International Immunopharmacology 84 (2020) 106535

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Breast cancer: Biology, biomarkers, and treatments

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ARTICLE INFO

Keywords:
Breast cancer
Treatment
Nanoparticles
Antibody-drug conjugation systems
Breast cancer stem cells
Immunotherapy

ABSTRACT

During the past recent years, various therapies emerged in the era of breast cancer. Breast cancer is a heterogeneous disease in which genetic and environmental factors are involved. Breast cancer stem cells (BCSCs) are the main player in the aggressiveness of different tumors and also, these cells are the main challenge in cancer treatment. Moreover, the major obstacle to achieve an effective treatment is resistance to therapies. There are various types of treatment for breast cancer (BC) patients. Therefore, in this review, we present the current treatments, novel approaches such as antibody-drug conjugation systems (ADCs), nanoparticles (albumin-, metal-, lipid-, polymer-, micelle-based nanoparticles), and BCSCs-based therapies. Furthermore, prognostic and predictive biomarkers will be discussed also biomarkers that have been applied by some tests such as Oncotype DX, Mamm αPrint, and uPA/PAI-1 are regarded as suitable prognostic and predictive factors in breast cancer.

1. Breast cancer biology

Breast cancer (BC) is a type of cancer with different presentations among women [1]. In 2018, 268,670 new cases with BC were reported in the United States [1,2]. BC is a common cancer that affects women all around the world [2]. Based on both molecular and histological evidences, BC could be categorized into three groups; BC expressing hormone receptor (estrogen receptor (ER^+) or progesterone receptor (PR^+)), BC expressing human epidermal receptor 2 ($HER2^+$) and triple-negative breast cancer (TNBC) (ER^-, PR^-, $HER2^-$) [3,4]. The treatment approaches should be based on the BC molecular characteristics. In addition, the TNBC divided into six categories; basal-like 1 (BL-1), basal-like 2 (BL-2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem cell-like (MSL), and luminal androgen receptor (LAR) [4] (Table 1).

The precise mechanisms by which breast cancer starts are not clear [5]. The BC expressing HR is the most prevalent type of BC and consists of 60–70% of BC cases in developed countries exclusively in premenopausal women. Therefore, hormonotherapy is the most commonly used therapeutic approach [6]. The most frequently medicines are tamoxifen as an estrogen blocker, aromatase inhibitors such as letrozole, anastrozole, and exemestane which prevent hormone production from the ovary [7].

In the case of BC patients expressing HER2, there are several anti-HER2 monoclonal antibodies such as trastuzumab, pertuzumab; which bind to different sites of HER2, ado-trastuzumab emtansine as anti-HER2 monoclonal antibody conjugated with mertansine, a microtubule inhibitor. The standard treatment for BC patients with positive HER2 is a combination therapy of anti-HER2 monoclonal antibody and chemotherapy [8].

The TNBC treatment is the most challenging in comparison to other groups of BC. The standard treatment for these group is chemotherapy. The alternative treatment could be combination therapy of chemotherapy and bevacizumab, the recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF) [3,9].

1.1. Biomarkers

In the case of breast cancer, the most important prognostic biomarker was/is the presence and number of axillary node metastases.

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https://doi.org/10.1016/j.intimp.2020.106535
Received 19 February 2020; Received in revised form 20 April 2020; Accepted 20 April 2020
Available online 29 April 2020

Table 1
Breast cancer subtypes category.

Breast cancer subtype	*Receptor profile*	*Subtype prevalence*	*Subcategories*
Hormone positive	ER+ or PR+	60%	Luminal A & B
HER2 positive	HER2+	20%	–
Triple negative breast cancer	ER−, PR− and HER2−	10–20%	Basal-like 1 (BL-1), basal-like 2 (BL-2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem cell-like (MSL), and luminal androgen receptor (LAR)

However, the extent of axillary node involvement does not determine the disease outcome. A report illustrated that about 30% of untreated breast cancer patients without nodal metastasis developed to metastatic/recurrent form of disease after ten years, while about 50% of patients with nodal involvement were cured by local treatment [10]. Another two important prognostic biomarkers are; tumor size and tumor grade which have been widely used [11–13]. There are limitations in tumor grading such as lack of reproducibility in tumor grading and pathologists do not share a common view and the second concern is about the heterogeneity of tumors, most of the tumors are classified as grade two [14].

Since we are going through the era of personalized treatment, these prognostic biomarkers (tumor size, tumor grade, and lymph node metastases) are not sufficient for the suitable management of early diagnosed breast cancer patients [15,16]. Through these recent years, many researches have been devoted to find and validate molecular biomarkers to serve as a prognostic and predictive biomarker. These new approaches are usually defined as multi-parameter, multi-analyte and multi-gene tests. Several of these tests are recommended by experts and have been used in clinical practice. Some of these validated tests are Oncotype DX, MammaPrint and uPA/PAI-1.

One of the validated and widely used multigene signature tests is Oncotype DX, which is commonly applied for predicting the breast cancer outcome. This test evaluates the expression of 21 genes at the mRNA level, using RT-PCR. Finally, the recurrence score (RS) according to the relative expression of the evaluated genes will be calculated. According to RS, the patients will be divided into 3 categories, scores more than 30 are considered as high risk, scores between 18 and 30 have an intermediate risk and scores lower than 18 are considered as low risk [17]. The Oncotype DX has two main purposes in patients with breast cancer, the first goal is to predict the possibility of the disease recurrence and the second goal is to find patients who are probably benefiting from adjuvant chemotherapy [18]. Besides the widely used and clinical application of the Oncotype DX, there are limitations such as lack of validation for long term follow-up and also, lack of validation for ER-negative patients.

MammaPrint is another validated molecular test that uses microarray to evaluate the relative expression of 70 genes which are mainly involved in the regulatory pathways of cancer. According to the relative expression of the genes, patients are divided into two groups, low risk and high risk for recurrence of cancer. The MammaPrint test has been validated and widely used for predicting the possibility of cancer recurrence and serves as an important marker for treatment [19–23].

Another molecular test is the evaluation of uPA and PAI-1 markers. This test evaluates these mentioned markers at the protein level in extracts of breast cancer tissue [21]. It has been documented that patients with an elevated level of these proteins have a worse outcome than patients with low levels.

These multigene signatures tests are not cheap and are prohibitively expensive in many countries. To set up a simple and inexpensive test to serve as a diagnostic and predictive biomarker test, considerable efforts have been devoted. Ki67 is one of those inexpensive biomarkers which is widely used [24]. IHC4 is another cheap biomarker which is consists of ER, PR, HER2, and Ki67 markers and serves as an inexpensive prognostic test for patients with breast cancer [25,26].

Tumor tissue is needed for the evaluation of all the mentioned biomarkers. Since the tumor tissue is a limitation, strong and clinically validated circulating biomarkers are recommended. There are circulating biomarkers with an elevated level such as TPS, CEA, and CA 15-3. These biomarkers besides their potential role in predicting poor outcome in breast cancer patients, could not yet fulfill the criteria to serve as a prognostic biomarker in clinical practice [27–31].

The most important and currently available predictive biomarker for BC is ER marker. All newly diagnosed patients with breast cancer must evaluate their ER. Although the ER could serve as a prognostic biomarker and also a predictive biomarker for therapy, its most important clinical application is its usage as a predictive marker for endocrine therapy. It is believed that estrogens through their associations with regulatory elements such as cyclin D and MYC in the genome could lead to cancer cell growth [32]. Since estrogens exert their effects through the ER, it is hypothesized that the ER level could be correlated with the beneficial effects of antiestrogenic therapy [33]. Another predictive biomarker which is usually evaluated in association with ER is the PR. The ration for evaluating PR in association with ER was according to the fact that the PR could be induced by estrogen. On the other hand, the presence of PR interprets as a marker for a functional ER [34]. As mentioned earlier, PR expression could be induced by ER and it is shown that the PR-progesterone interaction could bind and changes the ER chromatin binding site [35]. This change in chromatin binding site of ER favor the balance from the regulating genes involved in cell proliferation toward the modulating genes related to differentiation, apoptosis and cell cycle arrest [36,37]. Furthermore, the evaluation of ER in combination with PR is highly recommended by expert panels in all newly diagnosed patients with breast cancer [38,39]. Another predictive biomarker which its evaluation in combination with ER is mandatory in all the newly diagnosed patients is HER2 marker. High expression of HER2 through activation of signaling pathways such as PI3K/AKT and MAPK and cell membrane deformity leads to metastasis, invasion, and proliferation of cancer cells [40,41].

Many attempts have been exerted to develop and validate a new technique for patients with breast cancer. In breast cancer tissue the expression of single or multiple genes and single or multiple microRNAs (mi-RNAs) have been detected. Moreover, in peripheral blood expression of mi-RNAs, circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs) have been identified [42]. To discover a novel biomarker, databases could be considered as a helpful tool as well.

Recently, many researchers are working on CTCs, miRNAs, and DNA mutation testing (such as measurement of ctDNA) to find new prognostic and predictive markers. These novel biomarkers before their clinical applications should be validated through clinical and analytical assessments start our journey towards a personalized treatment for early diagnosed patients with breast cancer, we need the established prognostic biomarkers in combination with validated prognostic/predictive factors.

1.2. Cancer stem cells

Cancer stem cells (CSCs) are a small population of tumor cells that govern many tumor behaviors including invasion, metastasis, recurrence and resistance. Malignant transformation of a self-renewing stem or precursor cell can cause cancer [43,44]. The first CSC in solid tumors was described by Al-Hajj et al. in breast cancer, which was able to

induce xenograft tumors in immune-deficient mice [45]. Breast cancer stem cells (BCSCs) have stem cell characteristics and are identified by expression of surface markers such as CD44, EpCAM, CD133, CD49f, CD61 and the absence of surface markers such as CD24, CD2, CD3, CD10, CD16, CD18, CD31 and CD64 [45,46]. These cells also express a high level of aldehyde dehydrogenase-1 (ALDH1) and ATP-binding cassette (ABC) transporter G family (ABCG2), known as breast cancer resistance protein-1, and capable of forming mammospheres in vitro [46]. Different BCSCs are capable of producing diverse BCs with different behaviors. Among the BC types, basal-like triple-negative tumors had the highest BCSCs, and this high number of tumor stem cells was associated with its aggressiveness [47]. Several signaling pathways are involved in the maintenance and activity of CSCs that subsequently play a substantial role in tumor behavior such as growth, invasion, metastasis, and resistance to treatment. The Hedgehog, Notch, and Wnt signaling pathways play important roles in stem cell differentiation and self-renewal capacity. Therefore, disruption of these pathways could have participated in the BCSC phenotype [48,49]. In addition to these pathways, other transcription factors including Sox2, Oct4, and Nanog could be involved in the maintenance, proliferation, and tumorigenesis of the BCSCs [50]. These BCSCs use different mechanisms to gain resistance to treatment. Chemotherapy and radiotherapy resistance of tumors might be due to CSC resistance to these therapies. ABCG2 contributes to the rapid efflux of cytotoxic drugs, and ALDH1 can metabolize chemotherapeutic drugs into non-toxic compounds that make CSCs resistant to the drugs [51–53]. Another mechanism that CSCs use to resist drugs targeting cell division is the alteration of the cell cycle kinetics, which results in recurrences of the disease after a long time of treatment [53,54]. Chemotherapy drugs, with DNA damage mechanisms of action, are inactivated by the advanced DNA repair system of BCSCs [55,56]. Moreover, even miRNAs are involved in enhancing tumorigenesis, drug resistance and enhancing stemness of BCSCs [57,58].

Interaction of BCSCs with their surrounding microenvironment including the effects of cytokines, hypoxia and epithelial-mesenchymal transition increases resistance to chemotherapy and radiotherapy of BCSCs [59]. The BCSCs recruit mesenchymal stem cells from the breast stroma [60] and the bone marrow [61]. These cells could provide a shield for BCSCs by invoking immune regulatory cells [62]. The immune-suppressive cytokine profile results in recalling immunosuppressive cells, and the production of growth factors which lead to tumor growth and resistance to treatment for BC [63].

1.3. Immune response

Generally, the immune system is able to recognize and eradicate tumor cells (immunosurveillance). Lymphocytes like Cytotoxic T Lymphocyte (CTL) cells recognize foreign Ag-MHC I complex and kill tumor cells in a cell-to-cell manner. In some cases, tumor cells down-regulate MHC I expression to escape from mentioned CTL recognition and response. In this way, Natural Killer (NK) cells recognize low MHC I expressed cells and target it. Hence, NK and CTL are major players in anti-tumor immunity. Unfortunately, immune surveillance does not ended here and the story goes on. Immunosurveillance is a monitoring process of the immune system which consists of three stages [64]. First, targeting tumor cells (elimination which is described above), second, failure of immune response to tumor cells because of dormancy (equilibrium), and third, selection of tumor cells which can escape immune system surveillance [64]. As you can see, the immune system has great potential to eradicate tumors but after a while, it faces important obstacles. The number of infiltrated immune cells and the composition of them in the immune microenvironment can determine the outcome of BC therapy. It is reported that high Tumor Infiltrating Lymphocytes (TILs) ratio is associated with better prognosis in BC patients. TIL ratio is different among different BC subtypes. For example, in $HER2^+$ and TNBC patients TIL ratio is higher than hormone recptor positive patients [65]. Patients with a high TIL ratio ($HER2^+$ and TNBC subtypes) have a better prognosis [65,66]. They respond better to chemotherapy [66], also they show decreasing death and relapse rate [65].

In the case of immune cell composition, results from patients who undergo chemotherapy prove that the high number of plasma cells, neutrophils and tumor-associated macrophage (TAM) would lead to less overall survival (OS) of patients [64]. The high number of T $CD8^+$ and low number of T $CD4^+$ cells in mammary neoplastic sites increase OS [64]. In the absence of CTL, T $CD4^+$ cells activate TAMs and promotes metastasis in BC patients [67]. One of the most important subtypes of T $CD4^+$ cells that play a critical role in tumor immunity is T regulatory (Treg) cells which impair the function of effector immune cells [68]. Treg cells suppress anti-tumor immunity by different mechanisms, they are able to suppress immune cells by direct contact or by producing regulatory cytokines [68]. Moreover, studies show that Treg infiltration is correlated with a more invasive BC phenotype in patients [68].

Myeloid-derived suppressor cells (MDSCs) are another important cells in tumor immunity. Results show that BC patients have high MDSCs level and the highest level belongs to metastatic patients [68]. So, it can be concluded that they promote tumor growth in BC patients, but how? To answer this question we should know the diversity and composition of MDSCs. MDSCs are heterogeneous and they composed of granulocyte (like neutrophils), immature Dendritic cells (DC) and myeloid progenitor cells [68]. MDSCs can inhibit effector T cells activity by IDO or arginase1. These cells also, can secrete anti-inflammatory cytokines like IL-10 and TGFβ and suppress T cells activity [68]. Moreover, MDSCs are able to shift macrophage (MQ) to M2 and induce Treg cells clonal expansion [68].

The presence of MQs increases vascular density of breast tumor and followed by poor prognosis in BC patients [67]. M2 cells secrete VEGF, IL-8 and matrix metalloproteinases and promote angiogenesis [66]. Neutrophils negatively affect anti-tumor immunity. It is established that high neutrophil/lymphocyte ratio is linked to poor prognosis in BC patients [66]. In an animal models, a high number of systemic neutrophil promote metastasis [66]. Above all, immune cells can affect tumor development and growth differently. Some of them like Treg and MDSC cells are able to suppress effector immune cells and promote tumor growth. Understanding the exact role of these cells would be crucial for immunotherapy. At the following, we will survey immunotherapeutic strategies in BC.

2. Treatment

Patients with locally advanced or metastatic BC have poor prognosis. Their survival is approximately 2–4 years. Newly diagnosed breast cancer show about 10% growth to metastatic disease. It has been shown that 30–50% of patients who are diagnosed at earlier stages will increase the establishment of mbc [69]. Thus, due to the lack of the complete efficiency of hormone therapy, new approaches are essential which will be discussed below.

2.1. Traditional chemotherapy

These types of drugs attack all growing cells including immune cells which decrease immune response [70]. On the other hand, chemotherapy has positive effects on immune cells in the tumor microenvironment and promoting immune responses against tumors. Chemotherapeutic agents can help the immune system to eradicate or suppress tumor growth. Combination therapy of Granulocyte-MQ Colony Stimulating Factor (GM-CSF) and conventional chemotherapy in BC patients resulted in an efficient clinical outcome, however, a high dose of chemotherapeutic agents could suppress the immune responses [70]. Combination of chemotherapy and trastuzumab could increase the survival of BC patients up to 35% [71]. One of the most important of chemotherapy mechanisms is an Immune Cell Death (ICD), a type of cell death that triggers the immune responses [70]. Studies documented

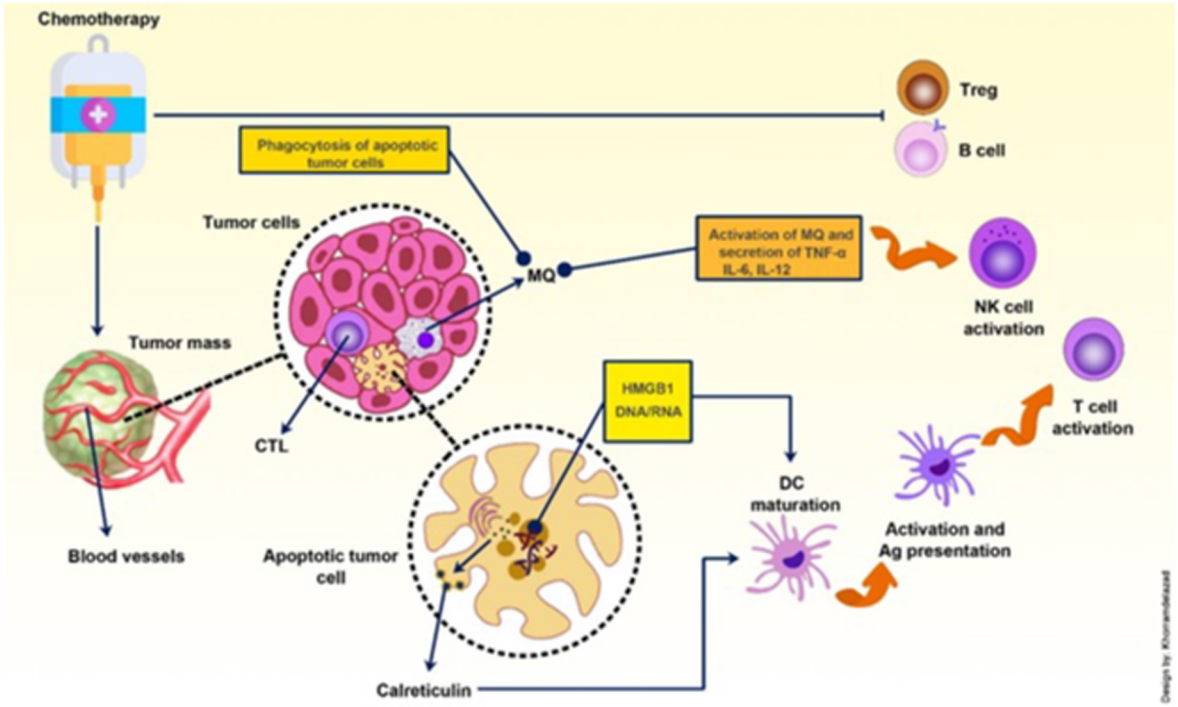

Fig. 1. One of the most important effects of chemotherapy is related to tumor microenvironment. Some immune cells in tumor microenvironment – Treg cells- promote tumor cells growth. Chemotherapeutic agents can target these cells and decreases Treg cells number. Hence, in the absence of Treg suppression, CTLs would be able to kill tumor cells. Chemotherapeutic agents also are able to polarize M2 MQs to M1 and inhibit growth promoting effects of M2 subtype on tumor cells. B lymphocytes have less effect on tumor cells, chemotherapeutic agents can decrease them. It seems that chemotherapeutic agents modulate composition of immune cells in tumor microenvironment. As illustrated above, chemotherapy also induces ICD and stimulates immune cells like CTLs, NKs, and DCs.

positive effects of chemotherapy in clinical outcomes of BC patients and murine models. However, in murine models, these beneficial effects were independent of the immune system. These results from murine models illustrated that chemotherapy could have its effects without influence the immune response [72]. Another study showed that there is a correlation between T and NK cells activation and efficacy of taxane in BC patients [73]. Different chemotherapeutic drugs have different potential to induce ICD [64]. Calreticulin (CalR) is the most important mediator of ICD [74]. A drug like cisplatin could not induce endoplasmic reticulum stress (ER stress) and also, CalR translocation to the cell surface. Therefore, this drug is not a potent ICD inducer [64]. Some chemotherapeutic agents can induce ICD. Therefore, these chemotherapeutic agents have a great potential to combine with immunotherapy and synergize the efficacy [75–77]. Chemotherapeutic agents not only can eliminate tumor cells but also, they can promote ICD, and it could enhance their efficacies [70]. ICD induction depends on tumor type, chemotherapeutic agent, dosage, and schedule [70]. Besides, Antigens (Ags) release during chemotherapy [75,78,79], could be helpful in immunotherapy of low tumor mutation burden [75]. Combination therapy of anti-VEGFR with a low dose of cyclophosphamide showed more efficacy than conventional therapy in BC patients [77,80]. It is documented that chemotherapeutic drugs can change the composition of the immune cell populations in the tumor microenvironment. The number of effector immune cells in BC patients who were treated with chemotherapeutic agents was increased and this issue could increase the OS of BC patients [64]. Studies showed that anthracycline could increase CTL infiltration in the tumor site which leads to successful treatment in BC patients [64]. Furthermore, both anthracycline and cyclophosphamide can increase the number of CTLs in comparison to Treg cells which increases CTL/Treg ratio these results showed beneficial effects in these patients [64,76,77,81].

Cyclophosphamide suppresses Treg cells [64,76,77,82] through decreasing expression of Forkhead Box P3 (FOXP3) and Glucocorticoid-Induced Tumor Necrosis Factor Receptor (GITR) in these cells [77]. On the other hand, gemcitabine can release tumor Ags and cross-priming of CTLs [76]. Combination therapy of paclitaxel and cisplatin at a low doses showed a strong response to CTLs. It is reported that 5FU (5-fluorouracil) could increase T cells responses. Furthermore, the combination of 5FU and cisplatin increased the infiltration of T $CD4^+$ and $CD8^+$ cells in the tumor site [83]. Doxorubicin or Fluorouracil (5FU) in BC patients increased the number of T and NK cells and reduced B cells [84]. Chemotherapeutic drugs like docetaxel have the potential to activate NK cells [72,73,83,85]. Another population of cells which could be increased by chemotherapy is DCs. It is mentioned that Toll-Like Receptor 4 (TLR4) and High Mobility Group Box 1 Protein (HMGB1) interaction can activate DCs. This activation leads to the processing and presentation of tumor Ags which eventually resulted in IL-1β secreting and CTLs activation [70]. Cyclophosphamide recruits DCs to the tumor site [83] and some chemotherapeutic agents in non-toxic doses increase DCs maturation and Ag presentation [77]. In BC patients, 5FU selectively kills Myeloid-derived suppressor cells (MDSCs). The low dose administration of cyclophosphamide also selectively suppresses MDSCs [82]. Gemcitabine decreases the number of MDSCs in the blood of BC patients [64]. Furthermore, gemcitabine could decrease these cells in the tumor site of an animal model of colon cancer. Paclitaxel could differentiate MSDCs to normal DCs through TLR4 activation [77]. Chemotherapy induces the death of tumor cells and also, increases phagocytosis by MQ [75]. Paclitaxel increases MQs recruitment to the site of the tumor and differentiates them to tumor suppressor type in BC patients [64,67,84]. Furthermore, paclitaxel could stimulate tumor-associated MQ (TAMs) for the production of IL-12 and TNF-α and eventually activate DCs, NKs, and CTLs [83]. Gemcitabine in pancreas cancer models could differentiate TAMs to their immune stimulator type [64]. Cyclophosphamide can polarize immune suppressor M2 to immune effector M1 cells [83,84].

Apoptotic tumor cells secrete molecules that are known as danger signals or in some cases eat me signals. These molecules are called damage-associated molecular patterns (DAMPs). The most important

DAMPs are CalR [64], HMGB1 [86], ATP [87], DNA [70], and RNA [80]. DAMPs can stimulate DCs, T cells, NK cells, and MQs and they could promote phagocytosis of tumor cells and trigger inflammatory signals (Fig. 1). DAMPs are also facilitate the presentation of tumor-associated antigens by DCs [74]. Nucleotides are the most important and potent extracellular danger signals [74]. Apoptotic tumor cells release ATP and DCs could recognize it by their P2X7 receptors and get activated [74,87]. Releasing ATP from lysosomes leads to MQs recruitment and maturation. Furthermore, ATP can stimulate NK to proliferate and resulted in IFN-γ secretion [70]. Nucleic acids can bind and activate TLR3, 7, and 9 in innate immune cells [74]. HMGB1 through binding to TLR4 can activates DCs [70,77,81,88,89]. HMGB1 could also bind to TLR9 which activates plasmacytoid DCs and cytokine production. Activating MYD-88 through TLR7-HMGB1 interaction could trigger an immune response against apoptotic tumor cells [74].

2.2. Novel strategies

There are emerging novel therapeutics methods for BC patients including; cell cycle management, signaling pathway and molecular-targeted therapy, monoclonal antibodies, antibody-drug conjugates and immunotherapy [1]. Up-regulation of signaling pathway molecules could change genomes make up which could be associated with resistance to conventional BC treatment. For example, some of these molecules associated with genome alternations are cyclin-dependent kinases 4 and 6 as the key players in cell cycle progression [90]. In the next sections, new approaches to breast cancer treatment will be discussed.

2.2.1. Repurposing drugs:

According to progress in genomics, proteomics and information computational biology, new applications of old drugs are being emerged as a novel treatment in cancer therapy. Thus, this concept considered as drug repurposing. Drug repurposing approach can lead to accelerate pharmaceutical developments and propose safer, more effective, economical and lower side effects [91]. Among drug repurposing of breast cancer treatment alkylating agents, anthracyclins, antimetabolites, CDK4/6 inhibitor, an aromatase inhibitor, mTOR inhibitor, and mitotic inhibitors have been suggested for breast cancer treatment[92]. There are some inhibitory drugs of CDK4 and 6 such as palbociclib, ribociclib, and abemaciclibwhich showed beneficial effects in combination with aromatase inhibitors. Combination therapy of the CDK4 and 6 inhibitors with fulvestrant, a drug against HR, increased survival time of BC patients in comparison to treatment with fulvestrant alone [93,94]. Combination therapy of aromatase inhibitors such as exemestane and tamoxifen with histone deacetylase (HDAC) inhibitors, entinostat, and vorinostat, showed the most anticancer clinical outcomes [95]. There are reports of resistance to hormonal therapy in 70% of BC cases which could be due to activation of PI3K/ACT/MTOR pathways [1]. One of mostly mutated and/or amplified gene subunit in this pathway is catalytic subunit P110 α (PI3KCA) which have been considered as a new target for intervention in both HER2 positive and negative BC cases [96]. Another signaling pathway inhibitor is everolimus, mTOR inhibitor, which is FDA approved. Combination therapy of everolimus with exemestane or trastuzumab showed a promising clinical outcome in both HER2 positive and negative BC cases [1].

2.2.2. Metronomic therapy

The term “metronomic chemotherapy” (MTC) referred to constant, regular and low doses of chemotherapeutic administration to patients suffering from cancer. This strategy could lead to more persistence and adequate concentration of chemotherapy with minimal side effects [69]. One of the most important roles of MTC is antiangiogenic effects. This activity when combined with anti-VEGF monoclonal antibody, has various effects. It has been shown that MTC as antiangiogenic agents, target vascular endothelial growth factor (VEGF) and impair angiogenic mechanisms of cells [69]. Also, the tumor endothelial cells (TEC) and endothelial progenitor cells (EPC) could be targeted via MTC because they play key roles in tumor vasculogenesis [69,97–100]. Furthermore, MTC could induces antiangiogenic protein Thrombospondin-1, inhibits angiogenic Hypoxia Inducible Factor-1 (HIF-1??), and decreases circulating VEGF levels [69,101].

2.2.2.1. Action on immune system. Another mechanism of MTC action is to restore and enhance antitumor immune responses in the altered tumor microenvironment [101]. One of the immune cells that are selectively targeted by MTC is regulatory Tcell (Treg). Since Treg is a key factor to decrease the cytotoxic immune responses and improve the tumor immune-tolerance, depleting of them results in restoring the natural killer (NK) and T cell functions [102,103]. Moreover, MTC induces immunogenic cancer death in the way that DCs recognize the immune-adjuvant DAMPs such as HGMB-1, CalR and ATP which subsequently lead to cytotoxic cell death. The third mechanism of MTC action is selective modulation of definite gene and protein functions in tumor cells. Therefore, MTC can act as an antiproliferative agent on tumor cells [69].

2.2.3. Antibody-Drug Conjugation Systems (ADCs)

Nowadays, among novel approaches to treat solid tumors, antibody-drug conjugates (ADCs) as a targeted therapeutics hybrid molecule have shown great potential to make a paradigm shift in the field of cancer therapy through the antibody-antigen interaction [103]. These biotherapeutics systems consist of tumor-specific mAb and potent cytotoxin (payloads) covalently conjugated through stable chemical linkers. In the same way, they covalently join to the antibody via an amino acid residue side chain and their modification of surface lysine on the antibody, then conjugation to the drug–linker and reduction of existing disulfide bonds for liberating free cysteine residues on the antibody are a few of the chemical conjugation strategies for drug conjugation.

Clinical efficacy of ideal ADCs relies on their molecular design, target tumor type, antigen type (according to differing internalization rate of each antigen and complex formation with an ADC molecule), prodrugs type, pharmacokinetics factors, ADC stability, linker stability in plasma during circulation in the bloodstream (so that the ADCs localizes to the cancer cell in the original formation), maintenance of immune reactivity, and efficient release of prodrugs at desired site (prodrugs can be chemically or enzymatically renewed to active forms of drugs to propel the death of tumor cell via its interference with the mechanism of cell division and/ or inducing the irreversible DNA damage [104]. Furthermore, linker hydrophobicity is one of the important factors since it promotes the aggregation of ADC molecules. Hydrophobicity of linkers leads to a better coupling with hydrophobic payloads, an improved efficacy, reduced systemic toxicity, and an enthusiastic ADC development. The critical factor in designing an ADC system is connecting antibodies to drugs with an acceptable biological linker. Therefore, the desired drug can reach target cells with limited side effects for the patient. Nonetheless, linker chemistries are critical for an effective structure of the ADC system. Most linkers are currently divided into two categories, cleavable and non-cleavable linkers which release drug with different mechanisms. In non-cleavable linkers [105], the antibody undergoes proteolytic degradation to release the drug which preserves the linker. However, in cleavable linkers (chemically labile linkers and enzyme cleavable linkers) that rely on physiological environment, active drug can be liberated via one of three intercellular processes such as reduction of disulfide bonds in the cytoplasm, exposure to acidic conditions in the lysosome (low-pH environment can activate hydrolysis of an acid-labile group), and cleavage by specific proteases. Generally, the ADC mechanism of action involves three steps: first, binding of mAb to target antigen and ADC-antigen complex formation, second, endocytosis (internalization of ADC-antigen complex into the tumor cell, and third, degradation and consequently release of drug. Antibodies and drug types in ADC systems for cancer therapy are

Table 2
Approved/under clinical evaluation of ADC systems in cancer treatment.

Trade name	Type of cancer	Status (Year) /Ref
Ado-trastuzumab emtansine	Breast	Approved (2013) [138]
Mirvetuximab soravtansine	Lung	Phase III (2019) [139]
Sacituzumab govitecan	Breast	Phase II (2019) [140]
Trastuzumab deruxtecan	Breast	Phase III (2019) [141]
PSMA-ADC	Prostate	Phase II (2019) [138]
Anetumab ravtansine	Ovarian	Phase III (2019) [138]
Rovalpituzumab tesirine	Lung	Phase III (2019) [138]
Ado-trastuzumab emtansine	Breast	Approved (2013) [138]
Mirvetuximab soravtansine	Lung	Phase III (2019) [139]
Sacituzumab govitecan	Breast	Phase II (2019) [140]
Trastuzumab deruxtecan	Breast	Phase III (2019) [141]
PSMA-ADC	Prostate	Phase II (2019) [138]
Anetumab ravtansine	Ovarian	Phase III (2019) [138]
Rovalpituzumab tesirine	Lung	Phase III (2019) [138]

PSMA; prostate-specific membrane antigen.

Table 3
Antibody-drug conjugate (ADC) systems in clinical trials or approved for breast cancer treatment [107].

Agent	Drug	Status
T-DM1	Maytansine	Approved
XMT-1522	Dolaflexin	Phase I
Syd985	Duocarmycin	Phase III ongoing
DS8201a	Deruxtecan	Phase II
MM-302	Liposomal doxorubcin	Terminated
RC48-ADC	Auristatin	Phase II
Ladiratuzumab vedotin	vedotin	Phase II
PF-06647263	auristatin	Phase I
Sacituzumab Govitecan	Govitecan	Phase III
Glembatumu Mab vedotin	vedotin	Phase II
SAR566658	DM4	Phase I

not part of this review and they are discussed elsewhere [106]. So far, many ADCs have been approved or are under study in different phases of clinical development by the FDA or EMU, as can be seen in Table2. In the treatment fields of BC, antibody-drug conjugation systems are elegant and innovative approaches that could yield optimal outcomes. This system minimizes drug toxicity and enhances antitumor immunity. Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate which its positive effects on HER2-positive BC has been confirmed. This system could be used in neoadjuvant and adjuvant therapies as well, and its drug antibody ratio (DAR) has been estimated at 3.5. Furthermore, T-DM1 has remarkable chemotherapeutic potency and consists of trastuzumab and emtansine which is linked through a non-reducible thioether and has been approved in phase I, II, and III trials. According to literature, the survival of patients receiving T-DM1 was similar to those received taxane with trastuzumab. However, it is reported that T-DM1 may lead to brain metastasis as it could easily cross the blood–-brain barrier. In this regard, there are various HER2-based ADC systems used in clinical trials or approved for BC treatment (Table3) [107].

2.2.4. Nanoparticles and micelles

Nanoparticles have excellent properties such as small sizes, large surface area, high surface reactivity, unique physicochemical properties, high surface-volume ratio, and superior reactivity over their bulk counterparts. These features give them unique physical properties resulting in new opportunities for early detection, improved treatment, and diagnosis of many human diseases such as cancer [108]. Additional advantages of nanomedicines are; capturing and traveling the drugs in nano carriers through the bloodstream, prevent rapid clearance, improve bioavailability, benefits for tumor imaging, ability to embrace thousands of drug molecules and also, their overwhelming solubility, stability, and resistance [109]. In recent years, thanks to heterogeneous vascularization of tumors, many researchers have strived to overcome the problems of existing chemotherapeutic agents using nanotechnology, as tools for personalized medicine. In the development of nanoparticles for cancer therapy, two significant approaches have been modified. First is surface-nano engineering of nanoparticles by conjugating active recognition moieties to their surfaces via biologically relevant ligands for successful targeting selectivity of chemotherapeutics, and the second is superior accumulation, which results in their enhanced permeability retention (EPR) effect of nano carriers for therapeutic payloads because of their nano sized particles [110]. To date, nano platforms like Albumin Nanoparticles, Metal-Based Nanoparticles, Lipid Nanoparticles, Liposomes, Polymeric nanoparticles, Micelles. Combination therapy of these available nanoparticles is a fantastic choice which could be a solution for various problems in the diagnosis and treatment of different types of cancer. There is a list of important and interesting NPs, which are widely used in diagnosis and cancer therapy.

In clinical practice, nanotechnology is considered to be an effective method for detection, diagnosis, and prevention of BC as a modern and noninvasive scenario based on nanoparticles. To date, reports have attributed no significant adverse chemotherapy complications for NPs compared to the conventional treatments. According to a recent study in this regard, multiple BC biomarkers could be detected by quantum dots [111]. In another research, hormonal agents were incorporated into nanoparticles coated with polyethylene glycol and subsequently enter into BC cells [112]. Furthermore, Gao incorporated TYKERB, lapatinib, into lipid nanoparticles to enhance their blood circulation time and bioavailability for BC treatment [113,114]. Other studies in this regard have also indicated that BC cells could readily uptake lipid nanoparticles, thereby reducing tumor growth in mice. One of the key limitations of clinical RNA use is the rapid intravascular degradation of RNA. According to the findings of Wang et al. [114] in this regard, RNA loading onto lipid nanoparticles led to an upsurge in the intracellular uptake of siRNA by the MDA-MB-468 triple negative BC cells in-vitro. In photothermal ablation (PTA), nanoparticles (especially metallic nanoparticles such as gold and silver) could produce heat at higher temperatures than 50 °C in BC tissues through the absorption and transformation of energy from near-infrared waves, resulting in the disruption of the cancer tumors through necrosis. Therefore, it is expected that further investigations in this regard will be oriented toward the use of targeted nanoparticles on human clinical levels with minimal damage to the surrounding healthy cells. Table 4 shows the approved nanoparticles in BC reports [115].

Albumin, as a biodegradable, bio acceptable transporter nanocarrier, nanospheres and nanocapsules protein with low antigenicity can bind to a wide variety of drugs and endogenous molecules.

Table 4
Examples of FDA approved nanoparticles and undergoing clinical trials for cancer therapy.

Nano Carrier	Trade Name	Status	Type of Cancer	Approved Year by FDA
Albumin Nanoparticle	Gemcitabine plus nabPaclitaxel	Approved	Pancreatic	2013 [142]
Metal Nanoparticle	CRLX101 (camptothecin)	Phase I & II	Rectal	2015 [143]
	Auroshell	Phase I	Solid tumor	2019 [144]
Liposomes	Doxil	Approved	Ovarian	2005 [144]
	Marqibo	Approved	lymphoma	2012 [144]
	Onivyde	Approved	Pancreatic	2015 [144]
	Eligard	Approved	Prostate	2002 [144]
	NC-6004	Phase II	Neck	2019 [143]
Micelle	NC-4016	Phase I & II	Various solid tumors	2018 [143]

Therefore, albumin has been used as a clinical excipient in many formulations. Using albumin-based nanoparticles could result in a long half-life, which maintains an efficient blood drug concentration. Also, covalent modification at the surface of albumin nanoparticles using free carboxyl and amine groups and diversified cross linkers can increase their ability in tumor targeting, especially for drugs having poor pharmacodynamics and pharmacokinetics properties. A wide range of drugs can be captured by simple functionalization to achieve a controlled and continued release [116].

Metal nanoparticles such as gold, silver and iron oxide NPs play a beneficial and powerful role in cancer therapy thanks to their low toxicity, small size-to-volume ratio, and excellent thermal stability. Their properties result in better targeting, gene silencing, drug delivery, and diagnostic assays. The surface functionalization strategy of metal nanoparticles with targeting ligands results in better control of energy deposition in tumors and prolongs the duration of drugs action which can revolutionize cancer treatment and management. Metal nanoparticles with certain sizes tend to accumulate more in tumor tissue (EPR effect) than they do in normal tissues, which leads to a decrease in the tumor progression rate [117].

Lipid-based nanoparticles such as liposomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) have high biocompatibility and biodegradability properties. Therefore, they have a remarkable capacity to diagnose and treat tumors. They can increase the time of drug action using a prolonged half-life, transport hydrophobic and hydrophilic molecules and cause an excellent controlled release of incorporated drugs. Interestingly, they can be prepared to be sensitive to pH and also be associated with different antibodies for recognizing tumor cells.

Liposomes have phospholipids as the main component with biocompatibility and biodegradability properties. They are constituted by a single or multiple bilayer surrounding an aqueous core that leads to form tiny spherical vesicles in the presence of water. This improves the stability of these nanoparticles in the blood to be transported to the tumor tissue and be taken up into individual cells in sufficient concentrations. Liposomes with size less than 400 nm, can rapidly penetrate to tumor sites from blood and can encapsulate hydrophilic molecules within the aqueous solution and hydrophobic agents within a hydrophobic membrane. Therefore, they can be considered as an excellent therapeutic nanocarrier. Since the membrane of liposomes is hydrophobic, they can carry both hydrophobic as well as hydrophilic drugs by molecular movement through the cellular membrane. Several drug studies based on liposome nanoparticles have currently undergone clinical trials (Table5) [118].

Polymeric nanoparticles, with a diameter ranging from 1 to 1000 nm, which consists of two or more different hydrophobicity chains, have been used in the diagnosis and drug targeting. Some of the general advantages of polymer-based nanoparticle systems are; drug release adjustment, the ability to switch the target of the therapeutic approach through active or passive targeting, and minimum degradation within the bloodstream. Therefore, by providing a sustainable controlled release of both hydrophilic and hydrophobic drugs, polymeric nanosystems can minimize the unwanted side effects through preventing climax of drug concentrations, while providing sufficient dose. Poly lactic-co-glycolic acid (PLGA) is an FDA-approved polymer employed in many biomedical applications due to its low cytotoxicity, great stability and favorable uptake by the EPR effect [119]. Some other examples of polymer-based nanomedicine approved by the FDA are listed in Table5.

Polymeric micelles have a relatively small size 10–100 nm with a supramolecular core–shell structure, which is formed from the self-assembly of biocompatible amphiphilic block copolymers in an aqueous condition. They are considered as a new platform for cancer diagnosis and treatment applications due to their ability to solubilize hydrophobic drugs as well as imaging agents. Moreover, encapsulating the drug within the polymer core can cause drug stability by delaying enzymatic degradation and inactivation. Some of these polymeric micelles have shown an antitumor effect, low systemic toxicity, which is currently undergoing phase I/II clinical trials [120]. However, in human trials, formulation and regulatory issues challenges are particularly still overwhelming. Nanoscale approaches have played a pivotal role in converting devastating cancers to be well on the verge of being cured thanks to improvements in materials chemistry, nanoscience, biology, and medicine. Table 3 lists some of the FDA-approved drugs that have been developed for clinical use.

Table 5
Approved or currently in clinical trials nanoparticles in breast cancer treatment.

Nanoparticle	Product	Status in USA
Liposomal	Doxil	Approved
Albumin	Abraxane	Approved
Liposomal	Myocet	Phase III
Polymeric	NK-105	Phase I & III
Polymeric	Genexol-PM	Phase III
Liposomal	LEP-ETU	Phase II
Liposomal	Nektar-102	Phase III
Liposomal	ThermoDox	Phase I & II
Liposomal	Liposomal annamycin	Phase I & II
Phospholipid	Rexin-G	Phase I & II
Liposomal	SPI-077	Phase I
Liposomal	S-CKD602	Phase I
Polymeric	Nanoxel	Phase I
Polymeric	BIND-014	Phase I

2.2.5. Targeting breast cancer stem cells (BCSCs)

The role of the BCSCs in the development of chemo-resistant and radio-resistant tumors raised a motivation for targeting this cell type. The BCSCs have a high expression of CD44 that can be used as a target. One of the mechanisms of drug delivery in various diseases, including cancer, is the use of nanomedicine. Different nanoparticles such as liposomes, PLGAs, carbon nanotubes, and graphene oxide coated with specific antibodies or aptamers against CSC markers can be used to deliver drugs to CSCs [63,121,122]. Nanoparticles loaded with various chemotherapeutic drugs and bound to anti-CD44 antibody were able to target the BCSCs [123,124]. The combination of autophagy-inhibiting drugs such as chloroquine along with chemotherapy drugs has introduced a new therapeutic line to target tumor CSCs and showed a decrease in ALDH1 of BCSCs [125,126]. The nanoparticles, such as cationic liposomes, had an important role in the delivery of siRNA inhibitors to CSCs in BC [126].

Another promising therapeutic approach to target BCSCs is the signaling pathways. Various reports indicated that Notch pathways are dysregulated in many types of BCs [127,128]. Activation of the Notch signaling pathway is dependent on the release of the intracellular domain of Notch receptors, which acts as a transcription factor for oncogenes [128]. The release of the intracellular domain of Notch receptors is managed by the γ-secretase enzyme. Therefore, inhibition of γ-secretase, alone or in combination with chemotherapeutic drugs in the early clinical phase, might regulate the Notch pathway. The most important adverse effect, reported from clinical trials, is hyperplasia of goblet cells resulting in gastrointestinal toxicity [129,130]. Inhibition of the Hedgehog pathway, another important pathway in BC stem cells regulation, has also been studied and their non-toxicity has led to the development of phase II studies in combination with chemotherapy drugs [131,132]. Targeting other signaling pathways including the PI3K/Akt/mTOR pathway that is aberrantly activated following trastuzumab therapy also showed promising results in targeting BCSCs in HER-2 positive cancers [132].

One of the interesting therapeutic approach to decrease BCSCs is to target the metabolism of the BCSCs. Like other CSCs, BCSCs mainly use the aerobic glycolysis pathway and oxidative phosphorylation (OXPHOS) to increase their survival [133]. The BCL2 protein inhibitors

and inhibition of peroxisome proliferator-activated receptor γ, co-activator 1α (PPARGC1A or PGC-1α) transcription factor lead to down-regulate the OXPHOS pathway and reduce BCSCs, invasion, and metastasis of cancer cells [134,135]. Recent studies have shown the role of fatty acid oxidation as well as iron metabolism in the growth and proliferation of the CSCs. Thus, BCSCs might be decreased via targeting these pathways [136–138].

Ultimately, all of the above-mentioned approaches are at the beginning of the road and their promising results guarantee further success in future studies targeting these cells for the treatment of BC. However, the emerging of evidence indicating the plasticity in CSCs and the conversion of non-stem cell tumors into CSCs [63] remains a major challenge that demonstrates the need for deep studies to target these dangerous tumor leaders.

3. Conclusion

This review concludes to the choice of promising strategy result in considerable achievement in BC treatment. Conventional approaches including hormone therapies showed not enough efficacy. Although chemotherapeutic agents have several side effects, they are still considered as the first line of therapy in aggressive BC owing to their high potency for inducing ICD. Furthermore, signaling pathways and metabolic components in BCSCs, could be targeted and considered as an appropriate treatment for BC patients. Antibody-drug conjugates as biological agents, which deliver drug components such as toxins and radioisotopes, could target specific tumor antigens on the cell surface. Furthermore, nanoparticles, when combined with chemotherapy, showed more efficacy than the antibody-drug conjugates alone. BCSCs are the most critical cells leading to chemo-resistance and radio-resistance in tumor therapy. Therefore, targeting signaling/metabolic pathways and cell surface molecules (by applied some tests such as Oncotype DX, Mamm aPrint, and uPA/PAI-1), and ADCs or nanoparticles in combination with chemotherapy might provide new approaches to increase survival of BC patients and clinical outcomes. Although the significant role of immunotherapy in breast cancer should be always taken into account, more conclusive experiments in this field are needed.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2020.106535.

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