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PROGNOSTIC SIGNIFICANCE OF TR53 GENE MUTATION IN PATIENTS WITH METASTATIC HER2-POSITIVE BREAST CANCER

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Abstract. The p53 protein participates in many cellular processes, including DNA repair, cell cycle control, autophagy, apoptosis, and senescence. Mutation in the TP53 gene is a factor of unfavorable prognosis. Loss of tumor suppressor function causes resistance to drug therapy, metastasis, and disease progression. However, breast cancer is a heterogeneous disease with unique and, at first glance, paradoxical biological mechanisms for each subtype. Several studies have shown that a mutation in the TP53 gene predicts the effectiveness of trastuzumab therapy and chemotherapy. The assessment of TR53 status may influence the treatment choice.

The aim of our study was to investigate the prognostic significance of the TP53 gene mutation in patients with metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer.

Materials and methods. Seventy-eight patients of the Sumy Regional Clinical Oncology Center were involved in the study. The criteria for inclusion in the study were a history of trastuzumab monotherapy or combined chemotherapy and trastuzumab, age 18 years and older. The exclusion criteria were the presence of another malignant tumor, infectious, autoimmune, or inflammatory diseases before the start of trastuzumab therapy and the absence of trastuzumab in the used therapeutic scheme. Immunohistochemistry with antibodies against the p53 protein was used to determine the status of the TR53 gene. Pearson test, Kaplan-Meier method, Log-rank test, and Cox regression were used for statistical analysis.

The results. 64.1% of patients with metastatic HER2-positive breast cancer have a TP53 gene mutation. Patients with a mutant type of TP53 more often received a combination of trastuzumab and chemotherapy ($\chi2$=6.9348, p=0.008). In patients with wild-type TP53, hormone-positive HER2-positive breast cancer was predominant ($\chi2$=5.0547, p=0.005). At the end of the follow-up period, death was recorded in 69/78 (88.5%) patients, including 26/28 (92.9%) patients with wild-type TP53 and 43/50 (86.0%) patients with mutant TP53. In patients with wild-type TP53, median survival was 13.6 months and 21.0 months for trastuzumab monotherapy and the combination of trastuzumab with chemotherapy, respectively (Log-rank p=0.9500). In patients with mutant TP53, median survival was 22.4 months and 36.6 months for trastuzumab monotherapy and the combination of trastuzumab with chemotherapy, respectively (Log-rank p=0.0063). In patients with wild-type TP53, median survival was 21.6 months and 13.0 months for hormone-positive and hormone-negative, respectively (Log-rank p=0.0095). In patients with mutant TP53, median survival was 34.2 months and 31.2 months for hormone-positive and hormone-negative, respectively (Log-rank p=0.3509). Hormonal status, the applied treatment regimen, and the status of the TR53 gene were determined as independent predictors of overall survival.

Conclusions. Among patients with wild-type TP53, hormone-positive breast cancer predominates, but patients with mutant TP53, especially those with negative hormone status, have better survival. Patients with mutant TP53 who receive a combination of trastuzumab and chemotherapy have better overall survival than those who receive trastuzumab monotherapy. Hormone-positive breast cancer, combination of trastuzumab and chemotherapy, and mutation in the TP53 gene are independent predictors of better overall survival in patients with metastatic HER2-positive breast cancer.

Keywords: TP53, trastuzumab, taxanes, survival, HER2, breast cancer, estrogen, mutant type.

Introduction. TP53 is a suppressor gene and a significant player responsible for carcinogenesis. The p53 protein participates in many cellular processes, including DNA repair, cell cycle control, autophagy, apoptosis, and senescence. Polymorphism of the TP53 gene ensures adaptation to various environmental conditions, such as cold, hunger, and hypoxia, and affects fertility and longevity [1].

Mutations in the TP53 gene are registered in almost all types of cancer [2] and in about 50 % of patients with breast cancer [3]. In patients with breast cancer, mutations in the TP53 gene can be caused by various factors. The most important among them are defects in DNA repair and damage, which is a consequence of exposure to tobacco smoking, excessive ultraviolet radiation, ionizing radiation, and chemical carcinogens [4]. Mutations in the BRCA1 and BRCA2 genes responsible for repairing damaged DNA also increase the risk of TP53 mutation [5]. Some genetic syndromes, such as Li-Fraumeni, cause hereditary mutations of TP53, which in turn increases the risk of breast cancer [6]. Infection with the human papillomavirus can lead to inactivation or degradation of the p53 protein and loss of its function [7]. The instability of the TP53 gene can be a consequence of epigenetic modifications and oxidative stress [8]. Even the hormone estrogen is evaluated as a potentially dangerous factor because of its proliferative effect on epithelial cells of the mammary gland. As a result, the probability of spontaneous mutation increases [9].

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Research rationale. Numerous studies have demonstrated that a mutation in the TP53 gene is a factor of unfavorable prognosis, mainly when it affects the regions encoded by DNA-binding domains. Loss of tumor suppressor function causes resistance to drug therapy, metastasis, and disease progression [10, 11, 12]. However, breast cancer is a heterogeneous disease with unique and, at first glance, paradoxical biological mechanisms for each subtype. Several studies have shown that a mutation in the TP53 gene predicts the effectiveness of trastuzumab therapy and chemotherapy [13, 14]. Based on these findings, the assessment of TR53 status may influence the treatment choice. At the moment, determining a mutation in the TP53 gene is not routine practice. However, more and more reports about the prognostic value of this mutation appear in scientific sources. Next-generation sequencing is the most modern and highly effective method for detecting mutations in the TP53 gene. It allows the examination of entire introns and exons and determines the spectrum of mutations, their localization, and the associated loss of function or gain of function of the p53 protein [15]. The problematic interpretation of the obtained results and the high cost of molecular genetic profiling force the use of more available immunohistochemistry (IHC). Armbruster et al. [16] compared the efficiency of next-generation sequencing and IHC to assess TP53 mutational status. The authors concluded that it is possible to determine the mutation using the p53 protein. This surrogate IHC marker has an accuracy of 96.2 % and a specificity of 100 %.

The aim of our study was to investigate the prognostic significance of the TP53 gene mutation in patients with metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer.

Materials and methods. ***Study design.*** Seventy-eight patients of the Sumy Regional Clinical Oncology Center were involved in the study. All patients were diagnosed with metastatic HER2-positive breast cancer. The criteria for inclusion in the study were a history of trastuzumab monotherapy or combined chemotherapy and trastuzumab, age 18 years and older. The exclusion criteria were the presence of another malignant tumor, infectious, autoimmune, or inflammatory diseases before the start of trastuzumab therapy, and the absence of trastuzumab in the therapeutic scheme. The study was approved by the Local Ethics Committee of the Sumy Regional Clinical Oncology Center (protocol 2/5 dated January 15, 2024) and was conducted following the Helsinki Declaration on Human Rights.

Treatment, assessment of response to treatment, and follow-up of patients. The treatment regimens, the doses of trastuzumab, and the assessment of response to treatment using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) were described in detail in our previous study [17].

Immunohistochemistry (IHC). For IHC of HER2-positive breast cancer tissues, serial histological sections with a thickness of 4 μm were applied to SuperFrost adhesive glass (Thermo Scientific, Waltham, MA, USA). Deparaffinized sections were subjected to antigen unmasking by heating in 0.1 M citrate buffer (pH 6.0) at 95–98 ◦C. The "In Vitro" detection system (Master-Diagnostica, Spain) was used to visualize the IHC results. To visualize the p53 protein, we used antibodies against p53 (Master-Diagnostica, Spain). A pathologist performed IHC staining and evaluated the results. In each tumor tissue sample, six fields of view with a diameter of 1 mm were analyzed. The evaluation was based on the determination of the immunohistochemical score (interval from 0 to 12) by multiplying the staining intensity (0–3) by the percentage of positively stained nuclei (0–4). The percentage of positively stained nuclei was transformed into scores: 0 – absence, 1 – <25 %, 2 – 25 %-50 %, 3 – 50 %-75 %, and 4 – 75 %–100 %. Complete absence (score 0) or overexpression of p53 (4 or more scores) indicated the presence of a mutation in the TP53 gene.

Statistical analysis. The relationship between the mutation in the TP53 gene and age, menopausal status, hormonal status, and the applied treatment regimen was evaluated using the Pearson test and Student's t-test. Recurrence-free and overall survival were visualized using Kaplan-Meier curves. The significance of the difference in survival between the mutant and wild-type TP53 groups was determined by the Log-rank test. Cox regression analysis was used to assess the mutual influence on overall survival of several clinicopathological characteristics. A p-value of less than 0.05 is considered an acceptable indicator of reliability. Statistical analysis was performed using Stata V.18.0 (StataCorp, Texas, USA; https://www.stata.com; 2024).

The results. ***Immunohistochemistry.*** Immunohistochemical visualization of p53 protein showed its localization in the nuclei of breast cancer tumor cells. Also, single p53-positive nuclei belonged to normal epithelial cells and tumor microenvironment ("wild type" reaction). We included cases of weak cytoplasmic expression of p53 in both tumor cells and cells of adjacent healthy tissues to the "wild type" reaction (Fig. 1A). We established the "mutant type" of immunohistochemical reaction in the presence of excessive expression of p53 (4 or more scores) in the tumor cells (Fig. 1B). In the case of negative expression (0 scores) of tumor cells, we also confirmed the presence of a mutation in the TP53 gene. In total, wild type T353 was found in 28 patients, and mutant type TP53 – in 50 patients.

Characteristics of patients. Among 78 patients whose tumor tissue was evaluated for TP53 gene mutation, 24 patients had premenopausal status, and 54 had postmenopausal status. The average age was 55 years (range 27 to 77). Hormone-receptor-positive breast cancer was registered in 46 (59.0 %), hormone-receptor negative - in 32 (41.0 %) patients. 27 (34.6 %) patients with metastatic HER2-positive breast cancer received trastuzumab monotherapy. When analyzing the relationship between clinicopathological characteristics and the mutational status of the TP53 gene, it was established that patients with a mutant type of TP53 more often received a combination of trastuzumab and chemotherapy ($\chi 2$=6.9348, p=0.008). In addition, patients with wild-type TP53 have a predominance of hormone-positive HER2-positive breast cancer ($\chi 2$=5.0547, p=0.005, Table 1).

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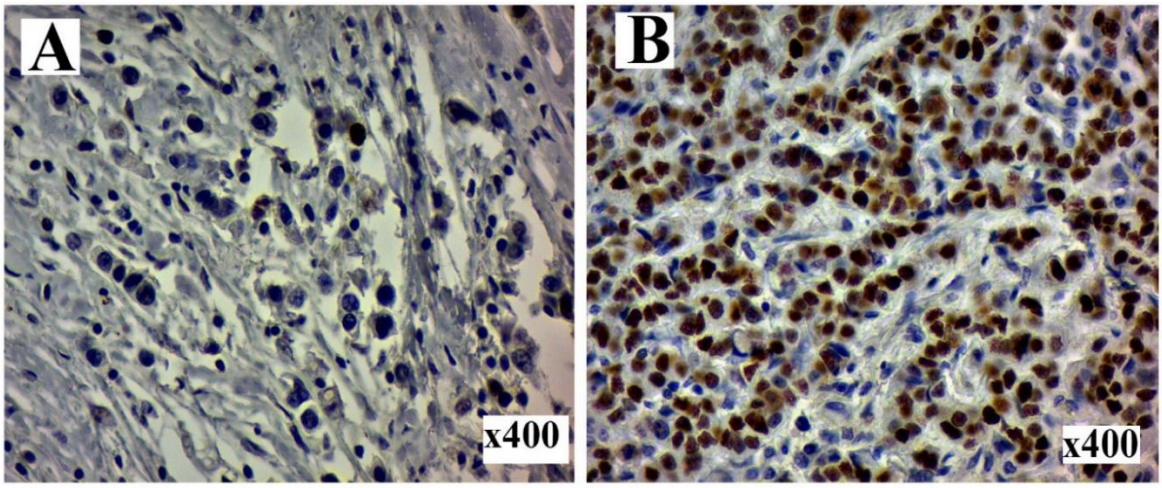

Figure 1. IHC staining with antibodies against p53 protein in breast cancer tissue, where A is the "wild type" of reaction, and B is the "mutant type" of the immunohistochemical reaction. Staining cell nuclei with Mayer's hematoxylin. Magnification is indicated in the lower right corner of the image.

Table 1

The relationship between clinicopathological characteristics and types of the TR53 gene in HER2-positive metastatic breast cancer patients

Clinicopathological characteristics	Total (%), n=78	Wild type TP53 (%), n=28	Mutant type TP53 (%), n=50	χ2 (p)
Age (years), n (%) Median Range <55 ≥55	 55 27-77 33 (42,3) 45 (57,7)	 53 27-77 14 (50,0) 14 (50,0)	 56 35-75 19 (38,0) 31 (62,0)	 0,3097*
Menopausal status, n (%) Premenopausal Postmenopausal	 24 (30,8) 54 (69,2)	 11 (39,3) 17 (60,7)	 13 (26,0) 37 (74,0)	 1,4873 (0,223)
Hormonal status, n (%) Positive Negative	 46 (59,0) 32 (41,0)	 22 (78,6) 6 (21,4)	 24 (48,0) 26 (52,0)	 5,0547 (0,005)
Trastuzumab-containing regimen: Trastuzumab monotherapy Trastuzumab+chemotherapy	 27 (34,6) 51 (65,4)	 15 (53,6) 13 (46,4)	 12 (24,0) 38 (76,0)	 6,9348 (0,008)
Response: Complete response Partial response Stable disease Disease progression	 3 (3,8) 45 (57,7) 22 (28,2) 8 (10,3)	 1 (7,2) 16 (57,1) 7 (25,0) 3 (10,7)	 1 (2,0) 29 (58,0) 15 (30,0) 5 (10,0)	 1,4046 (0,704)

*Student's t-test was used for analysis

Survival of patients. At the end of the follow-up period, death was registered in 69/78 (88.5 %) patients, including 26/28 (92.9 %) patients with wild-type TP53 and 43/50 (86.0 %) patients with mutant TP53.

We observed significant differences in the overall survival of patients depending on the treatment regimen. In patients with wild-type TP53, median survival was 13.6 months and 21.0 months for trastuzumab monotherapy and the combination of trastuzumab with chemotherapy, respectively (Log-rank p=0.9500, Fig. 2).

In patients with mutant TP53, median survival was 22.4 months and 36.6 months for trastuzumab monotherapy and the combination of trastuzumab with chemotherapy, respectively (Log-rank p=0.0063, Fig. 3).

In addition to the treatment regimen, the overall survival of patients with metastatic HER2-positive breast cancer was significantly dependent on hormonal status and type of TP53 mutation. In patients with wild-type TP53, median survival was 21.6 months and 13.0 months for hormone-positive and hormone-negative, respectively (Log-rank p=0.0095, Fig. 4).

In patients with mutant TP53, median survival was 34.2 months and 31.2 months for hormone-positive and hormone-negative, respectively (Log-rank p=0.3509, Fig. 5).

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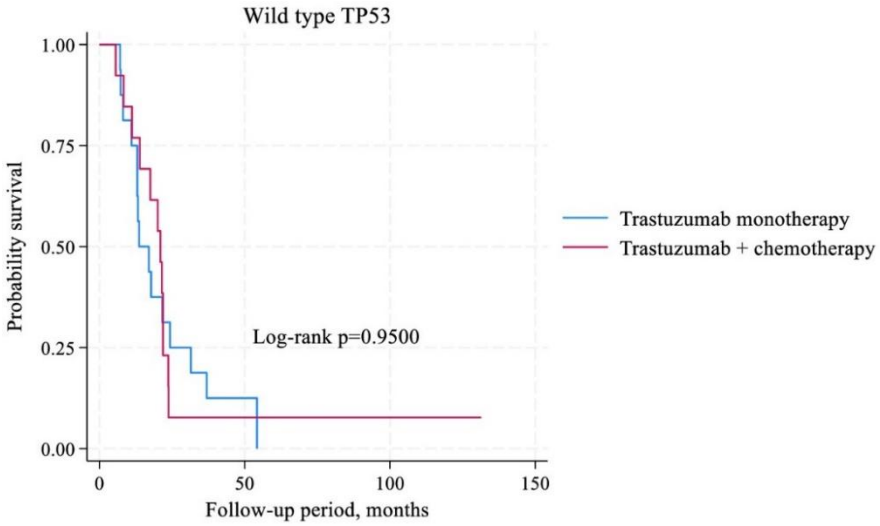

Figure 2. Kaplan-Meier curves show the overall survival of patients with metastatic HER2-positive breast cancer and wild-type TP53 depending on the treatment regimen.

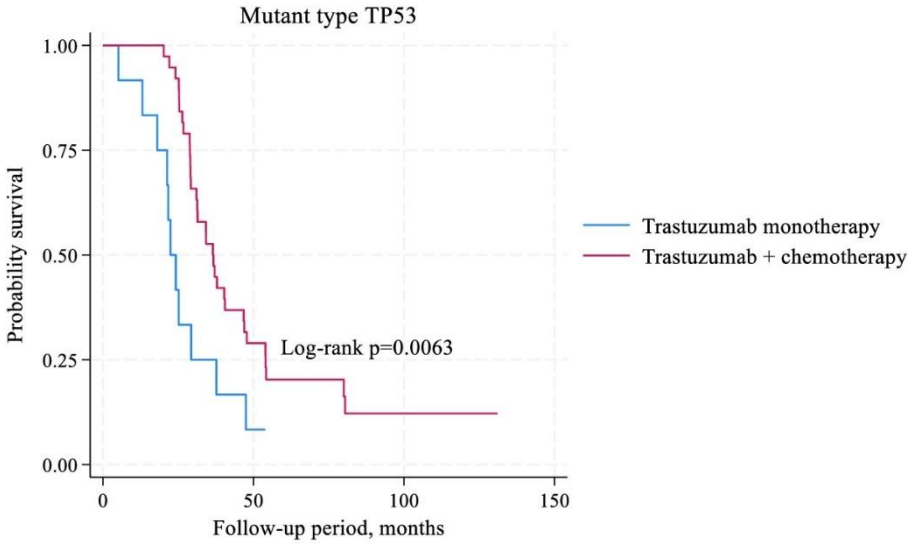

Figure 3. Kaplan-Meier curves show the overall survival of patients with metastatic HER2-positive breast cancer and mutant TP53 type depending on the treatment regimen.

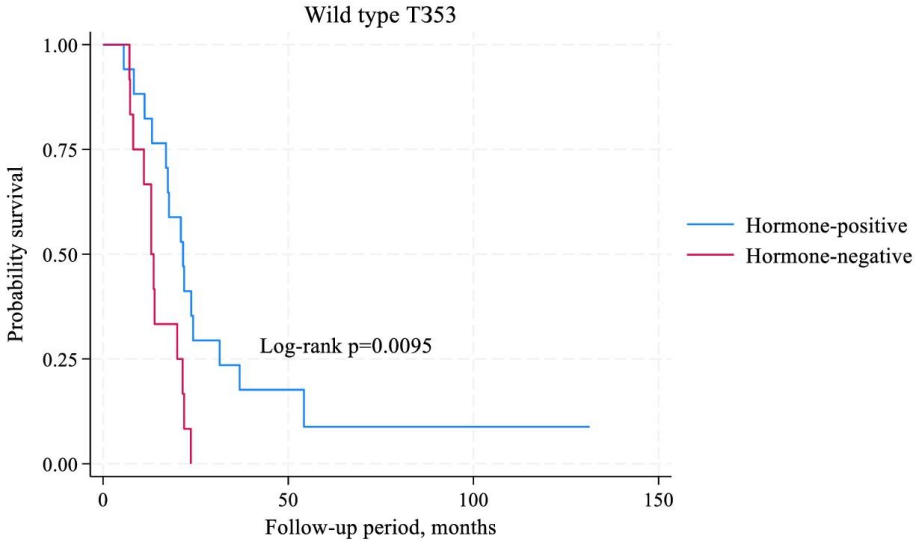

Figure 4. Kaplan-Meier curves show the overall survival of patients with metastatic HER2-positive breast cancer and wild-type TP53 depending on hormonal status.

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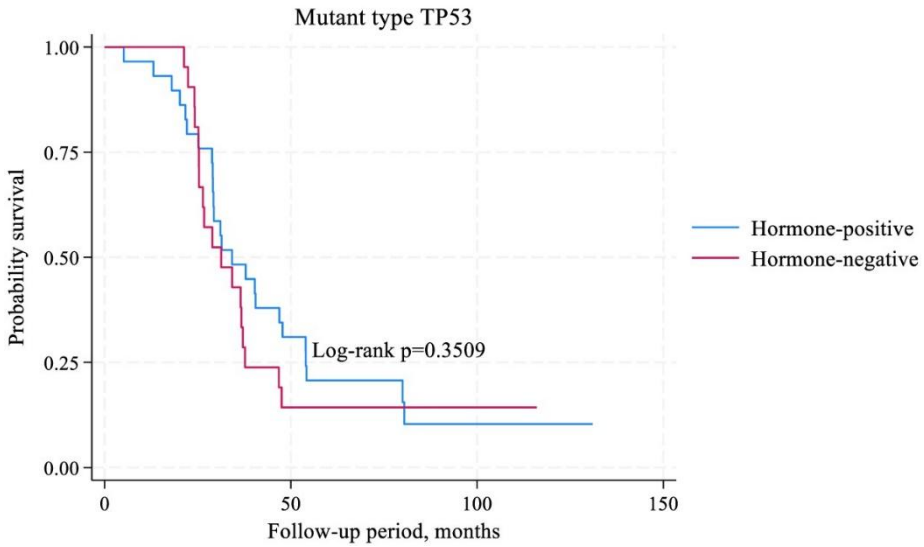

Figure 5. Kaplan-Meier curves show the overall survival of patients with metastatic HER2-positive breast cancer and TP53 mutant type depending on hormonal status.

Multivariate Cox regression analysis was used to assess the prognostic influence of menopausal and hormonal statuses, age, the applied treatment regimen, and the status of the TP53 gene. Hormonal status, the applied treatment regimen, and the status of the TP53 gene were determined as independent predictors of overall survival. Patients with metastatic HER2-positive breast cancer who have hormone-positive tumors, a mutant type of the TP53 gene, and those who received the combination of trastuzumab with chemotherapy have better overall survival (Table 2).

Table 2

Cox proportional hazards model for estimating the prognostic impact of clinicopathological characteristics on overall survival in patients with metastatic HER2-positive breast cancer.

Clinicopathological characteristics	HR	95% CI	p-value
Age (<55 versus ≥55)	0,60	0,28-1,27	0,186
Menopausal status (premenopausal versus postmenopausal)	1,32	0,58-2,99	0,504
Hormonal status (positive versus negative)	1,96	0,15-3,33	**0,013**
Trastuzumab-containing regimen (Trastuzumab monotherapy versus Trastuzumab+chemotherapy)	0,73	0,41-1,30	**0,005**
TP53 gene (wild type versus mutant type)	0,34	0,19-0,63	**0,001**

Discussion. In the current study, we found that most patients with metastatic HER2-positive breast cancer have a TP53 gene mutation. The relationship between the hormonal status of the tumor, the applied treatment regimen, and the type of TP53 was revealed. Patients with wild-type TP53 who received trastuzumab monotherapy and those who received the combination of trastuzumab and chemotherapy had no significant difference in overall survival. However, in cases of TP53 gene mutation, patients receiving combined therapy had significantly better survival. A study of patient survival depending on the hormonal status of the tumor showed the opposite results. In patients with wild-type TP53, hormone-positive patients had significantly better overall survival, whereas, in those with mutant TP53, no difference in survival was observed between hormone-positive and hormone-negative patients.

Protein p53 is primarily involved in biological processes leading to carcinogenesis in the mammary gland. Its main effects are 1) stopping cell division in response to DNA damage [18], 2) stimulation of DNA repair by upregulating genes responsible for nucleotide repair [19], 3) stimulation of cell apoptosis if DNA damage is significant and repair is impossible [20], 4) regulation of genes involved in oxidative phosphorylation, glycolysis, and antioxidant protection [21], 5) induction of cellular senescence [22], 6) modulation of the antitumor immune response [23] and inhibition of angiogenesis [24]. A mutation of the TP53 gene leads to a violation of the above functions, so the consequences for the organism should be catastrophic. However, drug therapy modifies natural biological processes and causes paradoxical results.

Numerous studies have demonstrated the negative impact of TP53 mutation on the survival of breast cancer patients [25, 26]. However, depending on the molecular subtype, the mutation frequency in the TP53 gene and the clinical consequences differ significantly. In general, about 50% of breast cancer cases are associated with a TP53 gene mutation. In patients with the HER2-positive subtype, the prevalence of the mutation largely depends on the pathological stage and reaches 60–73% in patients with metastatic disease [27].

The current study, TP53 gene mutation was confirmed in 64.1% of tumor tissue samples. It was found that patients with a TP53 mutation who received a combination of trastuzumab with chemotherapy had better survival. The standard regimen for the treatment of metastatic HER2-positive breast cancer is a combination of monoclonal antibodies against HER2 (trastuzumab, pertuzumab) and

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taxanes (paclitaxel or docetaxel) [28]. Taxanes are the anti-microtubule agents. These therapeutic drugs stabilize existing microtubules, enhance the activity of tubulin dimers, and inhibit their degradation. Together, these factors lead to increased stability of microtubules, distortion of mitotic spindles, and cell cycle arrest at the G2/M phase. Once abnormal and damaged cells recognize their inability to resume mitosis, they undergo programmed cell death [29].

Therefore, the sensitivity to taxanes largely depends on the work of microtubules and the formation of the division spindle. In patients with the wild-type TP53 gene, the p53 protein initiates cell cycle arrest, making the cell insensitive to taxanes. A mutation in the TP53 gene results in the expression of p53 protein with lost functions. Mitosis in an atypical cell continues, so taxanes, affecting microtubules, lead to mitotic catastrophe and massive induction of apoptosis. Clinical symptoms of this effect are reduction of the primary tumor and metastases and improvement of the overall survival of patients.

Anthracyclines are widely used to treat locally advanced HER2-positive breast cancer. Interestingly, in patients with wild-type TP53, anthracyclines cause cell growth arrest and senescence. Unlike taxanes, which are characterized by the development of apoptosis, the clinical effect of this group of drugs develops more slowly [30].

Our study demonstrated that wild-type TP53 is most prevalent in hormone-positive tumors. In HER2-positive tumors the hormone estrogen can inhibit the p53-mediated apoptotic response. In tumors with wild-type TP53, this leads to cell senescence and resistance to further treatment. In hormone-negative tumors with mutant TR53, on the contrary, the accumulation of genetic alterations leads to mitotic catastrophe and better clinical results [31].

Bakhtiar et al. [32] demonstrated that hormone-positive and hormone-negative patients with a mutation in the TP53 gene who receive neoadjuvant chemotherapy for the treatment of early breast cancer have a 56 % higher rate of pathological complete responses. In the current study, only patients with metastatic HER2-positive breast cancer participated. Patients with a TP53 mutation had a more prolonged overall survival, regardless of hormone status. Thus, the overall survival of hormone-positive patients was 21.6 months for wild-type versus 34.2 months for mutant TP53. For hormone-negative, the difference in survival was even more significant, with 13.0 months for wild-type and 31.2 months for mutant TP53.

This study has significant limitations. IHC was used to determine the status of the TP53 gene, which does not allow assessing the subtype of the mutation and its localization. We did not consider the hormonal therapy and the duration of trastuzumab therapy.

Conclusions. 64.1 % of patients with metastatic HER2-positive breast cancer have a TP53 gene mutation. Among patients with wild-type TP53, hormone-positive breast cancer predominates, but patients with mutant TP53, especially those with negative hormone status, have better survival. Patients with mutant TP53 who receive a combination of trastuzumab with chemotherapy have better overall survival than those who receive trastuzumab monotherapy. Hormone-positive breast cancer, combination of trastuzumab with chemotherapy, and TP53 gene mutation are independent predictors of better overall survival in patients with metastatic HER2-positive breast cancer.

Conflict of interest. Authors declare their absence conflict interests.

Prospects for further research. We plan to investigate the mutual influence of TP53 gene mutation and loss of signal transducer and activator of transcription 6 (STAT6) on the survival of patients with HER2-positive breast cancer. This study will be conducted considered the hormonal status of the patients. In addition, the mechanisms of resistance to trastuzumab and hormonal therapy will be studied.

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ПРОГНОСТИЧНЕ ЗНАЧЕННЯ МУТАЦІЇ ГЕНА TP53 У ПАЦІЄНТІВ З МЕТАСТАТИЧНИМ HER2-ПОЗИТИВНИМ РАКОМ МОЛОЧНОЇ ЗАЛОЗИ

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Резюме. Мутація у гені TP53 вважається фактором несприятливого прогнозу. Втрата функції супресора пухлини обумовлює стійкість до медикаментозної терапії та прогресію захворювання. Однак рак молочної залози є гетерогенним захворюванням з унікальними і на перший погляд парадоксальними біологічними механізмами, характерними для кожного окремого підтипу.

Метою нашої роботи було дослідження прогностичного значення мутації у гені TP53 у пацієнтів з HER2-позитивним раком молочної залози.

Матеріали та методи. Для проведення дослідження було залучено 78 пацієнтів Сумського обласного клінічного онкологічного центру. Для визначення статусу гена TP53 виконували імуногістохімічне дослідження з антитілами проти білка p53. Для статистичного аналізу використовували критерій Пірсона, метод Каплана-Майєра, логарифмічний тест та регресійний аналіз Кокса.

Результати. Мутацію гену TP53 діагностовано у 64,1% пацієнтів з метастатичним HER2-позитивним раком молочної залози. Пацієнтки з мутантним типом TP53 частіше отримували комбінацію трастузумаба та хіміотерапії ($\chi2$=6,9348, p=0,008). У пацієнток з диким типом TP53 переважав гормон-позитивний HER2-позитивний рак молочної залози ($\chi2$=5,0547, p=0,005). У пацієнтів з диким типом TP53 медіани виживаності становили 13,6 місяців та 21,0 місяців для монотерапії трастузумабом та комбінації трастузумабу з хіміотерапією, відповідно (Log-rank p=0,9500) та 21,6 місяців та 13,0 місяців для гормон-позитивних та гормон-негативних пухлин, відповідно (Log-rank p=0,0095). У пацієнтів з мутантним типом TP53 медіани виживаності становили 22,4 місяців та 36,6 місяців для монотерапії трастузумабом та комбінації трастузумабу з хіміотерапією, відповідно (Log-rank p=0,0063); 34,2 місяців та 31,2 місяців для гормон-позитивних та гормон-негативних пухлин відповідно (Log-rank p=0,3509).

Висновки. Кращу виживаність мають пацієнти з мутантним TP53, гормон-негативними пухлинами та ті, що отримували комбінацію трастузумаба з хіміотерапією.

Ключові слова: TP53, трастузумаб, таксани, виживаність, HER2, рак молочної залози, естроген, мутантний тип.

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