

UDC: 616-006.666

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## Demographic and clinical-morphological features of patients with metastatic breast cancer with over-expression of Her-2 / neu receptors based on the results of the PH + oeBE study

*The demographic and clinical-morphological parameters in patients with metastatic Her-positive breast cancer (BC) were presented based on the retrospective, descriptive, cohort study PH + oeBE. The study included relevant data from medical records of patients with diagnosed and morphologically confirmed HER2-positive metastatic breast cancer.*

**Keywords:** breast cancer (BC), metastases, HER2-positive cancer, demographic parameters, immunohistochemistry, morphology.

**Relevance.** Breast cancer (BC) is a heterogeneous disease, the prognosis and the course of which depends on the molecular-genetic and clinical patterns of tumour in each individual case. It is known that the over-expression of human epidermal growth factor receptor (HER2) is associated with low survival, high risk of metastasis and low susceptibility to cytostatics [1]. The potential of targeted therapy in oncology, in particular, the trastuzumab monoclonal antibody affecting the HER2 extracellular domain has been demonstrated in studies with trastuzumab in adjuvant mode. These studies showed a nearly two-fold reduction of recurrence risk, which reverse the prognostic value of the HER2 receptors over-expression [2-4].

In Kazakhstan the introduction of targeted therapy with trastuzumab was launched in 2001. Lapatinib is used only since 2011. However, lack of complete data about the treatment regimens for metastatic HER2 + breast cancer in CIS countries, including Kazakhstan, led to initiation of the retrospective observational study of treatment methods used in recent years in clinical practice in patients with HER2-positive locally spread or metastatic breast cancer.

The article presents the analysis of clinical and morphological parameters of metastatic BC with over-expression of Her-2/neu based on the retrospective, descriptive, cohort study PH + oeBE. The study included relevant data from medical records of patients with diagnosed and morphologically confirmed HER2-positive metastatic breast cancer.

**Study design.** The study PH + oeBE - is the retrospective, descriptive, cohort study of the phase IV. It was performed in 3 CIS countries: Russian Federation, Ukraine and Republic of Kazakhstan. Data on patients with primary-disseminated and metastatic HER2-positive BC were obtained from patient medical records. The study included patients with

breast cancer diagnosis established within the timeframe of January 1, 2010 to November 30, 2011. The follow-up period was from January 02, 2010 to November 30, 2013. Thus, the required data for patients were gathered for follow-up period of at least 24 months with one of the following outcomes: patient death, patient loss for follow-up, follow-up care, or completion of follow-up.

**Materials and methods.** The study included relevant data on women aged from 18 years old and upward with known date of diagnosis of metastatic or progressive breast cancer with morphologically confirmed HER2-positive type. The routine procedure for HER2-testing without re-sampling of tissues was an important pre-requisite for inclusion. The detection of synchronous cancer of other localization was the criteria for withdrawal.

The cohort size of 241 patients was determined on the basis of availability of suitable patients. The statistical methods for reflection of the study outcomes included the variables generalized for all patients within the study and descriptive statistics. The formal statistical comparison of the study outcomes between the treatment groups was not conducted. Missing or incorrect data were not included to the statistical analysis.

**Findings.** The demographic and clinical-morphological parameters of patients with metastatic Her-positive breast cancer presented in the Table 1.

The median age of patients with primary breast cancer diagnostics was 52.3±11.5 years, and with metastases - 53.8±11.2 years. Over 1/3 of patients, 35.7% (86), belonged to a premenopausal age, about half of them - 46.9% (113) had a postmenopausal status, and in 17.4% (42) of cases the menopause status was unknown.

The distribution of patients by disease stages (TNM) of the primary breast cancer diagnosis was as follows: more

than half of patients, 56.0% (135), had a tumour size of 2-5 cm during the primary diagnostics, which corresponded to the stage T2. The tumours less than 2 cm, T0-T1, were observed only in 12.0% of patients. In 11.2% of (27) cases, the tumour was classified as the cancer of stage T3. The tumour with lesion of chest wall or skin has been detected in 1/5 of patients during the primary diagnostics, classified as T4 stage of disease.

The regional lymph node involvement was observed in 192 (83.4%) cases, 9 (3.7%) patients did not have confirmed data (Nx). The remote metastases were detected in 24 (10.0%) patients, in 2 (0.8%) cases no evidence of presence or absence of remote metastases was found within the primary diagnostics (Mx).

Thus, the distribution of patients by clinical stages of disease was the following: stage I was diagnosed in 5.0% (12)

patients, stage II - in 47.3% (114), stage III - in 37.8% (91), and stage IV – in 10% (24) of patients.

Assessment of BC morphological subtypes showed that an invasive carcinoma was diagnosed in a majority of patients: flow type - 50.2% (121), lobular - 3.7% (9), mixed - 1.2% (3). The ductal carcinoma was detected in situ in 20.3% (49) of cases. In assessing the degree of tumour differentiation (G), it was found that the routine study of that indicator is not mandatory for all centres, therefore, in large proportion of patients - 105 (43.6%), the data on the tumour malignancy degree were not obtained. In remaining cases, the average (G2) and low (G3) degree of tumour differentiation was recorded with approximately same frequency - 25.7% (62) and 27.0% (65) of patients, respectively. In 1 (0.4%) case the morphological assessment corresponded to the anaplastic carcinoma (G4).

**Table 1** - Demographic and clinical-morphological parameters in patients with metastatic Her-positive breast cancer within the primary diagnostics of the disease

Profile of patients	
<b>Age of patients with primary diagnostics of cancer (n)</b>	<b>241</b>
Mean age at primary diagnostics of BC (CO)	52.3 (11.5)
Median age (min-max)	52.4 (23.0-88.0)
Interquartile range	(43.9-60.0)
<b>Menopausal status (n)</b>	<b>241</b>
Perimenopause	86 (35.7%)
Postmenopause	113 (46.9%)
Unknown status	42 (17.4%)
Distribution by disease stages	
<b>Primary tumour T (n)</b>	<b>241</b>
Tis	0
T1	28 (11.6%)
T2	135 (56.0%)
T3	27 (11.2%)
T4	50 (20.7%)
TX	0
<b>Regional lymph nodes N (n)</b>	<b>241</b>
N0	40 (16.6%)
N1	118 (49.0%)
N2	61 (25.3%)
N3	13 (5.4%)
NX	9 (3.7%) 0
<b>Remote metastases M (n)</b>	<b>241</b>
M0	215 (89.2%)
M1	24 (10.0%)
MX	2 (0.8%)
<b>Clinical stage (n)</b>	<b>241</b>
I	12 (5.0%)
II	114 (47.3%)
III	91 (37.8%)
IV	24 (10.0%)
<b>Histological type of tumour</b>	<b>241</b>
Flow carcinoma in situ	49 (20.3%)
Lobular carcinoma in situ	3 (1.2%)
Invasive flow carcinoma	121 (50.2%)
Invasive lobular carcinoma	9 (3.7%)
Invasive mixed carcinoma	3 (1.2%) 3
Other	7 (15.4%)
No data	20 (8.3%) 0
<b>Degree of the tumour differentiation</b>	<b>241</b>
G1: high degree of differentiation (low degree of malignancy)	8 (3.3%)
G2: average degree of differentiation (intermediate degree of malignancy)	62 (25.7%)
G3: low degree of differentiation (high degree of malignancy)	65 (27.0%)
G4: undifferentiated tumour (high degree of malignancy)	1 (0.4%) 0
GX: degree of differentiation is not possible to determine (unknown malignancy)	0
No data	105 (43.6%)

Table 2 presents the clinical parameters of patients with Her-positive metastatic breast cancer. The diagnostics of metastatic process revealed that the general status of patients in most cases (56.5%) was satisfactory and corresponded to 0-1 score of the ECOG scale. The medium severity condition (2 scores on the ECOG scale) was established in 29 patients (12.0%), and grave condition - only in

7 patients (2.9%), including 1 case (0.4%) classified as extremely critical condition.

Analysis of the metastases rate of various organs and systems showed that the extra-ostial metastases were detected in 237 cases (98.3%), at this the rate of visceral metastases with liver damage and/or lung was observed in 92 patients (38.8%).

**Table 2** - Clinical parameters of patients with Her-positive metastatic breast cancer

Indicators	Total number of patients (n=241)	Patients with primary-metastatic BC, IV stage (n=24)	Patients with BC progression, I-III stages (n=217)
<b>Age at remote metastases diagnostics</b>	N=241	N=24	N=217
Mean age at primary diagnostics of BC (CO)	53.8 (11.2)	56.3 (13.5)	53,5 (10,9)
Median age (min-max)	53.7 (25.0-88.0)	56.2 (36.0-88.0)	53,6 (25,0 -78,0)
Interquartile range	(45.9-60.9)	(45.5-63.4)	(45.9-60.9)
<b>Status according to ECOG in diagnostics of remote metastases</b>	N=241	N=24	N=217
0	24 (10.0%)	2 (8.3%)	22 (10.1%)
1	112 (46.5%)	6 (25.0%)	106 (48.8%)
2	29 (12.0%)	3 (12.5%)	26 (12.0%)
3	6 (2.5%)	0	6 (2,8%)
4	1 (0.4%)	0	1 (0,5%)
No data	69 (28.6%)	13 (54.2%)	56 (25,8%)
<b>Localization of metastases</b>	N=241	N=24	N=217
Liver	49 (20.3%)	11 (45.8%)	38 (17.5%)
Lung	63 (26.1%)	7 (29.2%)	56 (25.8%)
Bones	88 (36.5%)	15 (62.5%)	73 (33.6%)
CNS/cerebrum	30 (12.4%)	1 (4.2%)	29 (13.4%)
Soft tissues	51 (21.2%)	3 (12.5%)	48 (22.1%)
Other	132 (54.8%)	12 (50.0%)	120 (55.3%)

Note: patients could have one or more foci of metastasis

The bone metastases among patients within the study were detected in 36.5% of cases. Subsequently, the metastatic foci were distributed by the rate of secondary affection of various organs and tissues the following way: in lungs - 26.1%, in soft tissues - 21.2%, in liver - 20.3% of patients.

The demographic parameters and distribution of metastatic foci in patients with primary metastatic process had some peculiarities. The mean age in metastatic breast cancer diagnostics was  $56.3 \pm 13.5$  years, while the age ranged from 36 to 88 years old. In more than half of studied cases the data on status of patients with primary metastatic process were not provided. In remaining 11 cases (45.8%), the general status was assessed as "satisfactory" or "near satisfactory". In this category of patients, the visceral metastases with liver and/or lung affection were detected more frequently (62.5%), the bone metastases were found with the same frequency. During initial diagnostics the cerebrum metastasis was detected only in 1 patient (4.2%).

In detection of remote metastases the mean age of patients with stages I-III of disease composed  $53.5 \pm 10.9$  years. Within the course of metastatic disease development, the assessment of general status of patients according to ECOG scale was absent in the medical records in 56 cases (25.8%). The analysis of data of remaining 161

patients evidenced that the disease progression with development of remote metastatic foci had affected the general status of patients toward aggravation only in 7 patients (3.3%). The majority of patients, 154 (70.8%), had a satisfactory status.

The metastatic process was diagnosed within detection of deposits in liver – 17.5% (38) of patients, in lungs – 25.8% (56), in bones – 33.6% (73), in cerebrum – 13.4% (29), in soft tissues – 22.1% (48), accordingly. In 55.3% of patients (120) the metastases were detected in other tissues and organs.

Based on the immunohistochemical tests (IHC) findings, the positive oestrogen receptor (ER+) status was detected in 46.5% of patients (112), and progesterone receptor (PR) status was revealed in 38.2% of patients (92). The study of proliferative activity status by data of research centres was not obligatory. The index Ki6 was determined only in 60 patients (24.9%); in 75.1% of patients the status of index Ki6 was unknown. In 33 cases (55%) the index Ki67 has been rated as high (>15%) (Table 3).

As is evident from Table 3, luminal B-type tumours were found in almost half of the cases of metastatic breast cancer with Her-2/neu hyperexpression (49.8%). The frequency of Her-positive non-luminal breast cancer was 39.0%.

**Table 3** - Results of immunohistochemical studies in patients with metastatic HER2-positive breast cancer

Results of immunohistochemical studies	
The oestrogen receptors (ER) status	N=241
Positive	112 (46.5%)
Negative	102 (42.3%)
No data	27 (11.2%)
The progesterone receptor (PR) status	N=241
Positive	92 (38.2%)
Negative	122 (50.6%)
No data	27 (11.2%)
Hormonal receptor status	N=241
ER + / PR +	84 (34.9%)
ER + / PR -	28 (11.6%)
ER - / PR +	8 (3.3%)
ER - / PR -	94 (39.0%)
No data	27 (11.2%)
Proliferative activity, index Ki67	N=241
≤15% (low)	17 (7.1%)
16 - 30% (medium)	10 (4.1%)
>30% (high)	33 (13.7%)
No data	181 (75.1%)

**Discussion.** The article presents the data on demographic, clinical, morphological and molecular-biological parameters of metastatic breast cancer with confirmed high expression of Her-2 receptor. These data were obtained within the retrospective population study aimed at understanding of overall picture in diagnostics and treatment of patients based on examples of 7 cancer centres of the Russian Federation, Ukraine and the Republic of Kazakhstan. Eventually, the study had some limitations due to its retrospective nature and inability to request some missing data from research staff, especially when it was related to the primary staging and assessment of general status of patients. The morphological and IHC examinations in full range according to modern diagnostic protocols were available not in all cancer centres.

However, the findings obtained within the study permit to make the following **conclusions:**

The patients with metastatic breast cancer in the majority of cases (56.5%) remain the active satisfactory status, which corresponds to 0-1 score on ECOG scale. The share of patients with grave and extremely critical condition composes only 2.9%.

In patients with confirmed hyper-expression of Her-2/neu receptors, the bone metastases were detected in 1/3 of cases - 36.5%, the visceral metastases with liver and lung affection were revealed with approximately same frequency - 20.3% and 26.1%, respectively.

The luminal B type tumour among patients with metastatic Her-positive breast cancer is more common than the Her-positive non-luminal type of cancer (49.8% vs. 39.0%).

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