The State-of-the-Art of Immunotherapy in the Triple-Negative Breast Cancer Treatment: Main Drugs, Combinations, Mechanisms of Action and Future Perspectives

doi: https://doi.org/10.32635/2176-9745.RBC.2021v67n2.1014

O Estado da Arte da Imunoterapia no Tratamento do Câncer de Mama Triplo-Negativo: Principais Drogas, Associações, Mecanismos de Ação e Perspectivas Futuras

El Estado del Arte de la Inmunoterapia en el Tratamiento del Cáncer de Mama Triple Negativo: Principales Fármacos, Asociaciones, Mecanismos de Acción y Perspectivas de Futuro

Dione Fernandes Tavares[1]; Laércio Moreira Cardoso-Júnior[2]; Victoria Chaves Ribeiro[3]; Renata Lopes Britto[4]

ABSTRACT

Introduction: Breast cancer is the most commonly diagnosed cancer in women and is one of the leading causes of death from cancer in women worldwide. Despite, or perhaps because of its aggressive nature and current lack of targeted treatments, significant basic research and clinical trials are being conducted to provide new treatment options. Historically, chemotherapy has been the only viable systemic treatment option for early and advanced diseases. However, recently published clinical trials have shown that immunotherapy plays an important role in the treatment paradigm of this devastating clinical condition. **Objective:** To demonstrate the state-of-the-art results of immunotherapy in the treatment of triple-negative breast cancer. **Method:** An integrative literature review was carried out between January/2020 and March/2020, in PubMed, SciELO, International Clinical Trials Registry Platform and LILACS databases, using the keywords "Immunotherapy", "Breast Cancer", and "Triple Negative Breast Cancer" and its respective correspondents in Portuguese. **Results:** 465 articles were found; of those, 457 were excluded after applying the methodological criteria. Thus, 8 articles that met the inclusion criteria, showing the main therapeutic agents used, mechanisms of action and therapeutic combinations, remained. 25 clinical trials were found in progress on the International Clinical Trials Registry Platform. **Conclusion:** Although immunotherapy is somewhat recent, its results with PARP, PD-1 and PD-L1 inhibitors have shown satisfactory results. New trials with subgroups stratified according to specific tumor biomarkers are needed in order to assess if some subgroups have greater benefit to treatment.

Key words: Immunotherapy; Breast Neoplasms/therapy; Triple Negative Breast Neoplasms; Biomarkers.

RESUMO

Introdução: O câncer de mama é o mais comumente diagnosticado em mulheres e uma das principais causas de morte por câncer em mulheres em todo o mundo. Apesar, ou talvez por causa, de sua natureza agressiva e da falta de tratamentos direcionados atuais, pesquisas clínicas e laboratoriais significativas estão fornecendo opções de tratamento diferenciadas. Historicamente, a quimioterapia tem sido a única opção viável de tratamento sistêmico para doenças precoces e avançadas. No entanto, ensaios clínicos publicados recentemente mostraram que a imunoterapia tem um papel importante no paradigma de tratamento dessa condição devastadora. **Objetivo:** Demonstrar o estado da arte da imunoterapia no tratamento do câncer de mama triplo-negativo. **Método:** Revisão integrativa de literatura, entre janeiro/2020 a março/2020, a partir das bases de dados PubMed, SciELO, *International Clinical Trials Registry Platform* e LILACS, por meio dos descritores "Imunoterapia", "Neoplasias da mama" e "Neoplasias de mama triplo negativas" e seus respectivos correspondentes em inglês. **Resultados:** Foram encontrados 465 artigos; destes, 457 foram excluídos após aplicação dos critérios metodológicos. Assim, restaram oito artigos que atendiam aos critérios de inclusão, demonstrando os principais agentes terapêuticos utilizados, mecanismos de ação e combinações terapêuticas. Encontraram-se 25 ensaios clínicos em andamento na plataforma de registro de ensaios clínicos *International Clinical Trials Registry Platform*. **Conclusão:** Embora a imunoterapia seja algo recente, seus resultados com agentes inibidores da PARP, PD-1 e PD-L1 demonstraram resultados satisfatórios. Novos ensaios com subgrupos estratificados de acordo com biomarcadores tumorais específicos são necessários, a fim de avaliar se algum subgrupo tem maior benefício ao tratamento.

Palavras-chave: Imunoterapia; Neoplasias da Mama/terapia; Neoplasias de Mama Triplo Negativas; Biomarcadores.

RESUMEN

Introducción: El cáncer de mama es el más comúnmente diagnosticado en las mujeres y es una de las principales causas de muerte por cáncer en mujeres de todo el mundo. A pesar de, o quizás debido a su naturaleza agresiva y la falta de tratamientos dirigidos actuales, investigaciones clínicas y de laboratorio significativas están proporcionando opciones de tratamiento diferenciadas. Históricamente, la quimioterapia ha sido la única opción viable para el tratamiento sistémico de enfermedades tempranas y avanzadas. Sin embargo, los ensayos clínicos publicados recientemente han demostrado que la inmunoterapia desempeña un papel importante en el paradigma del tratamiento de esta condición devastadora. **Objetivo:** Demostrar el estado del arte de la inmunoterapia en el cáncer de mama triple negativo. **Método:** Revisión integradora entre enero/2020 y marzo/2020, utilizando las bases de datos PubMed, SciELO, *International Clinical Trials Registry Platform* y LILACS, empleando las palabras clave "Inmunoterapia", "Cáncer de mama" y "Cáncer de mama triple negativo" y los respectivos términos en inglés. **Resultados:** Se encontraron 465 artículos; de estos, 457 fueron excluidos después de aplicar los criterios metodológicos. Así, quedaron 8 artículos que cumplían los criterios, que mostraban los principales agentes terapéuticos utilizados, mecanismos de acción y combinaciones terapéuticas. Se encontraron 25 ensayos clínicos en progreso en la plataforma *International Clinical Trials Registry Platform*. **Conclusión:** Aunque la inmunoterapia es algo reciente, sus resultados con inhibidores de PARP, PD-1 y PD-L1 han mostrado resultados satisfactorios. Se necesitan nuevos ensayos con subgrupos estratificados según biomarcadores tumorales específicos para evaluar si algún subgrupo tiene un mayor beneficio.

Palabras clave: Inmunoterapia; Neoplasias de la Mama/terapia; Neoplasias de la Mama Triple Negativas; Biomarcadores.

[1,2,4]Federal University of Bahia. Medical College of Bahia. Post-graduation Program of Medicine and Health. Salvador (BA), Brazil. E-mails: dionefernandestavares@gmail.com; laerciop53@gmail.com; renatalopesbritto@gmail.com.
Orcid iD: https://orcid.org/0000-0002-2438-5297; Orcid iD: https://orcid.org/0000-0003-0649-1237; Orcid iD: https://orcid.org/0000-0002-8852-7039
[3]University of São Paulo. Chemistry Institute. São Paulo (SP), Brazil. E-mail: victoriaribeiro@usp.br. Orcid iD: https://orcid.org/0000-0003-4612-3009
Corresponding author: Dione Fernandes Tavares. Programa de Pós-Graduação em Medicina e Saúde, Hospital Universitário Professor Edgard Santos. Rua Doutor Augusto Viana, S/Nº - Canela. Salvador (BA), Brazil. CEP 40110-060. E-mail: dionefernandestavares@gmail.com

INTRODUCTION

Breast cancer is a pathology with known variability in the clinical presentations and highly heterogeneous behavior consisting of different molecular subtypes. In this context, the tumor that does not present any of the three most used biomarkers in the classification of breast cancer is called "triple-negative". They are: estrogen receptor (ER), progesterone receptor (PR) and protein HER-2 (HER2)[1,2].

Breast cancer is the most typically diagnosed in women and one of the main causes of death by cancer in women worldwide. In Brazil, except non-melanoma skin cancer, it corresponds to nearly 29.7% of new cases each year[3]. For 2020 in Brazil, the estimate was 66,280 new cases, corresponding to the extremely high incidence of 61.61 cases per 100 thousand women[3]. Like other types of cancer, early diagnosis increases substantially the odds of success of the treatment, allowing a reduction of 20% of the general rates of mortality[4].

Despite the significant benefit of the use of conventional chemotherapy and utilization of monoclonal antibodies in the prognosis of patients with breast cancer, triple-negative breast cancer is still a great challenge. In light of this, the immunologic treatment of breast tumors is in full development in the last ten years with several studies utilizing inhibitor of poly (adenosine diphosphate-ribose) polymerase (PARP) and immune checkpoints inhibitors. The recent approval of anti-ligand antibody of programmed cell death 1 (anti-PD-L1) atezolizumab in combination with chemotherapy was a milestone for the treatment of patients with triple-negative breast cancer[5-12].

Therefore, the objective of this article is to demonstrate the current state-of-art of immunotherapy studies for the treatment of triple-negative breast cancer, investigating the main drugs, associations, mechanisms of action and future perspectives in patients with triple-negative breast cancer and different approaches that can be useful to improve the tumors response to immunotherapies.

METHOD

The present article reports an integrative review of the literature based in the recommendations for the elaboration of this type of review[13], whose survey of studies on the utilization of immunotherapy for triple-negative breast cancer treatment was conducted after the formulation of the research question: "What is the state-of-the-art of immunotherapy treatment for triple-negative breast cancer?" Firstly, the number of articles indexed in different databases searched was calculated, among which: a) Scientific Electronic Library Online (SciELO); b) Latin American and Caribbean System on Health Sciences (LILACS); c) U. S. National Library of Medicine (PubMed). The search occurred from January to March 2020.

After analyzing the Descriptors in Sciences of Health (DeCS), the following descriptors were selected to search the databases ScIELO and LILACS: "*Imunoterapia*", "*Neoplasias de Mama*" and "*Neoplasias de mama triplo negativas*". The survey of the Medical Subject Headings (MeSH) resulted in descriptors "Immunotherapy", "Breast Cancer", "Triple Negative Breast Cancer" and "TNBC" for searching the databases PubMed and in the platform of registration of clinical trials International Clinical Trials Registry Platform to detect possible future clinical trials, utilizing immunotherapy for the treatment of triple-negative breast cancer, describe the study phase and future perspectives.

The inclusion criteria consisted of articles in Portuguese or English from March 2010 to March 2020; the study design should match clinical trials using immunotherapy in patients aged or older than 18 years with diagnosis of triple-negative breast cancer with anatomopathological confirmation and immunohistochemistry regardless of the methodology. Articles of opinion, editorials, case and/or experience reports, letter to the editor and comments were excluded. Based in the final selection of articles, the following information were collected: classification of the type of cancer, drugs utilized, clinical phase, associations among immunotherapy and other existing therapies, mechanism of action and future perspectives. From the platform of registration of clinical trials International Clinical Trials Registry Platform, the following information of ongoing clinical trials were extracted: number of the registration, configuration, study phase, drugs utilized, institution conducting the trial, country, status of the work.

RESULTS

Because of the lack of articles in the databases SciELO and LILACS, only articles found in PubMed were utilized. Based in the search strategies, initially 465 publications were encountered. After duplicates (n=69) were removed, 396 articles were screened with reading of titles and abstracts from which the reviewers excluded 347. The remaining 29 articles were read in full for application of the eligibility criteria, reaching the final inclusion of eight studies that met the inclusion criteria. The detailed search strategy can be seen in Figure 1. It is important to emphasize that in the search process, only three reviews about the theme were found, none of them addressed the work developed in this article.

After the methodological processes of identification, screening and eligibility of the studies (Figure 1), it was possible to identify and gather the main information about the classification of cancer and its current clinical stage, the immunotherapeutic drug and its mechanism of action in the immune system, in addition to its possible association with chemotherapic agents already widely utilized. The stratified data of the articles included in the qualitative synthesis can be seen in Table 1.

In relation to the future perspectives of utilizing immunotherapy in triple-negative breast cancer, a search of ongoing clinical trials in the PubMed-supported platform ClinicalTrials.gov with registries of studies of 210 different countries was conducted. In Table 2, different researches conducted in different regions utilizing immunotherapy in triple-negative breast cancer are presented.

DISCUSSION

Programmed cell death protein 1 (PD-1) is a regulating protein on the surface of effector cells of the immune system, the T cells with inhibitory action. In physiological conditions, its interaction with its ligand (PD-L1) promotes the regulation of the immune reaction, reducing the effector action of the immune system. Thus, when expressed in the surface of tumoral cells, ligand PD-L1 allows the evasion of the immune response by the tumor[13]. As scientific knowledge advances, the role of the interaction of PD-1 with its ligand-receptor PD-L1 was highlighted as important inhibitory pathway that can be sequestered by tumors to suppress the immune checkpoint[13].

When ligands PD-1 bind to PD-1, the activation of T cells through the receptor of T cells is inhibited. PD-L1, the PD-1 ligand is predominantly involved in the negative regulation of the functions of T cells in the peripheral tissue and can be expressed in several types of cancer, this is why the application of PD-1/PD-L1 inhibitory agents is also investigated in other types of cancer with promising results as in the case of melanoma. Consequently, the interruption of this regulating system has become one of the most attractive therapeutic targets in cancer immunotherapy in the last ten years as demonstrated in many clinical trials portrayed in this article (Table 1) with six to eight studies listed[13,14].

Atezolizumab is a monoclonal antibody already used in the treatment of lung and bladder cancers, its mechanism of action consists in the inhibition of PD-L1. Two clinical trials with this drug were encountered. In the first, atezolizumab was associated with a taxane, nab-paclitaxel, whose results demonstrated the extension of the survival-free progression of metastatic triple-negative breast cancer

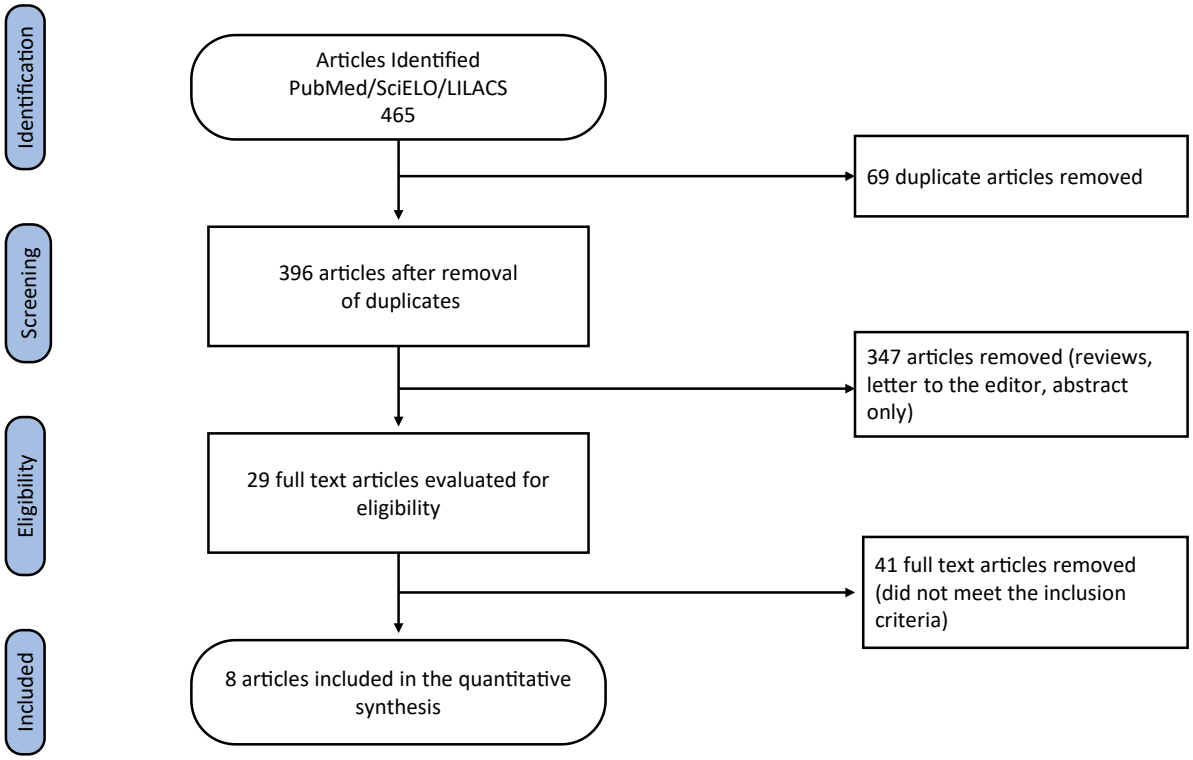

Figure 1. Flowchart of the selection of the articles in different stages of the review

Table 1. Main drugs, associations and mechanisms of actions of immunotherapy for the treatment of triple-negative breast cancer described in clinical trials

Author/year	N	Classification of cancer	Drug	Association	Mechanism of Action
Schmid et al., 2018[5]	902	Metastatic advanced triple-negative breast cancer	Atezolizumab	Nab-paclitaxel	PD-L1 Inhibitor
Emens et al., 2019[10]	116	Advanced triple-negative breast cancer	Atezolizumab	Monotherapy	PD-L1 Inhibitor
Dirix et al., 2018[9]	58	Triple-negative breast cancer	Avelumab	Monotherapy	PD-L1 Inhibitor
Nanda et al., 2016[6]	32	Advanced triple-negative breast cancer	Pembrolizumab	Monotherapy	PD-1 Inhibitor
Adams et al., 2019[7]	170	Untreatable advanced triple-negative breast cancer	Pembrolizumab	Monotherapy	PD-1 Inhibitor
Tolaney et al., 2018[8]	107	Advanced triple-negative breast cancer	Pembrolizumab	Eribulin	PD-1 Inhibitor + chemotherapy
Loibl et al., 2018[11]	316	Triple-negative breast cancer	Veliparib	Carboplatin	PARP Inhibitor + chemotherapy
Litton et al., 2018[12]	15	Operable triple-negative breast cancer with germline BRCA pathogenic variant	Talazoparib	Monotherapy + surgical resection	PARP Inhibitor

Captions: PD-1 = Programmed cell death protein 1; PD-L1= Programmed cell death ligand 1; PARP = Poly (ADP-ribose) Polymerase.

Table 2. Ongoing clinical trials utilizing immunotherapy for triple-negative breast cancer

Register	Configuration	Phase	Drugs	N	Institution (country)	*Status*
NCT03036488	Neoadjuvant/ Adjuvant	III	Pembrolizumab and chemotherapy versus placebo and chemotherapy as neoadjuvant therapy and pembrolizumab versus placebo as adjuvant therapy	1,174	*Merck Sharp & Dohme Corp.* (US)	Active, no enrollment currently
NCT03281954	Neoadjuvant/ Adjuvant	III	Chemotherapy and atezolizumab or placebo followed by adjuvant continuation of atezolizumab or placebo	1,520	*Nsabp Foundation Inc* (US)	Enrollment
NCT03197935	Neoadjuvant/ Adjuvant	III	Atezolizumab and neoadjuvant chemotherapy anthracycline/nab-paclitaxel based in comparison with placebo and chemotherapy	204	*Hoffmann-La Roche* (CH)	Active, no enrollment currently

to be continued

Table 2. continuation

Register	Configuration	Phase	Drugs	N	Institution (country)	*Status*
NCT03756298	Adjuvant only for patients with residual disease after neoadjuvant chemotherapy	II	Atezolizumab plus adjuvant therapy with capecitabine in comparison with monotherapy with capecitabine	284	*National Cancer Center* (KOR)	Enrollment
NCT03498716	Adjuvant	III	Atezolizumab and adjuvant anthracycline/ taxane based chemotherapy versus isolate chemotherapy	2,300	*Hoffmann-La Roche* (CH)	Enrollment
NCT03125902	Local or metastatic advanced triple-negative breast cancer	III	Atezolizumab in combination with paclitaxel compared with placebo associated with paclitaxel	540	*Hoffmann-La Roche* (CH)	Enrollment
NCT03164993	Local or metastatic advanced triple-negative breast cancer	II	Atezolizumab combined with immunogenic chemotherapy	75	*Oslo University Hospital* (NO)	Enrollment
NCT03206203	Local or metastatic advanced triple-negative breast cancer	II	Carboplatin with or without atezolizumab	185	*Vanderbilt-Ingram Cancer Center* (US)	Enrollment
NCT03371017	Local or metastatic advanced triple-negative breast cancer	III	Atezolizumab and chemotherapy	350	*Hoffmann-La Roche* (CH)	Enrollment
NCT02926196	Adjuvant	III	Avelumab as adjuvant treatment or post-treatment neoadjuvant	335	*Istituto Oncologico Veneto IRCCS* (IT)	Enrollment
NCT03639948	Neoadjuvant	II	Pembrolizumab and carboplatin plus docetaxel	100	*University of Kansas Medical Center (US)*	Enrollment
NCT03289819	Neoadjuvant	II	Neoadjuvant Pembrolizumab in combination with nab-paclitaxel followed by pembrolizumab in combination with epirubicin and cyclophosphamide	50	*Institut fuer Frauengesundheit* (GER)	Enrollment
NCT02954874	Adjuvant only for patients with residual disease after neoadjuvant chemotherapy	III	Pembrolizumab as adjuvant therapy	1,000	*National Cancer Institute* (US)	Enrollment
NCT02768701	Local or metastatic advanced triple-negative breast cancer	II	Cyclophosphamide in single dose associated with pembrolizumab	40	*UNC Lineberger Comprehensive Cancer Center* (US)	Active, no enrollment currently

to be continued

Table 2. continuation

Register	Configuration	Phase	Drugs	N	Institution (country)	*Status*
NCT03121352	Local or metastatic advanced triple-negative breast cancer	II	Carboplatin, nab-paclitaxel and pembrolizumab	30	*Case Comprehensive Cancer Center* (US)	Enrollment
NCT02819518	Local or metastatic advanced triple-negative breast cancer	III	Pembrolizumab plus chemotherapy versus placebo plus chemotherapy	858	*Merck Sharp & Dohme Corp.* (US)	Active, no enrollment currently
NCT02555657	Local or metastatic advanced triple-negative breast cancer	III	Pembrolizumab versus single agent chemotherapy	600	*Merck Sharp & Dohme Corp.* (US)	Active, no enrollment currently
NCT03644589	Local or metastatic advanced triple-negative breast cancer	II	Pembrolizumab and cisplatin	60	*Merck Sharp & Dohme Corp.* (US)	Not enrolled. Therapy based on medical choice
NCT02755272	Local or metastatic advanced triple-negative breast cancer	II	Pembrolizumab with carboplatin and gemcitabine	87	*Fox Chase Cancer Center* (US)	Enrollment
NCT02447003	Local or metastatic advanced triple-negative breast cancer	II	Monotherapy with pembrolizumab	285	*Merck Sharp & Dohme Corp.* (US)	Active, no enrollment currently
NCT03356860	Neoadjuvant	II	Durvalumab combined with neoadjuvant chemotherapy	57	*Grand Hôpital de Charleroi* (BE)	Enrollment
NCT02685059	Neoadjuvant	II	Durvalumab and chemotherapy with taxane/anthracycline	174	*German Breast Group* (GE)	Active, no enrollment currently
NCT03606967	Local or metastatic advanced triple-negative breast cancer	II	Nab-paclitaxel and durvalumab with or without neoantigen vaccine	70	*National Cancer Institute* (US)	Not enrolled. Therapy based on medical choice
NCT03616886	Local or metastatic advanced triple-negative breast cancer	II	Paclitaxel in association with carboplatin and durvalumab with or without oleclumab	171	*Jules Bordet Institute* (BE)	Enrollment
NCT03167619	Local or metastatic advanced triple-negative breast cancer	II	Durvalumab and olaparib in individuals treated with platinum-based chemotherapy	60	*Duke University* (US)	Enrollment

in the population treated and, in the subgroup, where PD-L1 was positive in the immunohistochemical evaluation. In addition, the adverse events were consistent with the safety profiles known of each drug, showing safety in the utilization[5]. The second brings the use of atezolizumab in individuals with metastatic triple-negative breast cancer who tried two lines of treatment before unsuccessfully. Now utilized as monotherapy, a durable clinical response was noticed in two years of follow-up. The patients with high infiltration of immune cells to the tumor, stained by immunohistochemistry had better clinical results[10].

Another PD-L1 inhibitor was found in one of the eight articles selected (Table 1). Avelumab was utilized in patients with local or metastatic advanced breast cancer who had previously submitted to three or more lines of treatment unsuccessfully. Because it is an initial study, the intention was to evaluate the safety of the drug use and the response was acceptable. There was a significantly enriched response for the group with immunohistochemistry expression of PD-L1, leading to the hypothesis that the expression of PD-L1 in immune cells associated tumors may be related to great likelihood of clinical response to avelumab[9].

In addition to PD-L1 inhibitors, there is also the PD-1 inhibitors represented here by pembrolizumab monoclonal antibody which was investigated in three of the eight articles included in this manuscript (Table 1). In the first, pembrolizumab was utilized as monotherapy in patients with advanced cancer where the preliminary evidences of the clinical activity and the safety profile were evaluated. The conclusion is that the drug is potentially acceptable although high rate of adverse events has been described. It is believed that they are connected to the dose administered[6]. In the second clinical trial, monotherapy was also utilized in patients with advanced cancer who had previously been treated unsuccessfully; in this case, three or more other lines of treatment failed. Monotherapy showed durable anti-tumor activity in a small subset of pre-treated patients with manageable safety profile and most of the adverse events were classified as low grade[7]. In the last article utilizing pembrolizumab, it was combined with eribulin in an initial study for safety evaluation with positive results. The adverse effects were compatible with what was observed with the treatment, utilizing one of the drugs as monotherapy[8].

Several combinations of different active principles have been utilized in clinical trials already completed (Table 1) and in ongoing clinical trials (Table 2). Chemotherapy, for instance, can induce multiple immunomodulatory alterations in the tumoral microenvironment, including the increase of the release of the antigen by tumoral cell, positive regulation of PD-L1 and hyper-expression of immunogenic markers of the cellular surface (for instance, MHC class I)[15,16]. Collectively, these modifications can influence the efficacy of immunotherapy positively, justifying the fact of the association with other drugs as eribulin.

The anthracyclines doxorubicin and epirubicin (Tables 1 and 2) exemplified here can induce immunogenic cell death, a form of apoptosis that can lead to an effective anti-tumor immune response through the activation of dendritic cells and cells specific response. In addition, the anthracyclines can also increase the proliferation of T cells CD8 +[17].

The association of immunotherapics with taxanes is also common in completed and ongoing clinical trials. It is believed that taxanes reduce selectively T-suppressors lymphocytes, partially reducing the immunosuppression within the tumor microenvironment. This immunomodulatory effect was reported in taxanes of the former generation (docetaxel and paclitaxel); no pre-clinical data about the activity of nab-paclitaxel in the immune system was described so far[18]. Initially, nab-paclitaxel was selected in the study IMpassion130, as it facilitates the reduced use of corticosteroids[5].

The alkilant agents as carboplatin impede the cell to reproduce, damaging its DNA, acting in all the phases of the cellular cycle, further to other specific functions as cyclophosphamide which, apart from its capacity of inducing the immunogenic death of cells, can suppress regulatory T cells and increase the proliferative capacity of T cells CD8 + and NK cells[19].

At last, PARPs inhibitors, the drugs veliparib and talazoparib represented in this study, were investigated in two of the eight articles included (Table 1). PARPs belong to a family of enzymes that catalyze the transference of ADP-ribose to target-proteins, utilizing nicotinamide adenine dinucleotide oxidized (NAD^+) as substrate. As such, PARPs perform important post-translational modifications. It is already described in the literature the relationship of PARPs with several cellular mechanisms as DNA repair, genomic stability and programmed cell death[20-22].

The poly (ADP-ribose) polymerase-1 (PARP-1) is found in the cell nucleus and is activated in response to single-strand DNA break. Once activated, PARP-1 catalyzes the transference of ADP-ribose to target proteins, utilizing NAD^+ as substrate with concomitant formation of nicotinamide. As NAD^+ is essential for the transport reaction of electrons, in the literature it was demonstrated that the super-activation of PARP-1 can lead to a repression of the mitochondrial function resulting in energy deficit, to the liberation of the factor of induction of apoptosis and occasionally to cellular death[21,23,24]. In non-proliferative cells as cardiomyocytes,

however, NAD^+ has been shown compartmentalized and is not easily depleted by the PARP-1 activation. In non-proliferative cells previously mentioned, it is believed that the super-activation of PARP-1 threatens the survival of the cell by inhibiting the activity of other dependent NAD^+ pathways[25,26]. Various factors are largely affected by changes of NAD+ cellular levels – the class III deacetylases histones also called sirtuins or SIRT proteins are an example – that are homologous to the gene yeast Sir2 described in the process of silencing of chromatin in the ageing and survival of the cell[27,28].

The involvement of PARP-1 was already described in process involving modulation of the response to DNA damages in order to ensure the genomic integrity. These mechanisms are strictly regulated and contribute for the amplification of damages to DNA, functioning as a type of interrupter of the DNA repair or induction of cell death, which justifies the constant researches with these therapeutic agents in the treatment of several types of cancers[29-33]. It is important to emphasize also the interaction of the synthetic lethality observed with PARP-1 inhibition and deficiency in genes BRCA1 or BRCA2, justifying the studies in patients with germinative mutations in BRCA[12,22].

The first trial evaluated in this article utilizing veliparib, inhibitor of PARP, demonstrated that the addition of carboplatin to a neoadjuvant chemotherapic regime improves the clinical response although the authors have reported that essential data of the studies are still in progress as biopsies and presence of biomarkers of different groups that would be predictive to define better the subsets of patients that benefit at the most with the inclusion of carboplatin together with veliparib[11]. In the second trial utilizing PARP inhibitors, talazoparib was used in patients with surgically resectable triple-negative breast cancer, and carrying BRCA mutation where a single therapeutic agent administered orally once a day in pre-operation without previous chemotherapy or during treatment produced significant clinical results with manageable toxicity[12].

CONCLUSION

Triple-negative breast cancer treatment based in the immune-checkpoint changed radically the therapeutic approaches for various types of tumors, mainly with the discovery of PD-1 and PD-L1 inhibitors.

PD-1 and PD-L1 inhibitors when combined with other agents appear to increase the benefits of the clinical response and the survival rate and progression of the diseases, mainly the metastatic cancer cases.

In addition, breast cancer in initial stage appears to be still more attractive than the metastatic scenario for the introduction of PD-1 and PD-L1 inhibitors either in the neoadjuvant or adjuvant scenario since primary tumors are seemingly more immunogenic than metastatic sites.

Regarding the combination of therapeutic classes, chemotherapy, for instance, can induce multiple immunomodulatory alterations in the tumor microenvironment as well as other modifications can influence the effectiveness of immunotherapy and other classes positively.

In relation to PARP inhibitors mentioned in this article, although other randomized studies in patients with triple-negative breast cancer have demonstrated that the inclusion of carboplatin, with or without poly-PARP inhibitors to neoadjuvant chemotherapy increases the likelihood of obtaining a complete pathological response, the use of these therapies remained controversial. In the evaluation of PARP inhibitors in patients with surgically resectable tumors that did not use any class of chemotherapics previously or during the clinical trial, it is anticipated better resolution of these tumors, unlike advanced and metastatic tumors described in other studies. The patients should be stratified according to specific biomarkers.

Several ongoing studies can shed light over the immune response biomarkers of triple-negative breast cancer and help to determine whether a set of tumor characteristics as immunohistochemistry staining can foresee improved efficacy while using immunotherapy.

CONTRIBUTIONS

Dione Fernandes Tavares and Renata Lopes Britto contributed for the study conception and/or design, collection, analysis and interpretation of the data, wording, critical review and intellectual contribution. Laércio Moreira Cardoso-Júnior and Victoria Chaves Ribeiro participated of the wording and critical review with intellectual contribution. All the authors approved the final version to be published.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

FUNDING SOURCES

Coordination for the Improvement of Higher Education Personnel (CAPES), Brazil – Funding Code 001.

REFERENCES

1. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747-52. doi: http://doi.org/10.1038/35021093

2. Sørlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A. 2001;98(19):10869-74. doi: http://doi.org/10.1073/pnas.191367098
3. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2020: incidência de câncer no Brasil [Internet]. Rio de Janeiro: INCA; 2019 [acesso 2020 ago 22]. Disponível em: https://www.inca.gov.br/publicacoes/livros/estimativa-2020-incidencia-de-cancer-no-brasil
4. Shah TA, Guraya SS. Breast cancer screening programs: review of merits, demerits, and recent recommendations practiced across the world. J Microsc Ultrastruct. 2017;5(2):59-69. doi: http://doi.org/10.1016/j.jmau.2016.10.002
5. Schmid P, Adams S, Rugo HS, et al. Atezolizumab and Nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med. 2018;379(22):2108-21. doi: http://doi.org/10.1056/NEJMoa1809615
6. Nanda R, Chow LQM, Dees EC, et al. Pembrolizumab in patients with advanced triple-negative breast cancer: phase Ib KEYNOTE-012 study. J Clin Oncol. 2016;34(21):2460-7. doi: http://doi.org/10.1200/JCO.2015.64.8931
7. Adams S, Schmid P, Rugo HS, et al. Pembrolizumab monotherapy for previously treated metastatic triple-negative breast cancer: cohort A of the phase II KEYNOTE-086 study. Ann Oncol. 2019;30(3):397-404. doi: http://doi.org/10.1093/annonc/mdy517
8. Tolaney S, Kalinsky K, Kaklamani V, et al. Abstract PD6-13: phase 1b/2 study to evaluate eribulin mesylate in combination with Pembrolizumab in patients with metastatic triple-negative breast cancer. Cancer Res. 2018;78(4 Suppl):PD6-13. doi: https://doi.org/10.1158/1538-7445.SABCS17-PD6-13
9. Dirix LY, Takacs I, Jerusalem G, et al. Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic breast cancer: a phase 1b JAVELIN solid tumor study. Breast Cancer Res Treat. 2018;167(3):671-86. doi: http://doi.org/10.1007/s10549-017-4537-5
10. Emens LA, Cruz C, Eder JP, et al. Long-term clinical outcomes and biomarker analyses of Atezolizumab therapy for patients with metastatic triple-negative breast cancer: a phase 1 study. JAMA Oncol. 2019;5(1):74-82. doi: http://doi.org/10.1001/jamaoncol.2018.4224
11. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol. 2018;19(4):497-509. doi: http://doi.org/10.1016/S1470-2045(18)30111-6
12. Litton JK, Scoggins M, Hess KR, et al. Neoadjuvant talazoparib (TALA) for operable breast cancer patients with a BRCA mutation (BRCA+). J Clin Oncol. 2018;36(Suppl 15):508. doi: http://doi.org/10.1200/JCO.2018.36.15_suppl.508
13. Souza MT, Silva MD, Carvalho R. Revisão integrativa: o que é e como fazer. Einstein (São Paulo). 2010;8(1):102-6. doi: https://doi.org/10.1590/s1679-45082010rw1134
14. Ribas A, Hu-Lieskovan S. What does PD-L1 positive or negative mean? J Exp Med. 2016;213(13):2835-40. doi: http://doi.org/10.1084/jem.20161462
15. Kythreotou A, Siddique A, Mauri FA, et al. PD-L1. J Clin Pathol. 2018;71(3):189-94. doi: http://doi.org/10.1136/jclinpath-2017-204853
16. Pol J, Vacchelli E, Aranda F, et al. Trial watch: immunogenic cell death inducers for anticancer chemotherapy. Oncoimmunology. 2015;4(4):e1008866. doi: http://doi.org/10.1080/2162402X.2015.1008866
17. Heinhuis KM, Ros W, Kok M, et al. Enhancing antitumor response by combining immune checkpoint inhibitors with chemotherapy in solid tumors. Ann Oncol. 2019;30(2):219-35. doi: http://doi.org/10.1093/annonc/mdy551
18. Galluzzi L, Buqué A, Kepp O, et al. Immunogenic cell death in cancer and infectious disease. Nat Rev Immunol. 2017;17(2):97-111. doi: http://doi.org/10.1038/nri.2016.107
19. Roselli M, Cereda V, di Bari MG, et al. Effects of conventional therapeutic interventions on the number and function of regulatory T cells. Oncoimmunology. 2013;2(10):e27025. doi: http://doi.org/10.4161/onci.27025
20. Ghiringhelli F, Menard C, Puig PE, et al. Metronomic cyclophosphamide regimen selectively depletes $CD4^+CD25^+$ regulatory T cells and restores T and NK effector functions in end stage cancer patients. Cancer Immunol Immunother. 2007;56(5):641-8. doi: http://doi.org/10.1007/s00262-006-0225-8
21. Leung AKL. Poly(ADP-ribose): an organizer of cellular architecture. J Cell Biol. 2014;205(5):613-9. doi: https://doi.org/10.1083/jcb.201402114
22. Sousa FG, Matuo R, Soares DG et al. PARPs and the DNA damage response. Carcinogenesis. 2012;33(8):1433-40. doi: https://doi.org/10.1093/carcin/bgs132
23. Bürkle A. Physiology and pathophysiology of poly(ADP-ribosyl)ation. Bioessays. 2001;23(9):795-806. doi: https://doi.org/10.1002/bies.1115
24. Bürkle A. PARP-1: a regulator of genomic stability linked with mammalian longevity. Chembiochem. 2001;2(10):725-8. doi: https://doi.org/10.1002/1439-7633(20011001)2:10<725::AID-CBIC725>3.0.CO;2-3
25. Virág L, Szabó C. The therapeutic potential of poly(ADP-ribose) polymerase inhibitors. Pharmacol Rev. 2002;54(3):375-429. doi: https://doi.org/10.1124/pr.54.3.375

26. Chiarugi A. Poly(ADP-ribose) polymerase: killer or conspirator? The 'suicide hypothesis' revisited. Trends Pharmacol Sci. 2002;23(3):122-9. doi: https://doi.org/10.1016/S0165-6147(00)01902-7

27. Ying W, Alano CC, Garnier P, et al. NAD+ as a metabolic link between DNA damage and cell death. J Neurosci Res. 2005;79(1-2):216-23. doi: https://doi.org/10.1002/jnr.20289

28. Imai S, Armstrong CM, Kaeberlein M, et al. Transcriptional silencing and longevity protein Sir2 is an NAD-dependent histone deacetylase. Nature. 2000;403(6771):795-800. doi: https://doi.org/10.1038/35001622

29. North BJ, Verdin E. Sirtuins: Sir2-related NAD-dependent protein deacetylases. Genome Biol. 2004;5(5):224. doi: https://doi.org/10.1186/gb-2004-5-5-224

30. Mortusewicz O, Amé JC, Schreiber V, et al. Feedback-regulated poly(ADP-ribosyl)ation by PARP-1 is required for rapid response to DNA damage in living cells. Nucleic Acids Res. 2007;35(22):7665-75. doi: https://doi.org/10.1093/nar/gkm933

31. Vodenicharov MD, Ghodgaonkar MM, Halappanavar SS, et al. Mechanism of early biphasic activation of poly(ADP-ribose) polymerase-1 in response to ultraviolet B radiation. J Cell Sci. 2005;118(Pt 3):589-99. doi: https://doi.org/10.1242/jcs.01636

32. Damiani RM, Moura DJ, Viau CM. et al. Pathways of cardiac toxicity: comparison between chemotherapeutic drugs doxorubicin and mitoxantrone. Arch Toxicol. 2016;90(9):2063-76. doi: https://doi.org/10.1007/s00204-016-1759-y

33. Damiani RM, Moura DJ, Viau CM, et al. Influence of PARP-1 inhibition in the cardiotoxicity of the topoisomerase 2 inhibitors doxorubicin and mitoxantrone. Toxicol In Vitro. 2018;52:203-13. doi: https://doi.org/10.1016/j.tiv.2018.06.013

Recebido em 8/5/2020
Aprovado em 10/11/2020