Minireview Article

The effect of molecular markers in the treatment of advanced breast cancer

ABSTRACT

Molecular markers may have an effect in the treatment of advanced breast cancers. Our aim is to review and analyze the studies on this subject and to reveal the effect of molecular markers in the treatment of breast cancer. In this review, current studies using molecular markers in the treatment and prognosis of advanced breast cancer were compiled, and the results were briefly discussed. Molecular markers have had a great impact on the prognosis and treatment of advanced breast cancers. In these cases, it has been shown that overall survival and prognosis-free survival are prolonged by molecular markers.

Keywords: molecular marker, breast cancer, survive, treatment.

1. INTRODUCTION

Breast cancer (BC) is the most common type of cancer in women in the world and ranks fifth in cancer deaths [1].According to the data of the International Cancer Agency, there has been a 66% increase in cancer deaths since 1960, and breast cancer occurs in one out of every 8 women in the US[2].

BCs often show molecular heterogeneity.Therefore, the determination of the molecular structure of each cancer focus is of vital importance for diagnosis, prognosis and treatment.New molecular markers(MM)s, portable biosensors, and multigene analysis tests have been developed that can reveal malignant progression of cancer cells and tumor subtypes. In advanced stage BC, it is tried to prolong overall survival (OS) and progression-free survival (PFS) with methods such as chemotherapy and immunotherapy. Despite this, various difficulties arise in the treatment of aggressive subtypes such as TNBC and metastases.

Today, MMs are widespread in all fields of medicine. The importance of MMs in screening and diagnostic tests, prognosis determination and treatment, especially in many types of cancer cases, has been understood and they have started to be used in routine clinical applications [3- 7].

Therefore, in our study, the effect of MMs was investigated by reviewed the current studies in the treatment of advanced BC.

2. OBSERVATION

The tumor microenvironment is very important in the treatment of BC, especially for immunotherapy.

In recent years, migrastatic agents such as graphene and graphen-based derivatives used to modulate tumor microenvironments have been used in cancer treatment. In order to overcome the problems that arise in the in vivo use of these substances, Diban et al., in a study they carried out, immobilized graphene nanoplates at high concentrations on polyacrylonitrile film substrates and used them as migrastatic in MCF7 BC cells and showed that they were significantly effective as an antimetastatic agent [8].

In order to identify the most important MMs regulating the tumor microenvironment in immunotherapy in BC, genes with general differential expression were investigated, 486 related genes were found, and CD40LG was found to be the most important gene downregulated in advanced cancer and poor prognosis cases by Yuan et al.[9] . In a review study by Vanhevel et al., it was reported that the active form of Vitamin D3, 1,25-dihydroxyvitamin D 3, is an immune modulator, its deficiency has a role in the development and progression of BC, and 25(OH)D acts as a biological marker[10].

In a review study by Samuel et al., it was reported that extracellular vesicles play an important role as mediators of therapy resistance in the BC microenviroment, cause drug resistance through changes in protein, lipid, and nucleic acid cargoes, and that the cargo content of extravesicles can be used as a target for treatment or as predictive biomarkers in therapy [11].

In a study by O'Leary et al., it was investigated whether genomic markers could be detected in the circulating tumor DNA of advanced ER+ BC patients with high risk of early progression in fulvestrant treatment with or without palbociclib, a CDK4/6 inhibitor. It has been reported that in patients at risk of progression, treatments that can be effective in the genomic context should be added[12].

As a result of studies with MMs in metastatic BC, important developments have been obtained regarding the increase in the life expectancy and quality of life of patients.

In a review by Venetis et al., they reported that after the heterogeneity of metastases in BCs with bone metastasis was determined by molecular methods, new drugs such as bisphosphonates and denosumab should be added to the classical treatments in order to increase the patient's life expectancy and quality of life[13].

In a study by Ring et al., it was shown that transcriptome RNA-Seq of circulating tumor cells isolated with an epitope-independent approach can serve as a macrometastasis proxy and can be used as a new target in the treatment of BC [14]. In a review study by Yu et al., it was stated that having 2 drugs on a single platform has both advantages and disadvantages.With a new technique developed by Celator, it is possible to develop different liposomal formulations with a methodical approach developed to evaluate different drug combinations in liposomal Technologies and for the treatment of metastatic BC, the production of CPX1(irinotecan:floxuridine) and CPX-351 (cytarabine:daunorubicin) has been reported to be in phase-II [15].

TNBCs are one of the most aggressive subtypes among BCs.

In a study by Maqbool et al., new treatment methods were reviewed in TNBCs, and it was reported that despite molecular subtyping, treatment is difficult in these cases, so new treatment methods should be shared quickly: DNA repair complex (platinum compounds and taxanes), p53 (taxans). such as cell proliferation (anthracycline-containing regimens) and target therapy. Target therapy based on the molecular properties of TNBC revealed in recent years; Poly(ADP-ribose) polymerase-1, thyrosine and non-thyrosine kinases, PARP1, androgen receptors, immune-checkpoints have been reported to be used[16]. Small molecule-based chemotherapy is applied in TNBCs due to the heterogeneity and lack of specific molecular targets. Since healthy cells are not off-target in this treatment method, they show a high toxic effect and often show resistance to treatment[17]. In a clinical review study conducted by Celesnik et al., it was reported that in the near future, peripheral blood transcriptomes as noninvasive immune biomarkers will be used much more in BCs, in screening, diagnosis, immunotherapy and monitoring of treatment, and that new treatment models can be developed, especially in TNBCs, with newly discovered immune biomarkers[18] . In a review by Mehraja et al., it was reported that new developments in the chemokine network regulating TNBC heterogeneity may pave the way for the development of therapeutic models for the effective treatment of TNBC[19]. In a study by Yang et al., when resveratrol is used together with cisplatin in treatment-resistant TNBCs, it has been shown in

vivo and in vitro that the expressions of some MMs such as P13K/AKT, JNK, and ERK have a synergistic effect on the regulation [20].

In a study by Cai et al., it was found that the increase in the expression of MRPL13, a mitochondrial ribosomal protein in BC cases, negatively affected the clinicopathological course, when the P13K/AKT/mTOR signaling pathway was inhibited by AKT and mTOR phosphorylation; It has been shown that tumor cell proliferation, migration and epithelial-mesenchymal transition process can be limited[21]. In a review study by Sneha et al., current studies on the proliferation of cancer cells, cell signaling, and cytochrome P450, an enzyme family that is effective in drug metabolism in standard BC treatment, were analyzed, and it was reported that future studies on this subject would contribute greatly to BC patients [22].

Cejuela et al., in a study on the molecular mechanisms of action of metformin, an insulin sensitizer, in the treatment of BC, in T2D and HER2-positive BC patients treated with neoadjuvant metformin and provided with invasive DFS and OS, they showed that at least one copy of the minor allele (C) of the SNP rs11212617 localized next to the ATM gene is present [23]. In a study by García-Sáenz et al., it was shown that progression-free survival was significantly prolonged when Fulvestrant was added to Sapanisertib treatment in postmenopausal ER+ HER2- patients with and without prior cyclin-dependent kinase-4/6 inhibitor therapy[24].

Bulska-Bedkowska et al., soluble cell adhesion molecules as a predictive factor in the treatment of advanced BC; E-selectin, P-selectin, VCAM-1,ICAM-1, EpCAM, IL-6Ra, TNF-R1 and TNF-R2 serum levels were investigated, high sICAM-1 and low sEpCAM levels were indicative of rapid progression and sICAM-1 and It has been reported that sVCAM-1 may pave the way for new treatment methods in BC [25]. In a study by Sun et al., it was reported that activated stem-like BC cells showed resistance to genetic stress through TGFBI-ZEB1, and this pathway was disrupted and "BRCAness" could be increased by increasing the sensitivity of these cells to PARP inhibitors [26]. Recurrence is seen in approximately 25% of HER2 + BC cases treated with trastuzumab in a short time. The molecular reasons for this are largely unclear. In a study by Ling et al., it was shown that circCDYL2, a circular RNA, was overexpressed in Trastuzumab resistance cases [27]. The emergence of endocrine resistance during antiestrogen therapy is an important problem in very common estrogen+BC cases. In a study by Törnroos et al., it was reported that SLC7A5 mRNA overexpression was observed in these cases, it was positively correlated with Ki-67 proliferation marker and hypoxi inducible factor 1 subunit alpha expression, and it could be used as a prognostic molecular marker in the clinic[28]. In a study by Li et al., they showed that ZBTB28, a tumor suppressor gene in BC, increased macrophage phagocytosis by blocking CD24 and CD47, activating IFNAR, and also activating interferon-stimulated genes[29].

It is known that especially chronic stress has an important effect on the occurence and prognosis of BC by revealing some neurotransmitters. Liu et al., in a review study on this subject, as a result of studies at the molecular level, for target-oriented alpha 1 adrenergic receptors in BC treatment; Tramadol, Doxazosine, Beta 2 adrenergic receptors; Atenalol, Propranolol, nicotinic acetyl for choline receptor; Garcinol, Darfenacine. for dopamine receptors; for Thioridasine, Sulpiride, for neurotensin; SR48692 is for glutamic acid; Riluzole and BAY36-7620 have been reported to have a positive effect[30].

There are many active substances in extra virgin olive oil (EVOO), such as triterpenes and phenolic alcohols. In a review study by Moral and Escrichin, it was reported that the molecular targets of EVOO components have an effect on the formation and development of cancer in some cancer types, including BC, and that these components may have preventive and therapeutic effects on BC occurence [31].

3. CONCLUSION

Based on the results of this review, studies with molecular markers have positively affected the treatment in advanced breast cancers, prolonging the overall survival and progression-free survival times. However, it is necessary to continue studies at the molecular level in order to obtain more effective treatments in advanced breast cancers.

DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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