Bondar O. V. Ki67 index importance in patients with breast cancer. Journal of Education, Health and Sport. 2024;75:60763. eISSN 2391-8306. https://dx.doi.org/10.12775/JEHS.2024.75.60763
https://apcz.umk.pl/JEHS/article/view/60763
https://zenodo.org/records//15351890

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences);
Health Sciences (Field of medical and health sciences). Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 21.10.2024. Revised: 17.11.2024. Accepted: 21.11.2024. Published: 23.12.2024.

UDC 616.379.008.64:616.137.86

Ki67 INDEX IMPORTANCE IN PATIENTS WITH BREAST CANCER

O. V. Bondar

Odesa National Medical University, Odesa, Ukraine

Abstract

Breast cancer oncosurgery in its therapeutic and diagnostic strategies largely bases upon a considerable spectrum of laboratory findings. In the following article is presented a deep analysis of the series of studies devoted to the importance of oncological markers in practice, the necessity in proliferative activity index of the tumor to be determined, the diagnostic value of Ki-67 marker expression level for solving such tasks as evaluation of malignancy, selection of the best treatment strategy, adjuvant or neoadjuvant therapy, as well as the medical intervention results evaluation. On the grounds of the results, conclusions regarding the importance of determining the Ki-67 marker expression level as a comprehensive part of breast cancer diagnostics, the choice of proper treatment strategy and estimation of the one were made.

Key words: tumor marker Ki-67; neoadjuvant therapy; proliferation marker; immunohistochemical study.

Breast cancer (BC), according to WHO, ranks first in whole-world structure of oncopathology. According to official data from National Cancer Institute (Kyiv, Ukraine), the standardized international BC incidence rate in Ukraine in 2022-2023 years was 67.5 per 100,000 population.

Approaches and protocols for BC diagnosing, treating and therapy final results evaluating for different age groups and for different clinical situations have changed significantly in the world. First of all, this is due to the identification of a spectrum of different morphological, histological, biochemical and genetic features of tumours. That's why the tactics for BC diagnosing and treating are entirely based on the most accurate tumour morphological verification with the determination of such key parameters as levels of expression of markers of proliferation, steroid hormone receptors and growth factors. The importance of the issue of certain tumours parameters both individual and complex evaluation is dictated by known nonlinear correlation between the biological properties of neoplasm.

A search of criteria that allow to verify objectively the degree of histological and biological malignancy is still underway. The leading factor in both the mechanism of cellular malignant transformation and already arisen tumour biological behavior is their proliferative activity. This is one of the most important characteristics of tumour phenotype which largely determines the neoplasm growth rate, the risk of metastasis, the potential response to therapeutic measures and oncological disease outcome. Many factors that determine the oncological diseases course and outcome mediate their pathogenetic influence on tumour through changes in proliferative activity [1].

Hence, the human tumour cells proliferative activity correlates with the degree of their histological and biological malignancy. The immunohistochemical determination of the proliferation index in Ki-67 (MIB-1) expression investigation is a necessary routine study in oncological diseases.

The Ki-67 antigen is a specific and optimal for widespread use in pathological practice marker of proliferation. It is a nuclear antigen that was first described by Gerdes et al. in 1983. It is the main part of the nuclear matrix which is associated with chromosomes of the mitosis phase during interphase. Ki-67 is a dimeric molecule that has a close relationship with chromosome 10; it consists of two polypeptide chains with molecular masses of 345 and 395 kDa. The specific role of this protein in the process of cell division has not yet been clearly established.

The aim of the work is to evaluate the role of proliferative activity biological marker as part of patients with uterine cancer and breast cancer complex treatment, to compare the results of cell proliferation before and after the specialized treatment.

1. Ki-67 biological role and properties

It is necessary to evaluate the tumour cells proliferative activity not only for tumours biological characteristics determination but also for a selective approach to therapy choice. The index of proliferative activity in different tumours has different values, being an independent prognostic sign that determines the disease both clinical course and prognosis.

Ki-67 protein is an objective marker of cellular proliferative activity. It expresses starting from the late G_1 phase of the cell cycle, then continues throughout the S, G_2 and M phases and thus allows to detect the entire proliferative pathway of the tumour. It was believed that since estrogens have a proliferative effect on hormone-dependent cells, including tumour cells, a high level of estrogen receptors should directly correlate with proliferative activity.

Various methods are used to assess tumour proliferative activity including counting mitotic figures in the field of view, labelled nucleotides using and assessing the signal from a drug incorporated into the DNA structure together with flow cytometry of the fraction of cells in the S phase of cell cycle [2]. One could stress that Ki-67-intranuclear antigen immunohistochemical determination during all cellular phases except of G_0 phase is the most practical tool [3].

There is no definitive opinion concerning the Ki-67 prognostic role for BC early till now despite a significant number of clinical studies aimed at establishing a relationship between therapeutic strategy and Ki-67 levels [4]. The meta-analysis conducted by Urruticoechea et al. included 18 case series studies with more than 200 patients. A statistically significant correlation was found between the BC prognosis and Ki-67 expression in 17 of the 18 studies although there was no single reference level of Ki-67. Therefore, there are no precise criteria for distinguishing between antigen both high and low levels [5]. The highest risks of low Ki-67 levels in these studies were data from 1 till 28.7% which slightly reduces this marker clinical value [5, 6].

The American Society of Clinical Oncology Tumour Marker Guidelines Committee found that there is still insufficient evidence to support Ki-67 prognostic value in clinical practice to recommend its routine use in patients with newly diagnosed BC [6].

If specific tumour groups are identified where this marker can be used, or Ki-67 is included as one of the biomarker panels, its clinical value for adjuvant BC therapy might be enhanced. Cuzick J. recommends an immunohistochemical panel using based on four markers detection including both estrogen and progesterone receptors, HER2/neu and Ki-67 [7].

Other research groups present data on the importance of Ki-67 determining as a step in the prognostic algorithm for recurrence detecting in patients with early ИС who are receiving tamoxifen and letrozole as adjuvant therapy.

Other scientific works indicate studies on Ki-67 predictive role in case chemotherapy necessity in patients with estrogen-positive tumours as well as a high Ki-67 index as a result of adjuvant chemotherapy.

In the randomized clinical trial PACS01, docetaxel was added to epirubicin and 5-fluorouracil as adjuvant chemotherapy in patients with estrogen-positive tumours and high Ki-67 index [8]. These results were confirmed in the Cancer International Research Group 001 trial [9]. However, the results are not consistent with the International Breast Cancer Study Group Trials

VIII and IX. These studies showed high Ki-67 expression predictive role in the group with receptor-positive BC without evidence of disease in the lymph nodes related to adjuvant therapy with methotrexate, cyclophosphamide and 5-fluorouracil in addition to endocrine therapy [10]. Therefore, it is very important to conduct studies aimed to patients with high Ki-67 indexes identification who will be able to get the maximum benefit from different adjuvant chemotherapy regimens.

2. Ki-67 predictive role in neoadjuvant therapy

The purpose of neoadjuvant chemotherapy is to improve the results of surgical treatment by reducing the volume of surgical intervention and tumour partial devitalization. Additionally, preoperative chemotherapy allows to evaluate the therapeutic pathomorphosis, thus, to determine the range of drugs for adjuvant therapy. At this stage, it is also important to search clinical, biochemical and molecular prognostic factors correlated with chemotherapy efficacy [11].

The predictive role of Ki-67 in hormonal therapy initiation is not as fully described as for chemotherapy, but some authors point the importance of Ki-67 determination [11]. Ki-67 index evaluation in hormonal therapy was performed within the framework of two studies: IMRACT, which compared the neoadjuvant therapy with anastrozole, tamoxifen and anastrozole and tamoxifen combination efficacy [12] as well as P024 study, which compared the letrozole administration with tamoxifen administration in neoadjuvant regimen [13]. While Ki-67 index comparing in these studies, a correlation was shown between the Ki-67 values suppression during treatment and the frequency of relapse after neoadjuvant hormonal therapy [12, 13]. The P024 study data demonstrated that Ki-67 index, additionally to such indexes as tumour size, regional lymph node status and PE expression, is an independent predictor of overall and relapse-free survival [13].

Therefore, a preoperative prognostic endocrine index (PPEI) was formed which is a valid predictor of long-term results in IMPACT study [12, 14]. In Ellis M.J. et al. study it was shown that groups of patients with a low risk of recurrence after hormonal therapy can be distinguished on the basis of PPEI. The additional chemotherapy course in not obvious for them. Using this index, one could identify the groups of patients resistant to hormonal therapy who require chemotherapy [14].

Thus, the zero category based on PPEI calculation includes tumours with a size of less than 5 cm after preoperative treatment, with a negative lymph node status, Ki-67 levels <2.7% and PE >2. In this group of patients, endocrine therapy can be continued in the adjuvant setting, while patients with Ki-67 levels of 10% should be prescribed chemotherapy. The above results were obtained in the Z1031 cohort study [14, 15].

These results were confirmed in large ATAC and Breast International Group 1-98 trials, which studied tamoxifen, anastrozole and a combination of drugs in the adjuvant setting [16, 17].

Similar results were obtained in Z1031 study performed by American College of Surgeons Oncology Group [18]. It compared the exemestane neoadjuvant administration and anastrozole administration. When compared these drugs efficacy, no differences in the degree of Ki-67 index reduction were found; the results are comparable to the results of the NCIC CTG MA.27 study, which obtained similar survival rates with therapy with the described drugs in the adjuvant regimen [19].

A number of experiments were performed based on these studies results including a 2-week course of neoadjuvant hormone therapy. The endpoint of the study was the Ki-67 index determination [19-21].

Smith I.E. et al. evaluated the efficacy of gefitinib and anastrozole combination. Ki-67 index was considered as the primary endpoint of the study, which was a measure of tumour response to therapy. A positive effect of gefitinib on both survival rates and the degree of Ki-67 reduction was shown [22].

3. Ki-67 as an endpoint in drug pharmacodynamics studies

The absence of Ki-67 decrease during treatment may be a predictor of adverse outcome. The IMPACT study demonstrated that Ki-67 is a reliable predictor of survival with endocrine therapy. The results of 2-week endocrine therapy showed that time to progression correlates with the level of Ki-67 before the start of therapy. According to Dowsett M. et al., the value of Ki-67 after the above therapy can be considered as an index of residual disease after endocrine therapy. The importance of Ki-67 index determination 2 weeks after neoadjuvant endocrine therapy was shown by the POETIC study, which included 4000 patients who received perioperative endocrine therapy [15].

The value of Ki-67 index changes dynamics throughout the neoadjuvant chemotherapy is less expressed than in the case of endocrine therapy. Ki-67 level decrease occurs in majority cases of neoadjuvant chemotherapy, but the degree of this sign reduction expression correlates with the degree of response [23]. Jones R.L. et al. showed that the absences of Ki-67 level reduction along with complete pathomorphosis absence are predictors of the disease unfavourable outcome [24].

Conclusions.

Thus, the tumor marker Ki-67 is one of the most necessary in oncology for morphological determination of the degree of neoplasm malignancy, one of the additional criteria for malignant neoplasms diagnosing and resolving the question concerning the type of additional conservative treatment in adjuvant and/or neoadjuvant regimens.

References

1. Moroz VM, Shandra OA, Vastyanov RS, Yoltukhivsky MV, Omelchenko OD. Physiology. Vinnytsia: Nova Knyha. 2016. 722.

2. Dressler LG, Seamer L, Owens MA, Clark GM, McGuire WL. Evaluation of a modeling system for S-phase estimation in breast cancer by flow cytometry. Cancer Res. 1987; 47(20): 5294-5302.

3. Gerdes J, Lemke H, Baisch H, Wacker HH, Schwab U. Cell cycle analysis of a cell proliferation-associated human nuclear antigen defined by the monoclonal antibody Ki-67. J Immunol. 1984; 133(4): 1710–1715.

4. Yerushalmi R, Woods R, Ravdin PM , Hayes MM, Gelmon KA. Ki67 in breast cancer: prognostic and predictive potential. Lancet Oncol. 2010; 11(2): 174-183. doi: 10.1016/S1470-2045(09)70262-1

5. Urruticoechea A, Smith IE, Dowsett M. Proliferation marker Ki-67 in early breast cancer. J Clin Oncol. 2005; 23(28): 7212–7220.

6. Harris L., Fritsche H., Mennel R., Norton L, Ravdin P, Taube S. et al. et al. American Society of Clinical Oncology 2007 update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol. 2007; 25(33): 5287-5312. doi: 10.1200/JCO.2007.14.2364

7. Cuzick J, Dowsett M, Pineda S, Wale C, Salter J, Quinn E. et al. Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. J Clin Oncol. 2011; 29(32): 4273-4278. doi: 10.1200/JCO.2010.31.2835.

8. Penault-Llorca F., Andre F., Sagan C, Lacroix-Triki M, Denoux Y, Verriele V. et al. Ki67 expression and docetaxel efficacy in patients with estrogen receptor-positive breast cancer. J Clin Oncol. 2009 Jun 10;27(17):2809-15. doi: 10.1200/JCO.2008.18.2808.

9. Hugh J, Hanson J, Cheang MC, Nielsen TO, Perou CM, Dumontet C. et al. Breast cancer subtypes and response to docetaxel in node-positive breast cancer: use of an immunohistochemical definition in the BCIRG 001 trial. J Clin Oncol. 2009; 27(8): 1168-1176. doi: 10.1200/JCO.2008.18.1024

10. Viale G, Regan MM, Mastropasqua MG, Maffini F, Maiorano E, Colleoni M. et al. Predictive value of tumor Ki-67 expression in two randomized trials of adjuvant chemoendocrine therapy for node-negative breast cancer. J Natl Cancer Inst. 2008; 100(3): 207-212. doi: 10.1093/jnci/djm289.

11. Dowsett M, Nielsen TO, A'Hern R, Bartlett J, Coombes RC, Cuzick J. et al. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. J Natl Cancer Inst. 2011; 103(22): 1656–1664.

12. Dowsett M, Smith IE, Ebbs SR, Dixon JM, Skene A, Griffith C. et al. Short-term changes in Ki-67 during neoadjuvant treatment of primary breast cancer with anastrozole or

tamoxifen alone or combined correlate with recurrence-free survival. Clin Cancer Res. 2005; 11(2): 951–958.

13. Ellis MJ, Coop A, Singh B, Tao Y, Llombart-Cussac A, Jänicke F. et al. Letrozole inhibits tumor proliferation more effectively than tamoxifen independent of HER1/2 expression status. Cancer Res. 2003; 63(19): 6523–6531.

14. Ellis MJ, Tao Y, Luo J, A'Hern R, Evans DB, Bhatnagar AS. et al. Outcome prediction for estrogen receptor-positive breast cancer based on postneoadjuvant endocrine therapy tumor characteristics. J Natl Cancer Inst. 2008; 100(19): 1380-1388. doi: 10.1093/jnci/djn309

15. Dowsett M, Smith IE, Ebbs SR, Dixon JM, Skene A, A'Hern R. et al. Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. J Natl Cancer Inst. 2007; 99(2): 167-170. doi: 10.1093/jnci/djk020

16. Baum M, Buzdar A, Cuzick J, Forbes J, Houghton JH, Klijn JGM. et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet. 2002; 359(9324): 2131-2139. doi: 10.1016/s0140-6736(02)09088-8

17. Thurlimann B, Keshaviah A, Coates AS, Mouridsen H, Mauriac L, Forbes JF. et al. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med. 2005; 353(26): 2747-2757. doi: 10.1056/NEJMoa052258.

18. Ellis MJ, Suman VJ, Hoog J, Lin L, Snider J, Prat A. et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype--ACOSOG Z1031. J Clin Oncol. 2011; 29(17): 2342-2349. doi: 10.1200/JCO.2010.31.6950

19. Goss PE, Ingle JN, Pritchard KI, Ellis MJ, Sledge GW, Budd GT. et al. Exemestane versus anastrozole in postmenopausal women with early breast cancer: NCIC CTG MA.27--a randomized controlled phase III trial. J Clin Oncol. 2013; 31(11): 1398-1404. doi: 10.1200/JCO.2012.44.7805

20. Guix M, Granja NM, Meszoely I, Adkins TB, Wieman BM, Frierson KE. et al. Short preoperative treatment with erlotinib inhibits tumor cell proliferation in hormone receptor-positive breast cancers. J Clin Oncol. 2008; 26(6): 897-906. doi: 10.1200/JCO.2007.13.5939.

21. Robertson JF, Nicholson RI, Bundred NJ, Anderson E, Rayter Z, Dowsett M. et al. Comparison of the short-term biological effects of 7alpha-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)-nonyl]estra-1,3,5, (10)-triene-3,17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer. Cancer Res. 2001; 61(18): 6739–6746.

22. Smith I.E., Walsh G., Skene A, Llombart A, Mayordomo JI, Detre S. et al. A phase II placebo-controlled trial of neoadjuvant anastrozole alone or with gefitinib in early breast cancer. J Clin Oncol. 2007; 25(25): 3816-3822. doi: 10.1200/JCO.2006.09.6578.

23. Assersohn L, Salter J, Powles TJ, A'hern R, Makris A, Gregory RK. et al. Studies of the potential utility of Ki67 as a predictive molecular marker of clinical response in primary breast cancer. Breast Cancer Res Treat. 2003; 82(2): 113-123. doi: 10.1023/B:BREA.0000003968.45511.3f.

24. Jones R.L., Salter J., A'Hern R, Nerurkar A, Parton M, Reis-Filho JS. et al. The prognostic significance of Ki67 before and after neoadjuvant chemotherapy in breast cancer. Breast Cancer Res Treat. 2009; 116(1): 53-68. doi: 10.1007/s10549-008-0081-7.

Funding

This research received no external funding.

Institutional Review Board Statement

This scientific report did not require IRB approval, any patients were used to receive the information.

Informed Consent Statement

The retrospective analysis of material was used. Written informed consent from the patients was not necessary to publish this paper.

Data Availability Statement

The data presented in this study are available on request from the author.