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Review Article

Current understanding of the cardiotoxicity-related treatment of immune checkpoint inhibitors in breast cancer

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Abstract

Immune Checkpoint Inhibitors (ICIs) as the most important and widely used currently, have changed the traditional approach to cancer treatment and significantly improved the prognosis of most patients with advanced malignancies. Breast cancer is the most dangerous threatening tumor to women's health and life globally, ICIs have shed light on the treatment for refractory breast cancer subtypes, including Triple-Negative Breast Cancer (TNBC) and trastuzumab resistance of human epidermal growth factor receptor 2 positives (HER2+). However, immune-related adverse events (irAE) associated with ICIs bring many extra considerations. Among these, potential cardiotoxicity is rarely seen but with the highest fatality rate. In the present review, we introduced the ICIs approved for the treatment of breast cancer and brief guideline for clinical application. Then we briefly summarized ICIs-related cardiotoxicity in breast cancer and mechanism based on immunology and basic medical research. Furthermore, we make a brief summary of the diagnosis methods.

Introduction

According to the global cancer statistics in 2018, breast cancer is still the most commonly diagnosed female cancer with over 2 million new cases, and remains the first leading cause of tumor death with over 600 000 in women [1]. Surgery and neoadjuvant therapy are still important treatments for breast cancer patients. The specific approach depends on the immunohistochemical characteristic of subtypes like neoadjuvant chemotherapy for TNBC, neoadjuvant targeted therapy combined with chemotherapy for HER2+ or Luminal B subtype accompanied with HER2+, neoadjuvant endocrine therapy for Luminal A subtype [2]. Although these comprehensive therapy approaches have improved the prognoses for breast cancer patients, patients diagnosed with unresectable locally advanced or metastatic TNBC as an aggressive disease have a low survival rate.

During the past decade, many prominent scientific successes have decisively shown the efficacy of cancer immunotherapy applied in oncotherapy. It has shed light on improving survival rates in breast cancer patients with poor prognoses, especially for TNBC or HER2+ subtypes [3,4]. Considering that tumor cells especially those of malignant cancer always escape from immune monitoring via activating the inhibitive signal pathway, the immune checkpoint pathway which inhibits the antitumor immune response [5]. The aim of cancer immunotherapy is to change the immunosuppression of tumor cells and reactivate the body's immune response to kill tumor cells. Medical researchers have been in hot pursuit of it as the most cutting-edge therapy in the anti-tumor field.

Among these, immune checkpoint inhibitors (ICIs) have become a new hope [6]. By blocking the signal pathway of co-suppression, ICIs activate antitumor immunity and facilitate the process of wiping out tumor cells mediated by immunity. Represented by both inhibitors of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and inhibitors of programmed cell death 1 (PD-1) on activated T cells, or inhibitors of programmed cell death 1 ligand (PD-L1) on tumor cells against

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these three upregulated significantly immunosuppressive molecules [7]. It has been proved by a previous study one of the PD-1 blockades, pembrolizumab has auxiliary improvement prognosis effects for patients with advanced, ER+/HER2+/PD-L1-positive breast cancer [8]. However, there are already a number of proven cases showing the distinctive adverse reaction of ICIs, the immune-related adverse events (irAE) [9]. Generally, irAE is the result of immunological enhancement and any organs of the body can be affected. Cardiotoxicity of irAE is a severe adverse reaction, including heart failure, myocardial infarction, cardiac arrest, cardiac tamponade, and myocarditis [10]. Medical workers should pay high attention to ICI-related cardiotoxicity as its life-threatening side effects. Here, we reviewed cardiotoxicity related to ICIs treatment for breast cancer patients.

Different combinations of ICIs and chemotherapy for breast cancer

Breast cancer is one of the less immunogenic tumors compared to non-small cell lung cancer (NSCLC) or melanoma, two types of malignant cancers with higher immunogenic [11]. Yet among all molecular subtypes of breast cancer, HER2+ and TNBC have relatively higher immunogenicity due to a higher count of tumor-infiltrating lymphocytes and higher expression levels of PD-1 or PD-L1 [12]. However, most clinical trials of monotherapy conducted with inhibitors of anti-PD-1 or PD-L1 in metastatic TNBC patients have not shown a benefit [13,14]. Given the antigenicity of tumor cells can be improved by chemotherapy through antigen release and tumor antigen presentation, the combination of ICIs and chemotherapy was that the next step for TNBC patients of PD-L1-positive, and many clinical trials have revealed the impressive efficacy [15,16]. Other clinical trials of partners for ICIs like PARP inhibitors have been studied with the expectation of efficacy [17]. Also, one research about one promising blockade target, an oncogene of signal transducer and activator of transcription 3 (Stat3) in breast cancer revealed that patients would benefit from an activated innate immune system and enhanced efficacy of ICIs with the help of lose dose of agents of Stat3-blocking [18].

Clinical trials or pre-clinical studies around PD-1, PD-L1, or CTLA-4 blockades for breast cancer including nivolumab, pembrolizumab, atezolizumab, avelumab, ipilimumab and tremelimumab [19-24]. Among them, pembrolizumab or atezolizumab is associated with chemotherapy in clinical trials that accounted for the most [25]. For early TNBC, several clinical trials showed pembrolizumab to neoadjuvant chemotherapy significantly increases the proportion of patients who have an immune response [26, 27]. In March 2019, the United States Food and Drug Administration (FDA) authorized the first approval for the treatment of atezolizumab combined with nab-paclitaxel used for PD-L1-positive advanced TNBC patients [28].

The aim of atezolizumab or pembrolizumab is to prevent interactive effects between PD-L1 and its receptor PD-1, reversing T-cell suppression. Benefits of atezolizumab or pembrolizumab as partners with nab-paclitaxel in PD-L1 positive patients of metastatic TNBC can be found in many previous clinical trials, which at least showed facts of the efficiency of ICIs for TNBC patients, Table 1 [29-32].

ICIs, immune checkpoint inhibitors; PTX, paclitaxel; TNBC, triple-negative breast cancer; PD-L1, programmed cell death 1 ligand; CPS, combined positive score; PFS, progression-free survival; OS, overall survival.

One clinical phase 3 trial (NCT02425891) published in The New England Journal of Medicine (NEJM) showed that compared with placebo plus nab-paclitaxel, patients with metastatic TNBC who received atezolizumab plus nab-paclitaxel showed a longer median overall survival (OS) and progression-free survival (PFS) [29]. The difference in both OS and PFS was more significant when the survival data only count patients with PD-L1-positive. This trial involved 902 patients at a 1:1 ratio for each group. Another clinical phase 1b trial (NCT01633970) involving 33 patients with metastatic TNBC published in JAMA Oncology revealed the manageable safety profile of atezolizumab plus nab-paclitaxel [30]. The efficacy of pembrolizumab combined with nab-paclitaxel was proved in one phase 3 clinical trial (KEYNOTE-355) [31]. In this placebo-controlled trial, researchers put more emphasis on TNBC patients with PD-L1-positive. The expression of PD-L1 was assessed by a Combined Positive Score (CPS). Patients with PD-L1-positive, CPS ≥ 10 showed a significant PFS compared with CPS ≥ 1. The phase 1b trial ENHANCE1 showed the efficacy of the combination of pembrolizumab with eribulin in TNBC [32]. Obviously, the PD-L1 expression level of breast cancer patients is crucial, when tumor-infiltrating immune cells need to be taken into consideration to inform treatment choices.

Table 1: Some clinical trials of ICIs in combination with chemotherapy for the treatment of breast cancer.

Study	Regimen	Phase	Subtype	Patients Number	PFS (median; months) [95% CI]	OS (median; months) [95% CI]
IMpassion130/ NCT02425891 [29]	Atezolizumab + nab-PTX vs. placebo + nab-PTX	III	TNBC TNBC/PD-L1+	451	7.2[-] *vs.* 5.5[-] 7.5[-] *vs.* 5.0[-]	21.3[-] *vs.* 17.6[-] 25.0[-] *vs.* 15.5[-]
NCT01633970 [30]	Atezolizumab + Albumin-bound nab-PTX	Ib	TNBC	33	5.5[5.1-7.7]	14.7[10.1-NE]
KEYNOTE-355 [31]	Pembrolizumab + nab-PTX	III	TNBC PD-L1 CPS≥10 PD-L1 CPS≥1	566 103 211	9.7[-] *vs.* 5.6[-] 7.6[-] *vs.* 5.6[-]	-
ENHANCE1 [32]	Pembrolizumab + eribulin	Ib /II	TNBC	167	4.1[3.5-4.2]	16.1[13.3-18.5]

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Cardiotoxicity caused by blockade of PD-L1/PD-1 / CTLA-4 in breast cancer

Though immunotherapy is expected to be a promising treatment strategy for breast cancer, irAE can be caused by using ICIs inevitably [9]. Immuno-enhancing activity causing irAE is associated with immune checkpoint blockade and can involve any organ including the skin, gastrointestinal tract, liver, endocrine system, and rare inflammatory reactions. For instance, anemia, neutropenia, and thrombocytopenia are commonly seen in the blood system; such as increased aspartate aminotransferase and alanine aminotransferase in the digestive system. Notable among them is immune-related cardiotoxicity which is likely to cause life danger and requires great attention as well as monitoring. Cardiotoxic reactions of irAE consist of arrhythmia, heart failure, myocardial infarction, cardiac arrest, cardiac tamponades, and myocarditis. Being conscious of cardiotoxicity related to irAE both oncologists and cardiologists is a prerequisite for preventing cancer patients die of heart disease unpredictably.

A growing number of researchers have reported cardiotoxicity related to ICIs for patients with advanced malignant melanocytoma or advanced NSCLC, two types of high immunogenicity in cancer. At present, there is a rare report on cardiotoxicity related to ICIs for combination chemotherapy in breast cancer whether in case reports or clinical trials, Table 2. However, it deserves medical workers to keep an eye on this scarce side effect of its highest fatality rate [9].

ICIs, immune checkpoint inhibitors; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progestogen receptor; TNBC, triple-negative breast cancer; RT, radiation treatment.

Metastatic HER2+ breast cancer is far from curable and ICIs combined with trastuzumab are needed to perform for patients. In one double-blind, randomized, phase 2, placebo-controlled study, multicenter trial (KATE2) [33], patients diagnosed with HER2+ breast cancer received treatment of either trastuzumab emtansine plus atezolizumab or trastuzumab emtansine plus placebo. Severe adverse events occurred with 33% in the atezolizumab group (43 of 132) and 19% in the placebo group (13 of 68). Among these, arrhythmia was observed with 1 case with atrial fibrillation and 1 case with supraventricular tachycardia (grade 3) in the atezolizumab group; 1 case with atrial fibrillation in the placebo group (grade 1-2). In another single-arm, multicenter, phase 1b-2 trial [34], intravenous pembrolizumab plus trastuzumab for breast cancer patients who received previous trastuzumab-based therapy with advanced HER2 positive and PD-L1 positive. 52 patients in phase 2 (PD-L1+/n = 40; PD-L1-/n = 12) were enrolled in this study and 6 of 40 with PD-L1 positive showed a positive response while no response was in PD-L1 negative group. Pericardial effusion was reported among serious adverse events with 3% in PD-L1-positive breast cancer. In one phase I dose escalation study [35], the safety of tremelimumab, a humanized monoclonal antibody of anti-CTLA-4 combined with radiation treatment was assessed at starting dose (3 mg/kg), and one dose-limiting toxicity occurred at 6mg/kg. Most patients received prior chemotherapy. Dyspnea (grade 1) happened in one patient approximately 1 week after receiving tremelimumab.

Myocarditis: potentially lethal cardiotoxicity of ICIs in breast cancer

In 2016, NEJM initially reported two cases of fatal myocarditis related to treatment with ipilimumab and nivolumab [36]. Subsequently, the occurrence of severe cardiac complications has raised concerns about tumor immunotherapy. Myocarditis-associated ICIs were the serious side effect and one literature reported the incidence of myocarditis related to ICIs is 0.1%~1.0% and the case fatality rate is 25%~50% [37]. Fulminant cases of ICI-related myocarditis are reported in melanoma and lung cancer, while there are rare reports in breast cancer. Obviously, it is a warning for clinicians when using ICIs for breast cancer patients.

One piece of literature first reported the life-threatening adverse effect of pembrolizumab, one type of ICI for anti-PD-1 immunotherapy [38]. A 73-year-old woman who was diagnosed with metastatic uveal melanoma developed severe heart failure due to autoimmune myocarditis mediated by pembrolizumab as a third-line treatment after five weeks. The clinical manifestations included gradual dyspnea depending on the Heart Association of New York (NYAH4), jugular vein congestion, moist rales in bilateral lungs, and edema of lower extremities. An Electrocardiogram examination suggested sinus tachycardia accompanied by ventricular premature contraction. A severe decrease in Left Ventricular Ejection Fraction (LEVF) was revealed by echocardiography and desynchrony of myocardial contractions. Laboratory examination showed an increase for Both Natriuretic Peptide (BNP) and hypersensitive troponin (hs-TnT) at 928ng/L and 0.63ug/L respectively. The cardiac check for a virus was negative. Myocardial tissue biopsy showed predominant lymphocyte infiltration of CD8 positive T cells while FOXP3 positive regulatory T cells decreased.

Table 2: Cardiotoxicity cases related ICIs treatment in breast cancer.

Study	Regimen	Phase	Subtype	Patients Number (ICIs/control)	Cardiotoxicity profile	Control
NCT02924883 [33]	atezolizumab +trastuzumab	II	HER2+	132/68	atrial fibrillation 1(1%) + supraventricular tachycardia 1(1%); grade 3	Atrial fibrillation 1(1%); grade 1-2
NCT02129556 [34]	Pembrolizumab + trastuzumab	Ib-2	HER2+	40/12	pericardial effusion 2(3%)	-
Di Maria Jiang, et al. [35]	Tremelimumab + RT	I	ER/PR+ 5 TNBC 1	6	dyspnea 1(17%); grade 1	-

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Symptoms improved and left ventricular function recovered after 2 weeks of treatment with prednisone at 2 mg/kg and guideline-conformed heart failure therapy. This was the first reported case of autoimmune myocarditis induced by PD-1 blockade, recovered after high-dose corticosteroid therapy.

In a study performed in 2017 using VigiBase, an individual safety case reported that 46 deaths occurred in a total of 101 cases with severe myocarditis according to WHO's database [39]. Besides, the case fatality rate of combining anti-PD-1 or PD-L1 with anti-CTLA-4 was 67%, which was higher than monotherapy with any of them at 36%. Clinical manifestations of myocarditis related to ICIs range from the asymptomatic increased level of cardiac biomarkers to heart failure, arrhythmias, and Cardiogenic Shock (CGS). Electrocardiograms, markers of myocardial injury, and imaging findings of the heart play a crucial role in the assessment of cardiotoxicity. The myocardial biopsy of the endocardium is the reference standard scale for diagnosing myocarditis. The recommended approach to symptomatic patients was drug withdrawal and intravenous methylprednisolone at a daily dose of 1 mg/kg [40].

The mechanism of ICIs-related cardiotoxicity in breast cancer

There are at least two mechanisms for the cause of cardiotoxic reactions from the immunological perspective. One is a decrease of cardiac peripheral tolerance of immune-mediated by PD-1 or CTLA-4 pathways. The other is a common antigen owned by the heart and tumor-targeted by T-cells simultaneously [10,41]. Two cases of fatal myocarditis were reported in one literature using the regimen of ipilimumab and nivolumab for melanoma patients, providing evidence of the hypothesis of common antigens [42]. Mechanistically, with the high level of muscular specific antigens such as desmin or troponin simultaneously present in cancers and myocardium, and then selective T-cell activation, as well as T-cell infiltrating populations can identify them equally.

Apart from immunological mechanisms, intracellular changes such as an increase of intracellular calcium overload or change of cytokines are accompanied by the occurrence of cardiotoxicity when ICIs used for breast cancer patients. Compared with the untreated group, the combination of pembrolizumab and trastuzumab in breast cancer cells revealed a threefold in intracellular calcium overload [43]. Furthermore, the survival rate of cardiomyocytes in the untreated group and treated group showed a significant difference at 65% and 20-25% respectively. It strongly suggested the cardiotoxicity of the combination of pembrolizumab and trastuzumab. Also, compared with treatment with trastuzumab alone, trastuzumab combined with pembrolizumab for myocardial cells increased the expressed level of NF-kB, interleukins, and leukotriene B4. Another study for the mechanism of cardiotoxicity-related Cardiac Irradiation (CIR) together with ICIs has found that radiation-induced cardiotoxicity (RICT) for breast cancer therapy was compounded by concurrent use of PD-1 blockade in a mouse model [44]. Researchers subsequently found an acute mortality of 30% within two weeks in CIR/anti-PD-1 compared with 0% of control. According to tissue analyses, CD8+ cells mediated the occurrence of toxicity.

Biomarkers of ICIs-induced cardiotoxicity are expected to for reducing cardiovascular side effects and improve anticancer responsiveness. A study focused on the ipilimumab-induced anticancer efficacy and its cardiotoxicity in breast cancer cells under the condition of hyperglycemia [45]. The result revealed that the NLR family pyrin domain containing 3 (NLRP3) is a valid biomarker of ipilimumab-induced cardiotoxicity under hyperglycemia. As hyperglycemia is considered a negative prognostic factor for breast cancer patients, researchers used human cardiomyocytes, ER+ (MCF-7), and TNBC (MDA-MB-231) cell lines. These cells were exposed to ipilimumab together with glucose at various concentrations and they found NLRP3 is the new biomarker of cardiotoxicity and resistance to ICIs. This study also revealed that hyperglycemia increases cardiotoxicity and reduces mortality of MCF-7 or MDA-MB-231 cell lines during the treatment of ipilimumab.

Diagnosis and evaluation of cardiotoxicity of ICIs-related in breast cancer treatment Electrocardiograph (ECG)

One literature reported myocarditis caused by ICIs can result in a series of changes in ECG, including conduction abnormalities (17%), ventricular arrhythmia (27%), and atrial fibrillation (30%) [46]. However, considering only 30 cases were counted in this literature, other types of ECG abnormalities also have important implications, including sinus tachycardia, atrial tachycardia, atrial fibrillation, and ventricular tachycardia. Taking the convenience of ECG into consideration, it is recommended that ECG should be performed for all patients who are about to receive ICIs treatment. Furthermore, regular ECG examination during late follow-up is needed in order to make a controlled and continuous assessment. In comparison with previous ECG results, an in-depth analysis of whether there is any dynamic and new change existing after medication in ECG or whether these changes are consistent with clinical manifestations is recommended.

Serum indicators of myocardial injury

A good indicator, the level of B-type Natriuretic Peptide (BNP) is useful in identifying Heart Failure (HF) as well as left ventricle dysfunction. Though it lacks specificity for diagnosing cardiac injury caused by ICIs-related cardiotoxicity, there are significant correlations exist between markers of inflammation and BNP and it is associated with increased left ventricular mass index (LVMI) and Left Atrial Volume Index (LAVI) of echocardiography [47]. For the diagnosis of ICIs-related myocarditis myocardial injury markers mainly includes troponin, CK-MB, and total CK. Compared with CK-MB and total CK, troponin I (cTnI) has the optimal specificity according to the guideline of Cardio-Oncology in 2019 [46]. One research found that the increased level of soluble suppression of tumorigenicity 2 (sST2) in serum is associated with an increased risk of cardiac failure according to the NYHA class in male patients with myocarditis less than or equal to 50 years old [48], but whether sST2 has indication effect of ICIs-related cardiotoxicity remains further exploration.

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Echocardiography (UCG) and Cardiovascular Magnetic Resonance (CMR)

In 2006, guidance papers promulgated by the European Society of Cardiology (ESC) recommend Speckle Tracking Imaging (STI) of echocardiography (UGG) should be used as a first-line method to screen and follow-up incidence of cardiotoxicity in cancer patients [49]. In multiple parameters of STI, one study revealed a sensitive and significant marker, low global longitudinal strain (GLS), that can strongly be correlated with Major Adverse Cardiac Events (MACE) in ICIs-related myocarditis for patients who received an ICI [50]. Considering the noninvasive and economical characteristics, UCG has great value for the diagnosis of ICI-related cardiotoxicity.

Cardiovascular Magnetic Resonance (CMR) plays an important role in identifying subtle morphological and functional changes in the myocardium. One literature revealed techniques of novel T1, T2, or extracellular volume mapping have possibilities of providing significant evidence of cardiotoxicity and therefore CMR is possibly a valuable tool to identify and predict subclinical cardiotoxicity in breast cancer [51]. However, another study showed the opposite view about the application of CMR for identifying cardiotoxicity. Their findings showed there is no obvious correlation between late gadolinium enhancement (LGE) and pathological fibrosis as well as T2-weighted Short Tau Inversion Recovery (STIR) and myocardial edema [52]. It may indicate that the predicting value of CMR for ICIs-related cardiotoxicity in breast cancer is not so reliable currently. Still, it remains to provide useful information about the heart and we need to be careful about the occurrence of cardiac reverse reaction even if it comes out with a negative result.

Conclusion

ICIs have become the most promising immunotherapies for cancer and bring new hope for the therapy of refractory and aggressive breast cancer subtypes. Better responsiveness for ICIs of TNBC can be due to its higher immunogenicity and higher enrichment of infiltrating immune cells. PD-L1 positive subtypes of breast cancer also appear to higher response to oncotherapy of ICIs. Compared with monotherapy of ICIs for breast cancer, many clinical trials of atezolizumab or pembrolizumab combined with chemotherapy indicate better efficacy, especially for PD-L1 positive in TNBC and HER2+ of trastuzumab resistance. Immune-related adverse events accompanied raise a concern about the use of ICIs especially potential cardiotoxicity in breast cancer treatment. Monotherapy or two types of PD-1, PD-L1, or CTLA-4 blockade can raise the likelihood of cardiotoxicity when compared to the combination of chemotherapy for breast cancer. We put more emphasis on the high mortality and severity of ICIs-related myocarditis even if it rarely reports breast cancer treatment. The theory of a common antigen as well as the decrease of peripheral immune tolerance can account for the occurrence of cardiotoxicity in breast cancer. Besides, an increased intracellular calcium overload in breast cancer cells and the increased expressed level of NF-kB, interleukins, and leukotriene B4 in myocardial cells when it occurs. To reduce cardiovascular side effects and improve anticancer responsiveness, biomarkers of ICIs-induced cardiotoxicity are informative. Routine diagnostic methods of myocardial disease including ECG, UCG, CMR, and indicators of myocardial injury are necessary for diagnosing ICI-related cardiotoxicity in breast cancer. Specific measurements of cardiotoxicity require great attention for cardiologists and breast cancer doctors. In short, we should not only understand the ICIs by their efficacy in immunotherapy of breast cancer, but we also need to apprehend the potential side effect meanwhile.

Author contributions

Jiajing Dai designed the main ideas, and table production, and wrote the original draft.

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