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PD-L1 in Breast Cancers and its Prognostic Significance

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ABSTRACT:

Breast cancer is the most common malignancy in females globally. Various factors are responsible for its development which include both genetic and hormonal causes. An important discovery is the role of the PD-1/PD-L1 axis in the development of cancers. The PD-1-/PD-L1 pathway plays a part in allowing tumour cells escape from the host's immune response and hence permits the proliferation of tumour cells. PD-L1 expression has been observed in various breast cancers at distinct levels such as in tissues and in blood. Different methods have been utilized for its detection including immunohistochemistry, RNA sequencing and ELISA, amongst others. The results have been conflicting regarding the expression of PD-L1 and the prognosis of breast cancer based on parameters such as overall survival and disease free survival. Different immunotherapies have also emerged as a new modality to treat breast cancer. This review intends to explore the prognostic significance of PD-L1 expression in breast cancers.

Keywords: Breast cancer, PD-L1, Prognosis

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INTRODUCTION:

Breast cancer continues to be the leading malignancy in females worldwide. In 2018, the incidence of breast cancer was 2,088,849, which consisted 11.6% of the total cancers in both genders combined. [1] It is also the number one cancer reported in Pakistan amongst adults.[1-2] It is a heterogeneous disease resulting from a mixture of genetics and hormonal interplay. Around 12% of breast cancers emerge because of a mutated gene inheritance. Mutations in the tumour suppressor genes such as BRCA1, BRCA2, TP53 and CHEK 2 are liable in the causation of familial cancers, the most common being BRCA 1 and BRCA2 mutations. The risk factors for harboring breast cancer include diet, hormonal changes (early menarche, late menopause) radiation exposure, having a first degree relative with breast cancer and genetics.[3] Breast cancer can be divided according to its histological status and molecular subtypes, which include Luminal A, Luminal B, HER2 enriched and triple negative.[3-5]

Over the years the PD1/PDL1 pathway has gained enormous attention for the role it plays in tumour immune escape.[6] PD-1, also known as CD 279, was originally cloned in 1992, and was primarily thought to be a part of the apoptotic pathway of cells[7]. It is a receptor located on T cells.[8] PD-L1, also known as B7-H1, is the ligand of PD-1.[9] Alongside being found on macrophages, dendritic cells and B cells, it is expressed on malignant cells.[8] The interaction of PD-1 and PD-L1 causes increased apoptosis of T cells, thus cancer cells have a route of evading the immune system.[10] It has been extensively studied that along with many other cancers, breast cancer cells overexpress the PD-L1 receptor.[11-17] PD-L1 has been found to be expressed in renal cell carcinomas, [11] non-small cell lung carcinomas,[12] colorectal carcinomas,[13] ovarian carcinomas [14] and melanomas.[15]

Prognosis can be defined as "the prospect of recovery as anticipated from the usual course of disease or peculiarities of the case"[18]. Prognosis in breast cancers is largely determined by the clinicopathological parameters. These include age, gender, tumor size, lymph node metastasis, lymphovascular invasion, neural invasion[19], histologic subtype, grade, stage, mitotic figure count and hormone receptor status.[20] High expression or overexpression of PD-L1 can also influence prognosis as reviewed.

METHODOLOGY:

A methodically comprehensive search was performed using NCBI PubMed database and Google Scholar. 73 relevant articles from the years 2000 to 2019 were found from this literature search. The studies were scrutinized and evaluated further for the magnitude and significance of breast cancer, and the prognostic value of PD-L1. Out of these articles, 50 were ultimately selected. Articles which were unrelated to the topic and obsolete texts were excluded. Based on these criteria, this review article was devised.

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Literature review:

The city of Karachi, Pakistan, is stated to have the topmost incidence of breast cancer in Asian populations, excluding Israeli Jews. The reasons for this are not all entirely obvious, however, certain risk factors make the women more vulnerable to harboring it. It also accounts for one third of all female cancers.[21] In the United States and Europe, breast cancer incidence rate is four to seven times higher as compared to other countries, but since developing countries are implementing Western lifestyles, such as decreased breastfeeding and fewer number of pregnancies, it is predicted that by this year, 2020, 70% of breast cancer cases would be found in the developing countries.[3]

The PD-1 and PD-L1 combination is an immune checkpoint. Working together, they prevent cytotoxic T cells from performing an excess of their function, thus maintaining a steady state of T cell function and preventing over stimulation. However, tumor cells can take advantage of this route by expressing PD-L1 themselves, hence avoiding the immune system and proliferating.[22]

PD-L1 expresses in a variety of forms in different regions. It is seen in tissues, where it can be detected as protein[23] or mRNA[24]. Current evidence has shown that the membrane bound PD-1 and PD-L1 have circulating forms as well and hence may be detected in blood in the soluble form[25,26] or as exosomes[27].

Consequently, there are a variety of methods and procedures for its detection which include immunohistochemistry (IHC), flow cytometry & ELISA, in situ hybridization, PCR, DNA microarrays and RNA sequencing[28-33.] There is currently no set standard for the evaluation and expression of PD-L1 and many challenges exist. PD-L1 expression had initially been determined through IHC in tumours but detection through IHC comes with its own share of limitations. Some include differences in antibody clones of different companies, the method used to score the variables, and the small innate differences in PD-L1 expression in the different types of specimens like surgical resection and biopsies, fresh frozen and archives, and primary and metastatic tumours[34-35]. Besides IHC, analysis at the protein or messenger RNA level have different cells involved in expression such as tumour cells or tumour infiltrating lymphocytes. Hence the availability and utilization of different techniques may be responsible for the differing results in literature[36].

Prognosis is usually based on various parameters which includes overall survival, when the cause of death is not specified; disease free survival, the time period after treatment when no disease, or cancer, can be identified; and metastasis free survival, defined as the time from the start of treatment for cancer in which the patient is alive with no metastasis.[37] PD-L1 can be used as a prognostic marker in breast cancer, however, the relationship among overall survival, clinicopathological features and prognosis in general amongst breast cancer patients is conflicting.

Several commentaries have suggested that expression of PD-L1 in breast cancer patients can be a favorable prognostic marker[17, 38-40]. It has been linked to negative lymph node metastasis and an increased tumour infiltrating lymphocyte count, leading to a better overall survival[17] and disease free survival.[17, 38] .Cytoplasmic expression of PD-L1 in tumour cells is associated with a lower risk of breast cancer specific deaths, and both PD-L1 expression and tumour infiltrating lymphocyte count are related to a better outcome[39].

Amongst the subsets of breast cancers, PD-L1 is seen to be more significantly expressed in the triple negative group or basal like tumors[28], and in this subcategory, PD-L1 expression is associated with a favorable prognosis due to a better disease free survival.[38] It has also been observed that PD-L1 expression, when linked to poor prognostic features such as high tumour grade, was associated with a good relapse free survival specifically in the basal type, and not with the outcome of breast cancers in general[40]. Remarkably, PD-L1 expression has led to a better overall survival in some breast cancer cases which presented with poor clinicopathological features, probably due to an anti tumour response[16,41]. The expression of PD-L1 has also been reported to activate immune-related pathways such as IFN á, IFN ã and TNF á, hence leading to a good prognosis and it seems to be the only prognostic element in metastasis free survival[42].

Some evidence has concluded an opposing relationship regarding PD-L1 expression in breast cancer and prognosis, with its expression being associated with a poor overall survival and an independent negative prognostic factor[43]. Higher PD-L1 expression has also been observed in patients who were younger than 35, who presented at an advanced stage and those with a larger tumour size and hence are linked with a poor disease free and overall survival[44]. A meta-analysis which comprised of 5 studies and a total of 2546 breast cancer patients also showed a link between PD-L1 expression and a reduced overall survival[45]. PD-L1 expression is a poor prognostic marker in those triple negative breast cancers which have a low tumour infiltrating lymphocyte count.[46]

Along with the traditional treatments of chemotherapy and radiotherapy for breast cancers, immunotherapies are also emerging which have encouraging results.[47] Drugs targeting PD-1 or PD-L1 have been discovered to improve the outcome of the patients; these drugs include Pembrolizumab, Atezolizumab, Avelumab and Nivolumab[48]. According to a review study, 500 studies were carried out on anti PD-1 and anti PD-L1, using nine types of antibodies from at least 8 pharmaceutical companies, on approximately 20 types of hematological and solid malignant tumors.[49] This study further mentioned that some of the anti PD-1 and anti PD-L1 drugs have already been permitted by the US Food and Drug Administration (FDA). Trials conducted have shown

that these drugs, when used alone, may enhance a more favorable prognosis, and when they are used in combination with other drugs such as chemotherapeutics, the response is strengthened.[50] Since there are conflicting results in literature regarding the prognostic significance of PD-L1 in breast cancers, and because very scarce data is available in Pakistan as well in this regard, there is a dire need for conducting further researches and clinical trials in this domain to gain coherent results. Doing so, the results will eventually aid in the selection of proper immunotherapeutic drugs for the treatment of breast cancer, alongside the existing therapies.

CONCLUSION:

Breast cancer continues to rank number one across the globe. Researches have demonstrated conflicting results regarding the expression of PD-L1 as an indicator of prognosis of breast cancer; which strongly supports the intense need of globally standardizing the detections methods & techniques, cut off values, scoring systems and sample sizes for obtaining consistent results. A finding revealed in most studies is that PD-L1 expression may be a good prognosis of breast cancer if it is associated with an increased tumour infiltrating lymphocyte count. This outcome may be due to the fact that increased PD-L1 expression causes a compensatory reaction of additional tumour infiltrating lymphocytes, which in turn provide the anti- tumour response, hence leading to a good prognosis. More research is warranted in this domain. Since plenty of research has also led to the conclusion that PD-L1 expression is a poor prognostic marker in breast cancer as well, anti- PD-1/PD L1 therapy is gaining momentum and is an encouraging breakthrough for treatment of breast cancer. Further studies and clinical trials are needed in this regard to evaluate the effect of immunotherapeutic drugs on breast cancers.

Authors Contribution:
Sayher Kazmi: Conceiving the idea, literature search, writing of the article
Sumayyah Shawana: Literature review, critical analysis of article
Nighat Jamal: Critical review of article

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