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Ki67- protein: a proliferation index in breast cancer

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ABSTRACT

Various clinicopathological factors are evaluated in different studies on carcinomas to demonstrate their prognostic and predictive significance during the diagnosis and therapeutic procedures of the malignancy. Ki-67 is a biomarker that was proposed as a cell proliferation related nuclear antigen, and it only expresses in growing and proliferating cells. This unique feature of Ki-67 makes it a subject of interest in different investigations. Evaluating the Ki-67 expression has been demonstrated to be beneficial in determining the tumor behavior including tumor size, stage, grading and patient survival. Moreover, it might be helpful in selecting the preferred subsequent treatment strategy. Due to the importance of Ki-67 index, we aim to briefly review its properties and the importance of its expression during various types of malignancies. At last, the prognostic and predictive value of Ki-67 would be overviewed regarding the efficacy of neoadjuvant and adjuvant therapies in breast cancer patients.

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Introduction

Ki-67 was firstly detected as an antigen in a study which aimed to apply mouse monoclonal antibody to identify antigens in the nucleus of the proliferative cell in the year 1983. Proliferation as an eminent feature of cancerous cells is measured during tumor diagnostic process, due to its important prognostic value, which facilitates determining the preferred subsequent treatment procedure for each patient (1). In this regard, Ki-67 has been widely applied as a striking potent biomarker in different basic science. Furthermore, it was applied in researches on human subjects or animal models, malignancies behavior, aging and regenerative process. According to the various investigations, this biomarker can accurately signify the extent and percentage of proliferating cells in various malignancies including renal cell carcinoma, adenocarcinoma, non-small cell lung cancer, soft tissue sarcoma and others. Breast carcinoma is widely investigated to reveal the predictive significance of Ki-67 regarding the advantageous of neoadjuvant or adjuvant therapies and the following treatment strategy.

In this study, we aim to review the properties of Ki-67 proliferation index and its association with different types of aggressive malignancies.

Literature review

Ki-67 as a proliferation marker

The long arm of human chromosome number 10 is proposed as the location of Ki-67 gene, which contains 15 exons and 14 introns. The KEFL epitope in a motif that is intensely preserved in different species on exon 13 is illustrated as the target of Ki-67 antibody (2,3). The outstanding and distinctive feature of Ki-67 antibody

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is its reaction, which is restricted exclusively to proliferating cell's nucleus, compared with other introduced antibodies. It has been detected that Ki-67 had no reaction with normal cells at resting stage, which shows that these normal cell lines do not have this specific nuclear antigen at their resting stage. Based on the results obtained in the study of Gerde et al. the presence of target antigen of Ki-67 antibody on cell nucleus chromosomes is obviously attributed to cell proliferation state; this can be beneficial in detecting tissues with unusual proliferation and growing rate (1). This nuclear antigen is suggested to be expressed during all different stages of mitosis and cell cycle (G1, S, and G2 phases), except for resting phase (G0 level) of cell cycle; however the expression level varies between stages with its peak expression during mitosis (1,4).

Based on recent findings, there are different methods that can estimate the cell proliferating rate through DNA counting with various ethical complications. Nevertheless, Ki-67 is the only protein with the expression pattern, which is exclusively dependent on cell proliferation, thus its expression is proposed as an indicator of cell proliferating. Various types of antibodies have been applied in different carcinomas to reveal the amount of Ki-67 expression as a diagnostic method for neoplasms, because it can be associated with the growth fraction of the cells in tissue samples. According to these articles, applying function-blocking antibodies and inhibition of phosphorylation mechanisms can inhibit the Ki-67 gene expression, which consequently can arrest the proliferation process of the cells. In this regard, Ki-67 expression has an effect on cell kinetics (5,6). Immunohistochemistry is frequently used for Ki-67 immune-staining of different types of tissue preparations. A specific monoclonal antibody, MIB-1, was proposed in 1992 to be used for formalin-fixed, paraffin embedded blocks, which was equal to the original antibody of Ki-67, but it should be used after microwave processing of sections (7).

Ki-67 expression and tumor behavior

According to the findings of different studies, Ki-67 index labeling > 10% is proposed as a sensitive criterion of carcinoma behavior and mortality rate. The efficacy of Ki-67 immunostaining has been studied in different types of malignancies including multiple myeloma, soft-tissue sarcoma, tubal intraepithelial carcinoma, endometrial adenocarcinoma, pituitary tumors, glioblastoma multiforme, renal carcinoma, adenocarcinomas, prostate cancer and lymphatic metastasis, to evaluate its application in detecting the staging and aggressiveness of the carcinomas.

It has been reported that, the level of ki-67 expression will increase in bone marrow biopsies by increasing the stage of multiple myeloma and it is better to be evaluated during routine analysis of bone marrow because of the prognosis significance of Ki-67 (8). In addition, the relation between Ki-67 expression and angiogenesis has been revealed through immunohistochemistry of vasculature in bone marrow biopsies of patients with multiple myeloma. Despite the association between plasma cell proliferation and infiltration, Ki-67 index can be significantly related to tumor angiogenesis and survival rate in multiple myeloma patients (9). Similar results have been revealed regarding the direct association between Ki-67 expression and renal cell carcinoma tumor size, stage, grade and patients' survival (10). In renal cell carcinoma, the intensity of pathological indexes is related to the clinical parameters of the carcinomas.

Serous tubal intraepithelial carcinoma (STIC) is a subject of considerable attention due to its relation with ovarian high-grade serous carcinoma (HGSC). Based on immune-reactivity studies, Ki-67 expression is significantly higher in patients with STIC and those with simultaneous (HGSC) while compared with normal fallopian tube epithelium (11). Evaluating this immunohistochemistry marker is suggested to be beneficial in the diagnosis of patients with STIC.

Despite the investigation of the prognostic and predictive value of Ki-67 index during diagnosis of non-small cell lung cancer, no convincing result has been achieved regarding its efficacy. Further studies are needed to clarify the efficacy of assessing this immunohistochemistry biomarker in selecting the optimum treatment for patients (12). Moreover, further studies are needed to accurately reveal the predictive and prognostic value of this biomarker in granular cell tumor and Ewing's sarcoma (13,14). In one retrospective study performed by Sanchez-Tejada, no association was found between Ki-67 expression rate and pituitary tumor behavior (15).

In-vitro examination of human gallbladder carcinoma cell line (GBC-SD), which is a highly aggressive malignancy with poor prognosis, showed that inhibition of Ki-67 expression as a proliferation-related gene protein, could restrict the growth and proliferation of malignant cells (16).

Ki-67 and breast cancer

During invasive breast cancer, various pathological variables and biomarkers are evaluated to reveal the efficacy of primary treatments including adjuvant and neoadjuvant chemotherapy and hormone therapy. These biomarkers are proposed as prognostic and predictive indicators of treatment response including estrogen receptor

(ER), human epidermal growth factor receptor 2 (HER2), and Ki-67. By proofing the value of these prognostic and predictive factors as the indicators of response to primary therapies, they might be standardized as an everyday therapeutic strategy. Ki-67 is used as a proliferation and prognostic criterion in more than two decades to reveal the efficacy of primary treatments in patients with developed breast cancer and to specify the best subsequent therapeutic decisions. Although different clinical trials used Ki-67 to reveal primary hormonal or chemotherapies in patients with invasive breast disease, further evidence are needed to provide sufficient proof regarding the advantageous of Ki-67 application. According to the conducted studies, Ki-67 provide considerable data regarding the preferred subsequent therapeutic approaches in breast carcinoma; the most advantageous have been detected in patients with ER+ breast cancer (16).

In 2008, Viale et al. showed the prognostic value of Ki-67 labeling index in postmenopausal patients with breast cancer. According to their findings, elevated levels of Ki-67 was related with the requirement of adjuvant letrozole therapy in breast cancer patients (17). In another study, they showed that the higher Ki-67 was not the indication of enhanced response to adjuvant chemotherapy (18).

In the study of von Minckwitz et al. patients with low number of Ki-67 positive cells revealed better response while treated with tamoxifen, unlike patients with elevated number of Ki-67 positive cells that did not show suitable response to tamoxifen treatment (19). This was similar with the results obtained in the study of Penault-Llorca et al. which suggested Ki-67 expression as the optimum predictor of adjuvant therapy in breast cancer patients (20). In this regard, Ki-67 expression is proposed as the indication of adjuvant therapy in breast cancer patients.

Evaluating Ki-67 index would be significantly beneficial in patients who are candidates for neoadjuvant chemotherapy due to its prognostic value, which reveals the response to neoadjuvant chemotherapy (21). The beneficial effect of measuring biological markers has been recognized in some studies; low Ki-67 index was the indication of favorable prognosis after adjuvant hormonal therapy of breast cancer patients (22).

Although various studies have shown the efficacy of Ki-67 as a prognostic factor on breast cancer patients, limited number of studies has considered its benefits after neoadjuvant therapy (the frequency of this method has significantly increased in recent years). In 2008, Ellis et al. showed that Ki-67 post-neoadjuvant hormonal therapy reliably revealed the efficacy of hormonal therapy and they suggested this biomarker as a prognostic index (22). Similar results have been obtained in the study of Lee, et al. who evaluated and compared the efficacy of various biological variables and proposed Ki-67 proliferation indexing as the only prognostic indicator of survival rate in breast cancer patients following neoadjuvant chemotherapy (23). In one retrospective study, pre- and post-chemotherapy Ki-67 has been proposed as the best predictors of overall survival rate when compared with other biological markers including Ki-67, ER, PgR, HER2 in breast cancer patients (24). Moreover, in another study, the prognostic value of Ki-67 was estimated after increasing pathological complete response through specific chemotherapy setting of consecutive taxane and anthracycline and they eventually resulted in similar outcome with previous studies about the significant prognostic value of Ki-67 factor after the treatment. It was mentioned that despite the considerable decrease in Ki-67 index after the neoadjuvant chemotherapy, the absolute level of Ki-67 was a determinant of response to treatment; high Ki-67 proliferation index after neoadjuvant chemotherapy was associated with higher risk of tumor relapse (25). Ki-67 measurement through immunohistochemistry (IHC) technique is not standardized between laboratories and each laboratory has its specific cut-offs for Ki-67 measurement. According to the 13th St Gallen international breast cancer conference, despite a considerable difference between laboratories applied IHC method, a threshold of ≥20% as a result of IHC, is indicative of 'high' Ki-67 status. Eventually, St Gallen conference proposed the need for standardization of the Ki-67 measurement for breast cancer treatment strategies (26).

Conclusion

Ki-67 is an exclusive biomarker which is used in different fields of research. This marker is the indicator of cell proliferation and growth. In this regard, it has shown a prognostic and predictive value for various types of malignancies; however further studies will provide more evidence. The efficacy of examining this factor expression has been widely studied in breast cancer patients. Based on results obtained in studies conducted on patients under neoadjuvant chemotherapy, Ki-67 proliferation index can reveal the success rate of chemotherapy.

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Conflict of Interest

The authors declare no conflict of interest.

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