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Review Article

Immunotherapy in Breast Cancer

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Introduction

Fifty years ago, Burnet proposed the immune surveillance theory [1]. Immune surveillance is a process by which body can react to any transformed cells and destroy them before they multiplied and become tumors. Immune cells recognize transformed cells via new antigen which expressed on their surface and destroy them. Based on this theory the concept of immunotherapy for elimination of refractory tumors was gained interest [2]. However, outcome of clinical immunotherapies was not satisfying as expected. In past two decade, studies on understanding why certain cancers, mostly breast cancers harness immune recognition and elimination or evade body's immune response, led to the concept of immunoediting which was proposed by Schreiber [3] to explain the immunodynamics between tumors and immune system. Immunoediting describes interactions between tumor cells and immunocytes in three phases: Elimination, Equilibrium, and Escape [4]. Immunoediting is characterized by changes in the immunogenicity of tumors due to the anti-tumor response of the immune system, resulting in the emergence of immune-resistant variants. During elimination phase of immunoediting process, effector immunocytes such as natural killer (NK) cells, with the help of dendritic cells and CD4+ T cells recognize tumor cells which poses relatively high immunogenicity and eliminate them before forming clinically significant mass. In contrast, tumor cells which are less immunogenic are able to escape elimination phase. Equilibrium phase is next step in cancer immunoediting, during which tumor cells that have escaped the elimination phase due to genetic and epigenetic changes to be resistance to immune system attack, become dormant as occult cancer cells and grow to emerge tumor mass which caught in the balance between anti-tumor and pro-tumor immunity in the tumor microenvironment. In the escape phase, tumor cells with poor immunogenicity continue to grow and expand in an uncontrolled manner and may eventually lead to malignancy [5]. Microscopic examination of these established malignant tumors, demonstrate presence of remarkable immune cells called tumor infiltrating lymphocytes (TILs). TILs are seen as a refection of tumor related immune response [6]. In spite of the fact TILs are present next to the tumor cells but can not destroy them. There is increasing evidence that biological vesicles such as exosomes secreted by tumor cells help to develop an immunosuppressive tumor microenvironment [7]. During the escape phase, tumor cell variant selected in the equilibrium phase have braked the host immune defenses with various mechanisms that lead to escape of cancer cells from effective immune response such as down regulation or loss of expression of major histocompatibility complex class I (HLA-A, B, C) which essential for effective cell mediated immune response development in tumor microenvironment [8]. This immunosuppressive effect works as a protective barrier to cancer cells [9]. Furthermore, escaped cancer cells are able to produce cytokines which can cause apoptosis of activated t cells [10]. Another mechanism of tumor cell evade immune response is upregulation of major histocompatibility complex class I (HLA-E, F, G) which inactivate NK cells [11] necessary for eliminating cancer cells. In addition, expression of immune checkpoints increased the frequency of immunosuppressive cells including regulatory T cells, myeloid-derived suppressor cells, immunomodulatory factors including tumor growth factor, and vascular endothelial growth factor in tumor microenvironment cause peripheral tolerance [12]. Tumors also can evade destruction by immune system expressing surface ligands (PD-L1) that engage with inhibitory receptors on the tumor- specific T cells (PD-1) in order to deactivate cytotoxicity function of T-cells and survive in the body. PD-1 is a member of immunoglobulin superfamily and acts to inhibit the immune response by inactivation of the T cells on which it is expressed. PD-1 is also expressed on B-cells, myeloid cells, and natural killer cells. PD-1 is activated by its ligand PD-L1 which is expressed on many immune cells as well as on some cancer cells [13].

Breast Cancer is the most common non-cutaneous cancer in women worldwide. This cancer affects 14% women and comprise more than 22% of invasive cancers in women and 16% all female cancers [14]. management of breast cancer depends on various factors including genetic background of patients, type of cancers which identified by tumor histological examination followed by immune-histochemistry (IHC) staining of patient's biopsy, stage of the cancer, and patient's age. Treatment is usually starting with surgical removal of the tumor and followed by chemotherapy and/or radiotherapy, and/or immunotherapy depending on aggressiveness of the tumor. In some cases, neoadjuvant therapy may be required prior to surgery and in case of advanced stage with risk of disease relapse, adjuvant therapy using hormone-blocking agents or chemotherapy or monoclonal antibodies may be necessary to prolong

patient's disease-free life [15].

In order to overcome limited efficacy of the immune response against tumor, concept of cancer immunotherapy gained attention. Using this type of therapy, immune system can be educating to recognize and attack specific cancer cells, boost immune cells activity to eliminate cancer cells, and provide the body with additional components to enhance the immune system. Adaptive immunotherapy was among the first regimens of immunotherapy used for treating solid tumor [16]. Adaptive immunotherapy means transfer of immune cells with anti-tumor activity into patient to attack tumor and kills cancer cells. This type of cancer treatment is gaining in popularity due to reports of success is increasing high specific activity with minimal toxicity side effects contributed to acceptance immunotherapy by clinicians as either single therapy or in combination with chemotherapies and/or radiotherapies. There are four major types of adaptive T cells transfer therapy which clinically being used: Epstein-Bar virus (EBV) specific T cells for EBV-associated malignancies; Tumor-infiltration lymphocytes (TIL) for metastatic malignancies and ovarian cancer; genetically modified T cells directed against various solid and hematological malignancies; natural killer (NK) cells as an immunotherapy [17]. Currently, many other types of cancer immunotherapies are applied: immune checkpoint inhibitors therapy; tumor-infecting virus therapy; gene therapy; immunomodulator therapy; targeted antibody therapy; oncolytic virus therapy; biologic therapy. While all these immunotherapies showed promising for elimination of tumor cells in patients, it should be noted that the recent clinical success using checkpoint inhibition blockade and CAR T cell therapies has marked beginning of new era in cancer immunotherapy [18,19].

Breast cancer is one of the most commonly studied tumors for the presence of immune system cells in the lesion and scores of ongoing clinical trials are evaluating the role of immunotherapy in breast cancer prevention and treatment [20]. The study of the immune microenvironment in breast cancer started with the identification od cancer associated antigen. One of the first breast cancer associated antigens identified was the glycosylation of MUC-1 [21]. It has been shown that breast cancer possesses type II immune microenvironment that supports the development of a primary antibody response, but not support the proliferation and maintenance of CD8+ cytotoxic T cells which is important immune cell for tumor elimination. An evaluation of cytokine release by antigen specific T cells directed against HER2, CEA, and MAGE3 demonstrated that breast cancer patients were lacking CD4+ T cells that were capable of secreting INF [22]. Additional investigations have shown that as breast cancer progresses, Type I immune responses that had developed against breast cancer antigen such as HER2 or HER3 began to diminish and eventually decrease to the point of no detection. Loss of immunity was associated with persistent disease after standard therapy [23]. Breast cancers that show a high degree of pre-existing immunity have been described as inflamed cancer types and are characterized by presence of high TIL cells population, program death ligand-1 (PDL-1) positivity of tumors or immune cells, high CD8+ T cells or presence of strong INF producing T cells [24]. Non-inflamed tumors are generally poorly infiltrated by TIL cells, exhibit low expression of PDL-1 and are characterized by low antigen presentation and are incapable of mounting an effective anti-tumor immune response [25]. Triple negative breast cancer (TNBC) and HER2 positive breast cancers are immunogenic as reflected by higher proportion of TIL cells compare to hormone-sensitive breast cancers which are considered non-inflamed tumors [26].

TNBC accounts for 15-20% of all breast carcinoma and associated with earlier age of onset, aggressive clinical course, and hopeless prognosis compared to HER2-positive breast carcinoma [27]; thus, most of the initial cancer immunotherapy have focused on TNBC. Given the lack of effective treatment in this type of breast cancer, several studies conducted in recent years to increase the therapeutic opportunity for TNBC patients [28]. It has been shown that chemotherapy with neoadjuvant increase TIL cells in tumor microenvironment with high number of CD8+ cytotoxic t cells or a high CD8+/FOXP3+ ratio which define TNBC patients with better prognosis following immune checkpoint inhibitors therapy [29]. The ability of immune system to detect and fight cancer cells is largely based on two key components: immune system has to recognize cancer cells as being different from normal cells meaning expression of neoantigens in cancer cells, and the second determinant of the immune response is the ability to change the number and function of immune cells when needed. One of the parameters in this context presence of great number of TILs in tumor microenvironment [30]. In breast cancer higher population of TILs is associated with aggressiveness of tumor type and also linked with improved outcome and response to chemotherapy and/or immunotherapy [31]. TILs also have been shown to be an independent prognostic marker in TNBC, whereas they are not predictive in ER-positive disease. It has also shown that TILs can be linked with an increased therapeutic response in HER2-positive breast cancer and TNBC [32].

Although immune checkpoint inhibitors [ICIs] therapy has demonstrated substantial single agent effectivity, it is only a relatively small subgroup of patients get benefit by this regimen therapy. For those breast cancer tumors subtypes which lack of great population of TIL cells in their microenvironment, it would be necessary to enhance immunogenicity of the breast cancer in order to increase population of TILs in the tumor for more effective ICIs. Many agents such as anthracyclines, platinum salts, taxanes, cyclophosphamide, and gemcitabine are a few agents that increase infiltration of immune cells into tumor microenvironment [33]. In addition, chemotherapy can induce multiple immunomodulatory changes in the tumor microenvironment, including increased antigen release by tumor cells, PDL-1 upregulation, and hyperexpression of immunogenic cell surface markers like MHC class I. It has been shown these modifications will positively influence the effectiveness of breast cancer immunotherapy [34].

Discussion

It has been well stablished that TIL cells are present in tumor microenvironment but they are ineffective at tumor elimination in vivo. However, if they are present in high number, various type immunotherapies like checkpoint inhibitors therapy shows better prognosis and longer patient's survival. This is because cancer cells develop mechanisms to avoid recognition and elimination by immune system. If TIL cells removed from tumor mass and activate them ex vivo the infused them back to the patient body, they are able to kill tumor cells. Most breast cancer patients, including TNBC patients have low to moderate amount of TIL in their tumor; therefore, one clinical strategy might be to increase the number of TIL cells prior to the

administration of an immune checkpoint inhibitor antibody. Another method to potentially increase TIL cells number, is by active immunization. It has been shown that vaccines targeting tumor specific antigen could generate T cells that had capacity to migrate to tumor. In a case report by Stanton et al [35], the patient with widely disseminated HER2+ breast cancer had previously received a HER2 epitope-based vaccine then patient underwent leukapheresis followed by vaccine primed T cells expansion ex vivo. An aliquot of the expanded T cells was labeled with indium and imaging modalities were used both to track the T cells as well as assess changes in glucose metabolism in the tumor over 48 hours. data showed that T cells migrated to all sight od disease and metastatic sites within 48 hours. A similar study performed in patients with ductal carcinoma in situ (DCIS). In most patients, there was a marked post vaccination increase in TIL cells gathering at periductal sites surrounding regions of residual DCIS. Investigators observed pronounced declines in the strength of HER2 staining in the majority of vaccinated patients in compare to the control group [36]. It should ne noted that standard therapies like radiation therapy or chemotherapy can also can increase number of TIL cells in tumor microenvironment. Radiation therapy can increase secretion of type I cytokines, upregulate the expression of adhesion molecules on the surface of TILs led to draw antigen presenting cells into area of the tumor and stimulate antigen specific t cells [37]. many common chemotherapies used as standard treatment of brest cancer are capable of augmenting tumor specific immune response [38]. Taxanes have been shown to induce tumors to secrete INF and activate T cells. Anthracyclines enhance the function of dendritic cells. Gemcitabine can decrease the number of myeloid derive suppressor cells which will inhibit T cells function, hence potentiate effective immune response against tumor cells.

It is clear that all types of breast cancer patients show some evidence of immune response either in peripheral blood or tumor but some subtypes of cancers may be more readily treated with immunotherapy than the others. Based on lesson learned, immune checkpoint inhibitors have achieved durable a clinical response in patients with advanced cancer that was refractory to the standard treatment. However, ICIs should be implemented in the first-line setting of metastatic treatment to improve success rate. Additionally, early-stage breast cancer is even more appealing than the metastatic type for administration of ICIs, both in the neoadjuvant and adjuvant settings, since primary tumor is more immunogenic than metastatic sites.

References

1. Burnet M. Cancer a biologicalapproach.1. process of control. Br. Med. J, 1957; 1: 779-786.
2. Dunn GP, Old IJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity*, 2004; 21: 137-148.
3. Schreiber RD, Old IJ, Smyth MJ. Cancer immunoediting: immunity's role in cancer suppression and promotion. *Science,* 2011; 311: 1565-1570.
4. Vesely MD, Kershaw HM, Schreiber RD, et al. Natural innate and adaptive immunity to cancer. *Annu. Rev. Immunol,* 2011; 29: 235-271.
5. Mittal D, Gubin MM, Schreiber RD, *et al*. New insights into cancer immunoediting and its three-component phase-elimination, equilibrium and scape. *Curr. Opin. Imuunol,* 2014; 27: 16-25.
6. Odunisk K, Old LJ. Tumor infiltrating lymphocytes: indicators of tumor-related immune responses. *Cance*r, 2007; 7: 3-10.
7. Syn N, Wang L, Sethi G, *et al*. Exosome-mediated metastasis: from epithelial-mesenchymal transition to escape from immunosurveillance. *Trend Pharmacol. Sci,* 37: 606-617.
8. Garrido F, Romero I, Aptsiauri N, *et al.* Generation of MHC class I diversity in primary tumors and selection of the malignant phenotype. *Int. J. Cancer,* 2016; 138: 271-280.
9. Balkwill FR, Capasso M, Hageman T. The tumor microenvironment at a glance. *J. Cell Sci,* 2012; 125: 5591-5596.
10. Dong H, Storm SF, Salomao DR, *et al*. Tumor associated B7-H1 promotes T cell apoptosis: A potential mechanism of immune evasion. *Nature,* 2002; 8: 793-800.
11. Borrege F, Ulbercht M, Weiss EH, *et al*. Recognition of human histocompatibility leukocyte antigen (HLA. -E complexed with HLA class I signal sequence-derived peptides by CD94/NKG2 confers from natural killer cell-mediated lysis. *J. Exp. Med,* 1998; 187: 813-818.
12. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature,* 2011; 480-489.
13. Nathan MR, Schmid P. The emerging word of breast cancer immunotherapy. *Breast,* 2018; 37: 200-206.
14. Balasubramanian R, Rolph R, MorganC, Hamed H. Genetics of breast cancer: Management sxtrategies and risk-reducing surgery. *Br. J. Hosp. Med,* 2019; 80: 720-725.
15. Leit AM, Macedo AV, Jorge AJ, Martins WA. Antiplatelet therapy in breast cancer using hormonal therapy: Myths, evidence and potentialities-systemic review. *Arquivous Brasileiros de Cardiologia,* 2018; 111: 205-212.
16. Rosenberg SA, Yang JC, Sherry RM, *etal*. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. *Clinical Cancer*, 2011, 17: 4550-4557.
17. Shaffer DR, *et al.* In cancer immunotherapy: Paradigms, Practice, Promise. Curiel, TJ *ed.* Springer publishing, New York, 2013; 47-70.
18. Yiping Y. Cancer immunotherapy: Harnessing immune system to battle cancer. *J. Clin. Invest,* 2015; 3335-3337.
19. Fein S, Kong W, *et al*. An introduction to chimeric antigen receptor (CAR. T-cell immunotherapy for cancer. *Am. J. Hematol,* 2019; 94: S3-S9.
20. Disi ML, Stanton SE. Immunotherapy in breast cancer: An introduction. *Breast,* 2018; 196-199.
21. Magarian-Blander J, et al. Differential expression of MUC1 on transfected cell lines influences its recognition by MUC1 specific t cells. *Glycoconj. J,* 1996; 13: 749-756.
22. Inokuma M, et al. Functional T cell responses to tumor antigens in breast cancer patients have a distinct phenotype and cytokine signature. *J. Immunol,* 2007; 179: 2627-2633.
23. Fracol M, et al. Loss of anti-HER-3 CD4þ T-helper type 1 immunity occurs in breast tumorig-enesis and is negatively associated with outcomes. *Ann. Surg. Oncol,* 2017; 24: 407-417.
24. Woo SR, Corrales L, Gajewski TF. The STING pathway and the T cell-inflamed tumor microenvironment. *Trends Immunol,* 2015; 36: 250-256.
25. Chen DS, Mellman I. Elements of cancer immunity and cancer the cancer-immune set point.
26. *Nature* 2017; 541: 321-330.
27. Cimino-Mathews A, Thompson E, Taube JM, Ye X, Lu Y, Meeker A, *et al*. PD-L1 (B7-H1. expression and the immune tumor microenvironment in primary and metastatic breast carcinomas. *Hum. Pathol*, 2016; 47: 52-63.
28. Garrido-Castro AC, Lin NU, Polyak K. Insights into molecular classifications of triple-negative breast cancer: improving patient selection for treatment. *Cancer Discov,* 2019; 9: 176–198.
29. Marra A, Viale G, Curigliano G. Recent advances in triple negative breast cancer: The immunotherapy era. *BMC Medicine,* 2019; 17: 90-96.
30. Li X, Li M, Lian Z, *et al*. Prognostic role of programmed death ligand-1 expression in breast cancer: a systematic review and meta-analysis. *Target Oncol,* 2016; 11: 753–761.
31. Bae SB, Cho HD, Oh MH, Lee JH, Jang SH, Hong SA, *et al*. Expression of pro- grammed death receptor ligand 1 with high tumor-infiltrating lymphocytes is associated with better prognosis in breast cancer. *J. Breast Cancer,* 2016; 19: 242-251.
32. Luen SJ, Salgado R, Fox S, Savas P, *et al.* Tumor infiltrating lymphocytes in advanced HER2-positive breast cancer treated with pertuzumab or placebo in addition to trastuzumab and docetaxel: a retro- spective analysis of the CLEOPATRA study. *Lancet Oncol,* 2017; 18: 52-62.

33. Tung NM, Winer EP. Tumor-infiltrating lymphocytes and response to platinum in triple-negative breast cancer. *J. Clin. Oncol. Off J. Am. Soc. Clin. Oncol*, 2015; 33: 969-971.
34. Kroemer G, Senovilla L, Galluzzi L, *et al.* Natural and therapy-induced immunosurveillance in breast cancer. *Nat. Med,* 2015; 21: 1128–1138.
35. Pol J, Vacchelli E, Aranda F, *et al*. Trial watch: immunogenic cell death inducers for anticancer chemotherapy. *Oncoimmunology*, 2015; 4: 66-88.
36. Stanton SE, *et al*. Concurrent SPECT/PET-CT imaging as a method for tracking adoptively transferred T-cells in vivo. *J. Immunother.* Cancer, 2016; 4: 27-31.
37. Czerniecki BJ, *et al*. Targeting HER-2/neu in early breast cancer development using dendritic cells with staged interleukin-12 burst secretion. *Cancer Res,* 2007; 67: 184-152. 37. Shiao SL, Coussens LM. The tumor-immune microenvironment and response to radiation therapy. *J. Mammary Gland Biol. Neoplasia,* 2010; 15: 411-421.
38. Zitvogel L, *et al.* Mechanism of action of conventional and targeted anticancer therapies: reinstating immunosurveillance. *Immunity,* 2013; 39: 74-88.