tissue and after neoadjuvant chemotherapy (NACT) in different groups of patients of breast cancer (BC).* ***Object and methods:*** *specimens of the primary tumour and specimens after chemotherapy in 106 patients with invasive BC. The observed patients were treated at the National Cancer Institute. Immunohistochemical staining for CD44 and CD24 was performed in tumour specimens. The survival analysis was performed depending on the clinical and pathological data and the expression of markers CD44, CD24, $CD44^+/CD24^-$, $CD44^+/CD24^+$.* ***Results:*** *different expressions of markers in the primary tumour tissue and after NACT were detected. An increase of the expression of $CD44^+$ and $CD44^+/CD24^-$ has been noted in tumour tissue after NACT, which may play a role in the development of chemoresistance and the possible mechanism of relapse of invasive BC. The prognostic value of triple negative subtype of BC, tumour size, coexpression of noninvasive $CD44^+/CD24^+$ cells was revealed in the Cox regression model.* ***Conclusion:*** *the differing expression of surface-cells markers in the primary tumour and after NACT may reflect intratumoral heterogeneity of the BC and the possible development of chemoresistance. Triple negative subtype and tumour size were revealed as the risk factors associated with survival. Markers CD44 and CD24 were insufficient factors to determine the prognosis.*

INTRODUCTION

Breast cancer (BC) is the main cause of women's death from cancer [1]. After radical treatment of patients with BC some of them have relapses and metastases. According to the theories their appearance is associated with cancer stem cells (CSC) — small population of stem cells which is the cause of growth of tumour [2] and resistance to radiation therapy [3] and chemotherapy [4].

The majority of current investigations have identified a subpopulation of BC stem cells through surface-cell markers — CD44 and CD24 [5, 6]. One of the most investigated CSC is the phenotype $CD44^+/CD24^-$, but its clinical significance remains controversial. This phenotype is associated with more aggressive clinical and pathological data of BC [7], it is more common in patients with distant metastasis [8, 9] and it has a link with three-negative [10] and basal type of tumour [11, 12]. The correlation of immunophenotype $CD44^+/CD24^-$ with resistance to anthracyclines is emphasized in some researches [13, 14], but the main mechanisms are still unknown. Investigations to find CSC markers predicting drug resistance continue nowadays.

CD24 expression was detected in various types of carcinoma while it is seldom expressed in normal tissues [15]. Some research reports indicate that low CD24 expression is a characteristic biomarker, which promotes the initiation and progression of tumour process [16], as well as demonstrates the resistance to doxorubicin [13]. The other ones show that high $CD24^+$ expression is considered to be an unfavorable prognostic factor of BC, associated with short-term disease-free survival (DFS) and may be a marker of sensitivity to adjuvant chemotherapy [17, 18]. Besides CD24 expression was significantly correlated with the aggressive HER2-positive status of BC [19] and with drug resistance in the HER2/neu expression [20].

CD44 is a well-known transmembrane glycoprotein. It is a contributing factor to carcinogenesis and a progression to a variety of neoplasms [21]. Previous investigations have demonstrated that aberrant expression of CD44 is associated with invasion, metastasis and has a negative effect on DFS in patients with HER2 expression or a basal-like BC [21]. But Horiguchi [22] substantiated that DFS is higher with high expression of CD44. At the same time, the other authors do not observe any differences in clinical outcomes and survival in regards to the expression of CD44 and CD24 [19].

Thus, numerous investigations about the role of CD44, CD24 in carcinogenesis and contradictory data of their prognostic significance have determined our interest for further research. In addition, the predictive potential of these biomarkers has not been sufficiently studied. Therefore, our task is to evaluate prognostic and predictive value of biomarkers CD44 and CD24 in primary tumour and after chemotherapy in different groups of patients with BC.

MATERIALS AND METHODS

Specimens of the primary tumour and specimens after chemotherapy in patients with invasive BC have been studied separately. The observed patients were treated at the National Cancer Institute from 2008 to 2013.

The criteria for inclusion in this research were the following: women samples; histologically confirmed BC; tumour samples available for study. The medical records, pathology reports of the patients for obtaining clinical information were analyzed. The disease stage was classified according to the TNM AJCC categories (6th edition). A local ethical committee approved the study protocol.

From 130 cases of BC included in this research specimens only 106 patients were suitable for staining and informative for immunohistochemical (IHC) results. Patients were divided into two groups: group 0 — the patients with directly examined the primary tumour; group 1 — the patients after neoadjuvant chemotherapy (NACT). The median of observation was 48.5 months (interquartile range Q1 = 36.5 months, Q3 = 63.5 months).

Clinical and pathological characteristics of patients are indicated in Table 1. NACT was conducted mainly to patients up to 50 years old (the difference between the groups by age is statistically significant, $p = 0.02$). The median age for group 0 was 52.5 years old, for group 1 — 47 years old.

The distribution of disease stages according to T and N categories between the groups was different ($p < 0.05$). It was caused by NACT criterion for grouping. Among the patients having operative treatment immediately, 82.5% of them had early stages of BC, and 19.2% of the patients had the IIIA stage. It is due to staging of disease after surgery considering the regional lymph node involvement. NACT was performed for the majority of patients (66.7%) with the locally advanced BC in accordance with standard treatment protocols. Regimens of NACT included mainly anthracyclines (90.7%) and paclitaxel were used in 9.3% of cases. The distribution of tumour phenotype did not reveal a statistically significant difference between the groups ($p = 0.75$). The majority of patients were patients with luminal tumour subtypes in both groups.

IHC analysis. The original hematoxylin-eosin-stained patients' glasses in the retrospective sample were examined and noted by the pathomorphologist for further analysis of cell surface markers. Specific primary anti-CD44 antibodies (polyclonal rabbit antibodies, 1:100, Thermo Scientific, USA) and CD24 (SN3, monoclonal mouse antibodies, 1:200, Thermo Scientific, USA) were used for IHC staining according to the methodology described in previous research [23]. Two pathologists who weren't aware the clinical outcomes of patients independently carried out assessment of staining results. IHC surrogate panel (ER, PgR, HER2) was used to determine the subtypes of BC [24].

Statistical analysis. DFS was defined as a period from the date of operations to the documented date of recurrence and/or distant metastases. Overall survival was defined as a number of months from the diagnosis to the date of death. Censored overall survival was taken into account when the date of death of a patient was unknown and the date of the last observation was the indication point. Differences in the frequencies of the main clinical-pathological parameters and subtypes were analyzed using the chi-square test. Survival curves were constructed using the Kaplan — Meier method and ranking test was used to compare the meaning of survival rates by subtypes. Cox model was used for multivariate analysis in order to predict the survival relationship with patient age, tumour size, lymph node involvement, various subtypes of BC, NACT and cell-surface marker content. Hazard ratio (HR) and its 95% confidence interval (CI) were calculated to assess the degree of relationship.

Table 1

Clinical and pathological characteristic of patients in groups

Characteristics		Absolute value (%)		p
		Group 0 (n = 52)	Group 1 (n = 54)	
Age (X ± SD), years old		50.6 ± 10.5	46.2 ± 9.4	0.02
Age range, years		27–71	28–64	
Median, years		52.5	47	
25–75 quartiles, years		42.5–58.5	30–55	
Stage (AJCC)	I	4 (7.7)	0	< 0.001
	IIA	20 (38.5)	6 (11.1)	
	IIB	18 (34.6)	22 (40.7)	
	IIIA	10 (19.2)	25 (46.3)	
	IIIB	0 (0.0)	1 (1.9)	
Category T	1	6 (11.5)	2 (3.7)	0.002
	2	46 (88.5)	40 (74.1)	
	3	0 (0.0)	10 (18.5)	
	4	0 (0.0)	2 (3.7)	
Category N	0	22 (42.3)	9 (16.7)	0.008
	1	20 (38.5)	24 (44.4)	
	2	10 (19.2)	21 (38.9)	
Subtype	Luminal A	19 (36.5)	17 (31.5)	0.75
	Luminal B (HER2–)	18 (34.6)	19 (35.2)	
	Luminal B (HER2+)	1 (1.9)	4 (7.4)	
	Triple negative BC (TNBC)	12 (23.1)	12 (22.2)	
	HER2/neu expression	2 (3.9)	2 (3.7)	

A critical level of significance was chosen at $p < 0.05$. The analysis was performed using statistical software packages MedCalc 17.9.2 (MedCalc Software bvba, 1993–2017).

RESULTS AND COMMENTS

Analysis of expression of immunophenotypes CD44, CD24, CD44$^+$/CD24$^-$, CD44$^+$/CD24$^+$ in different groups of patients. IHC analysis of the expression of CD44, CD24, CD44$^+$/CD24$^-$ as presumed CSC was performed in 106 patients with an invasive BC in order to identify the association of these markers with the treatment (Table 2).

There was no statistically significant difference for biomarker of the CD24 ($p = 0.16$) in the groups of patients with and without NACT. But there was a tendency ($p = 0.08$) to increase CD44$^+$ expression in the tumour tissue after NACT (59.3% of cases), as there was a predominant lack of CD44 expression (59.6% of cases) in the primary tumour tissue.

Table 2

Association of immunophenotypes CD44, CD24, CD44⁺/CD24⁻, CD44⁺/CD24⁺ in groups

Marker	Expression	Absolute value (%)		p
		Group 0 (n = 52)	Group 1 (n = 54)	
CD24	–	34 (65.4)	27 (50.0)	0.16
	+	18 (34.6)	27 (50.0)	
CD44	–	31 (59.6)	22 (40.7)	0.08
	+	21 (40.4)	32 (59.3)	
CD44⁺/CD24⁻	–	40 (76.9)	32 (59.3)	0.08
	+	12 (23.1)	22 (40.7)	
CD44⁺/CD24⁺	–	39 (75.0)	38 (70.4)	0.48
	+	9 (17.3)	7 (13.0)	
	++	3 (5.8)	8 (14.8)	
	+++	1 (1.9)	1 (1.8)	

In the distribution of the CSC putative marker, such as CD44⁺/CD24⁻, there was also a tendency (p = 0.08) to increase the level for patients after NACT. The expression of this immunophenotype was detected in 40.7% of cases after NACT and in 23.1% of cases in the primary tumour.

The coexpression of CD44⁺/CD24⁺ in the observed groups was also analyzed (Table 2) and there was approximately uniform absence of markers coexpression in both groups (75.0 and 70.4% of cases). High expression (2+ and 3+) of CD44⁺/CD24⁺ was detected in the tumour tissue after NACT more often (16.6%) than in the primary tumour (7.07%). Despite of revealed shift of CD44⁺/CD24⁺ statistically significant difference between the different groups of patients was not detected (p = 0.48). Thus, the data obtained in the research show a tendency to increase the expression of CD44⁺ and CD44⁺/CD24⁻ (p = 0.08) in tumour tissue of breast in patients after NACT.

Survival analysis depending on clinical and pathological data and status of markers CD44, CD24, CD44⁺/CD24⁻, CD44⁺/CD24⁺. Univariate and multivariate analysis were performed in order to identify risks factors associated with survival. Cox proportional hazards regression model was used. In this model the categorical variables were clinical pathological data and the expression of the following specific cell surface markers: CD44, CD24, CD44⁺/CD24⁻, CD44⁺/CD24⁺.

Cox regression model allowed estimating the influence of the following factor signs on the survival distribution: CD24 and CD44 expression (negative or positive), CD44⁺/CD24⁻, CD44⁺/CD24⁺ (negative or positive), age, tumour size (pT1, pT2, pT3 and pT4), lymph node status (negative and positive), disease stages and subtypes of BC. The analysis of Cox univariate model (Table 3) identified that survival is associated with coexpression of CD44⁺/CD24⁺ (p = 0.06, HR = 1.73; 95% CI 0.98–3.06) and tumour phenotype. A worse prognosis was for triple negative subtype of BC (p < 0.001, HR = 3.29; 95% CI 1.72–6.28) and HER2/neu expression subtype (p = 0.09, HR = 2.89; 95% CI 0.86–9.73).

Age, stage of disease, category T and N and NACT are not significant for survival in Cox univariate model. The differences in the expression of immunophenotypes CD44, CD24, CD44⁺/CD24⁻ also were not found (Table 3).

Table 3

Analysis Cox univariate model of survival prognosis depending on clinical and pathological data and expression of cell surface markers

Factor	Index, b ± m	p	HR (95% CI)
Group 1 *vs* 0	0.06 ± 0.28	0.84	1.06 (0.61–1.84)
Age	0.000 ± 0.014	0.97	1.00 (0.97–1.03)
CD24⁺ *vs* CD24⁻	–0.01 ± 0.28	0.98	0.99 (0.57–1.71)
CD44⁺ *vs* CD44⁻	–0.02 ± 0.28	0.95	0.98 (0.57–1.70)
CD44⁺/CD24⁺ + *vs* –	0.55 ± 0.29	0.06	1.73 (0.98–3.06)
CD44⁺/CD24⁻ + *vs* –	–0.24 ± 0.30	0.44	0.79 (0.44–1.42)
TNBC *vs* luminal	1.19 ± 0.33	<0.001	3.29 (1.72–6.28)
HER2(+) *vs* luminal	1.06 ± 0.62	0.09	2.89 (0.86–9.73)
Luminal B (HER2+) *vs* luminal	0.58 ± 0.51	0.34	1.79 (0.56–4.85)
Category T	0.20 ± 0.18	0.25	1.22 (0.86–1.74)
Category N – *vs* +	–0.04 ± 0.30	0.89	0.96 (0.53–1.73)

Results of Cox univariate analysis can be presented graphically (Figure).

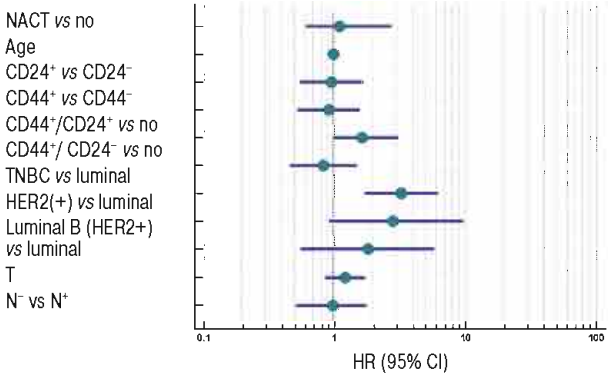

Figure. Cox univariate model for survival analysis

Multivariate analysis of survival. We also have considered applying multivariate forecasting model, while objective estimation of prediction seldom depends on one isolated factor.

After the selection of significant features using the step-by-step inclusion/exclusion method (threshold of inclusion p < 0.2, exclusion threshold p > 0.4), a multivariate model of prognosis was constructed (Table 4).

Table 4

Cox multivariate model for survival analysis

Factor	Index, b ± m	p	HR (95% CI)
TNBC *vs* luminal	1.21 ± 0.33	< 0.001	3.4 (1.7–6.5)
HER2(+) *vs* luminal	0.99 ± 0.63	0.12	2.7 (0.8–9.3)
Luminal B (HER2+) *vs* luminal	0.45 ± 0.62	0.46	–
Category T	0.31 ± 0.19	0.10	1.4 (0.9–2.0)
CD44⁺/CD24⁺ + *vs* –	0.47 ± 0.30	0.12	1.6 (0.9–2.9)

In the multivariate model, TN subtype of BC was the only significant prognostic variable which influenced on survival (p < 0.001, HR = 3.4; 95% CI 1.7–6.5). Nevertheless, the factors that influence on survival indirectly were also HER2/neu expression subtype (p = 0.12, HR = 2.7; 95% CI 0.8–9.3), luminal B (HER2+) positive subtype (p = 0.46), coexpression of CD44⁺/CD24⁺ (p = 0.12, HR = 1.6; 95% CI 0.9–2.9) and category T. It was revealed that the increase in tumour size resulted deterioration of survival (p = 0.12; HR = 1.6; 95% CI 0.9–2.09).

In the research we show that clinical and morphological features of patients of BC are different in groups having operative treatment immediately or NACT before surgery. It is known that chemotherapy has the selectivity for proliferating cells and how much chemotherapy acts on the clone of stem cells capable to be predictors of drug resistance and poor prognosis is still being studied [14].

We have found variable patterns of markers' expression in different tumour samples. Our data are consistent with some previously observed trends — an increase of the number of $CD44^+$ and $CD44^+/CD24^-$ in tumour tissue after NACT [25]. We have noticed that CD44 was markedly expressed in tumour tissue of breast after NACT, which indicates that CD44 is involved in tumorigenesis of BC. This result coincides with the data: $CD44^+$ shows a more mesenchymal, mobile and less proliferative profile and is similar to stem cells [26]. An increase of $CD44^+$ expression after chemotherapy may indicate the development of resistance to cytostatics [14, 27].

The same tendency in the expression of $CD44^+/CD24^-$ tumour cells was noted in patients after NACT ($p = 0.08$). This shift of $CD44^+/CD24^-$ was probably due to increase in the subpopulation of $CD44^+$. The profile of $CD44^+/CD24^-$ was previously widely investigated and their invasive nature was proved. It made this population possible CSC [9, 16]. The fact that a small population of CSC survives after chemotherapy and causes the relapse of invasive BC [28] is still interesting for many researchers. It was stressed in some articles that $CD44^+/CD24^{-/low}$ cells demonstrate properties of CSC and chemoresistance [29] and $CD24^-$ cells enhance the resistance to doxorubicin [13]. The content of another cell surface marker, CD24, did not differ in tumour tissue of both groups in our research. Although the predictive significance of CD24 cells after NACT in patients with BC was previously reported by other researchers [22], and in particular the stability of $CD24^{-/low}$ cells to the treatment of anthracyclines was mentioned [13].

Thus, analysis of cell surface markers expression revealed the differences between groups with a tendency to a significant increase of $CD44^+$ and $CD44^+/CD24^-$ in tumour tissue of breast after NACT, which may play a certain role in the development of resistance to chemotherapy and in the possible mechanism of relapse after treatment.

We estimated the prognostic value of clinical-pathological indicators and cell surface markers CD24, CD44. We noticed that the TNBC showed a poor prognosis for survival, which corresponds to the previous investigations [30]. The trend towards a significant effect of the HER2/neu expression subtype on the survival in the univariate analysis has lost its significance in the Cox multivariate analysis. But the increase in tumour size resulted deterioration of survival in multivariate analysis.

In the Cox univariate and multivariate analysis we did not find any relationship between age, disease stage, lymph node involvement, NACT, CD44, CD24, $CD44^+/CD24^-$ expression and clinical outcome — survival. Our data coincide with the research result [11] that there is no link between the status of $CD44^+/CD24^-$ and survival.

However, according to other scientists' investigations, $CD44^+/CD24^-$ tumour cells were significantly associated with poor survival [10], CD24 expression was a marker of poor prognosis for the luminal A subtype [31]. It was also shown that negative CD24 tumours have a very low risk of tumour progression, while CD24 positive tumours are associated with a short-term DFS [17]. Some researchers note that high expression of CD44 correlates with reduced DFS and the existence of distant metastases [13, 21, 32], other scientists [22] — on the contrary, emphasize that $CD44^+$ contributes to a favourable prognosis in patients with primary BC.

In our study, one of the prognostic factors was tumour cells with coexpression of $CD44^+/CD24^+$, which showed a tendency to a significant effect on survival in the univariate analysis. Presented data show that non-invasive $CD44^+/CD24^+$ cells are plastic and can easily generate offspring of invasive $CD44^+/CD24^-$ cells through activation of signalling Activin/Nodal [27]. The hypothesis of the variable existence of tumour cells, which are either $CD44^+$ or $CD24^+$, can reflect the current state of tumour with undergoing constant cell renewal, differentiation and interaction with the surrounding stroma [11]. It is permissible that $CD44^+$ and $CD24^+$ cells can undergo the independent clonal evolution [26] and thereby it emphasizes the biological heterogeneity of BC.

CONCLUSION

Research results underline biological intratumoral heterogeneity of BC and demonstrate different expression of CD44, CD24 in tumour tissue of the primary BC and in samples after NACT. The investigated cell surface markers can undergo certain changes after NACT and, possibly, can increase resistance to the chemotherapy. CD44 and CD24 are markers associated with carcinogenesis in BC, but in our research they were insufficient factors to determine the prognosis.

Further investigations are necessary to determine the place and role of CD24, CD44 in chemoresistance and prognosis of patients of BC.

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ПРЕДИКТИВНИЙ І ПРОГНОСТИЧНИЙ ПОТЕНЦІАЛ ЕКСПРЕСІЇ CD44 І CD24 У ПЕРВИННІЙ ПУХЛИНІ ТА ПІСЛЯ ХІМІОТЕРАПІЇ У ПАЦІЄНТІВ З РАКОМ МОЛОЧНОЇ ЗАЛОЗИ

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Резюме. ***Мета:*** *оцінити прогностичне і предиктивне значення маркерів CD44 і CD24 у первинній пухлині та після проведення неоад'ювантної хіміотерапії (НАХТ) у різних групах хворих на рак молочної залози (РМЗ).* ***Об'єкт і методи:*** *зразки тканини пухлин 106 хворих на інвазивний РМЗ, які проходили лікування в Національному інституті раку. Експресію маркерів CD44 і CD24 визначали за допомогою імуногістохімічного методу. Проведено аналіз виживаності пацієнтів залежно від клініко-патологічних даних і експресії CD44, CD24, $CD44^+/CD24^-$, $CD44^+/CD24^+$.* ***Результати:*** *виявлено відмінності в експресії досліджуваних маркерів у первинній пухлинній тканині та після проведення НАХТ. Підвищення експресії $CD44^+$ і $CD44^+/CD24^-$ у пухлинній тканині після проведення НАХТ може відігравати певну роль у формуванні хіміорезистентності та можливому механізмі розвитку рецидиву інвазивного РМЗ. За допомогою регресивної моделі Кокса виявлено прогностичне значення тричі негативного підтипу РМЗ, розміру пухлини, коекспресії неінвазивних клітин $CD44^+/CD24^+$.* ***Висновок:*** *відмінність експресії поверхневих клітинних маркерів у первинній пухлині та після проведення НАХТ відображає внутрішньопухлинну гетерогенність РМЗ та, можливо, ймовірність розвитку хіміорезистентності. Прогностичними факторами, які пов'язані з виживаністю, виявилися тричі негативний підтип та розмір пухлини. Рівні експресії маркерів CD44 і CD24 виявилися недостатніми факторами для визначення прогнозу.*

Ключові слова: рак молочної залози, стовбурові пухлинні клітини, CD44, CD24, виживаність, хіміотерапія, прогностичне значення.

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