Breast Cancer: Targets and Therapy

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REVIEW

Breast Cancer: An Overview of Current Therapeutic Strategies, Challenge, and Perspectives

Jun Wang[1], San-Gang Wu[2]

[1]Department of Head and Neck Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, People's Republic of China; [2]Department of Radiation Oncology, the First Affiliated Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, 361003, People's Republic of China

Correspondence: San-Gang Wu, Department of Radiation Oncology, the First Affiliated Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen, 361003, People's Republic of China, Tel +86 592 2139531, Fax +86 592 2137322, Email unowu12345@hotmail.com

Abstract: Breast cancer is the most commonly diagnosed cancer and the leading cause of death among female patients, which seriously threatens the health of women in the whole world. The treatments of breast cancer require the cooperation of a multidisciplinary setting and taking tumor load and molecular makers into account. For early breast cancer, breast-conserving surgery with radiotherapy or mastectomy alone remains the standard management, and the administration of adjuvant systemic therapy is decided by the status of lymph nodes, hormone receptors, and human epidermal growth factor receptor-2. For metastatic breast cancer, the goal of treatments is to prolong survival and maintain quality of life. This review will present the current advances and controversies of surgery, chemotherapy, radiotherapy, endocrine therapy, targeted therapy, immunotherapy, gene therapy, and other innovative treatment strategies in early-stage and metastatic breast cancer.

Keywords: breast cancer, surgery, chemotherapy, radiotherapy, endocrine therapy, targeted therapy, immunotherapy, gene therapy

Introduction

Breast cancer is the most commonly diagnosed cancer among female patients and is the leading cause of cancer-related death.[1] There were 300,590 new cases and 43,700 deaths of invasive breast cancer in the United States based on the 2023 prediction, accounting for approximately 30% of female cancers.[1] The treatments of breast cancer include surgery, chemotherapy, radiotherapy (RT), endocrine therapy, targeted therapy, and immunotherapy, and the therapeutic schedules require the cooperation of multiple subspecialties. For non-metastatic breast cancer, surgery-based treatment is the standard management, and chemotherapy-based preoperative systemic therapy can reduce tumor volume of the breast, making breast conservation possible, and decreasing the need for axillary lymph node dissection (ALND).[2] Systemic treatment remains the preferred option for metastatic breast cancer, and surgery is only used for palliative therapy in selected metastatic patients.[3] The advances in endocrine therapy, targeted therapy, and immunotherapy provide additional treatments for patients with metastatic and non-metastatic breast cancer. Some innovative therapies are also being investigated, such as gene therapy, vaccines, adoptive cell therapies, including T cell receptor therapy and chimeric antigen receptor T (CAR-T) therapy, and achieved promising results. This review aims to summarize the current status and controversies of surgery, chemotherapy, RT, endocrine therapy, targeted therapy, immunotherapy, gene therapy, and other innovative therapies in breast cancer, and provides better management for oncologists.

Surgery

Breast-conserving surgery (BCS) and mastectomy with or without immediate reconstruction are both well-established local managements for early invasive breast cancer. The widespread use of systematic treatments in past decades led to the reduction of locoregional recurrence rates (LRR) and distant metastasis rates, and the 10-year LRR of BCS followed by RT was 2–3% for estrogen receptor (ER) positive and human epidermal growth factor receptor-2 (HER-2) positive breast cancer and 5% for triple-negative breast cancer (TNBC), which was similar to that after mastectomy in early breast

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cancer.[4,5] In addition, patients with BCS+RT had better cosmetic effects and life satisfaction compared with mastectomy.[6] Therefore, BCS following RT is the intended surgical standard of care for most breast cancers. However, the selection of BCS should still be cautious for patients with diffuse suspicious micro-calcifications, multicentric cancer, unable to obtain negative margins, and having contraindications to RT.[7] Younger age, lobular carcinoma, and aggressive subtypes, such as triple-negative and HER2 positive diseases are not contraindications for BCS. For patients with large tumors, neoadjuvant chemotherapy (NAC) can be chosen to downstage the tumor for BCS.

The management of axillary lymph nodes (ALNs) is decided by the status of ALNs at diagnosis and the administration of neoadjuvant systemic therapy. ALND remains the standard in patients with clinically proven axillary involvement at initial diagnosis.[8] For patients with clinically node-negative (cN0) breast cancer, the management of axillary is controversial. There seemed to be comparable recurrence and survival outcomes between ALND and sentinel lymph node (SLN) biopsy in the era of contemporary systemic treatments.[9] In addition, several prospective trials demonstrated that there was no significance of recurrence and survival between SLN biopsy alone and SLN biopsy plus RT in patients with cN0 and one to two SLN involvement.[10–12] Therefore, SLN biopsy might be sufficient for most cN0 patients, and additional axillary radiation only for selected patients, such as patients with three SLN involvement. Further studies are needed to explore the value of ALND, SLN biopsy, and RT in patients with cN0 disease.

Surgery also plays an important role in the management of local-regional recurrent breast cancer. Total mastectomy remains the standard of care for recurrent patients initially receiving BCS, and salvage mastectomy ± ALND could achieve 85–95% loco-regional control in this disease.[8,13] Patients suffering chest-wall recurrence after initial mastectomy had a higher risk of metastasis than those initially treated with BCS.[14] In addition, previous studies showed that limited resection was related to a higher second local recurrence of 60–70%; therefore, the routinely recommended management for patients initially treated with mastectomy is wide resection of the recurrent lesions when possible.[15,16]

Chemotherapy

The modalities of chemotherapy in breast cancer include NAC, adjuvant chemotherapy (AC), and salvage chemotherapy. The administration of chemotherapy could reduce the risk of recurrence by approximately 30% in early breast cancer.[17] NAC could downstage the breast and axilla for receiving breast conservation in operable breast cancer, convert inoperable breast cancer to resectable, and eliminate micrometastatic lesions. NAC is recommended for patients with a large tumor, multiple ALNs involvement, and aggressive subtypes, especially for triple-negative and HER2-positive breast cancer.[18] The application of NAC in aggressive breast cancer subtypes could evaluate the response to treatment, predict cancer prognosis, and guide subsequent treatment decision-making. Previous studies showed that NAC followed by surgery had similar LRR and survival outcomes compared with surgery followed by chemotherapy, but patients treated with NAC decreased 17% of mastectomy rates.[19,20] NAC or AC should be administrated in high-risk patients, such with large tumor size, nodal involvement, low expression of hormone receptor (HR), younger age, and lymphovascular invasion.[8] Sandwich chemotherapy should be avoided outside of clinical trials.[21] In addition, multigene assays and molecular types could be used to stratify and identify patients who benefit from chemotherapy, especially for node-negative ER-positive, triple-negative, or HER2-positive diseases.[22–24]

The current optimal chemotherapy regimen is taxane with or without anthracycline, given in sequence or combination, both in NAC and AC settings.[8] The application of anthracyclines remains controversial, but it seems to be essential in high-risk patients, such as triple-negative and HER-2 positive subtypes.[25,26] For patients with TNBC, the addition of platinum to standard regimens (anthracycline and taxane-based regimen) achieved an absolute improvement of pathological complete response (pCR) (15%); however, long-term survival outcomes are less convincing due to the small sample size and short follow-up time.[27,28] Another Phase 3 randomized clinical trial including 647 patients explored the value of docetaxel and carboplatin regimens in place of standard regimens in patients with TNBC, and docetaxel and carboplatin showed improved disease-free survival (DFS) and relapse-free survival, but comparable overall survival (OS) compared with standard regimens.[29] Therefore, the docetaxel and carboplatin regimen can be used as an alternative to the conventional regimen in the treatment of TNBC. In addition, another Phase III study included 443 patents with early TNBC to assess the effect of low-dose and high-frequency capecitabine maintenance, and result showed that patients receiving capecitabine maintenance had higher 5-year distant disease-free survival (85.8% vs 75.8%, $p = 0.02$); therefore,

low-dose and high-frequency capecitabine maintenance could be used as consolidation therapy in patients receiving standard adjuvant therapy.[30,31]

AC is commonly recommended for 3–4 weeks after surgery.[32] A population-based study explored the effect of the wider time window, and the authors found that delays beyond 91 days from surgery to the start of AC were related to worse survival, especially in TNBC.[33] Therefore, the administration of AC within 3 months after breast surgery is acceptable. With regard to optimal chemotherapy interval, a dose-dense regimen (every 14 days) had better DFS and OS than the conventional interval (every 21 days) in early breast cancer.[34]

Radiotherapy

Two large-scale randomized trials evaluating the effect of omitting RT in low-risk patients receiving BCS achieved negative results, thus adjuvant RT remains the standard of care for patients receiving BCS.[35,36] Whole breast irradiation (WBI) is a convenient option used for adjuvant RT following BCS. Hypofractionated WBI appeared to have comparable local recurrence, survival outcomes, and toxicity profiles compared with WBI.[37,38] Therefore, hypofractionated WBI is also supported for early breast cancer not requiring nodal therapy.[37,38] In addition, partial breast irradiation (PBI) demonstrated similar local recurrence, but improved cosmetic results and reduced toxicity compared with WBI, thus PBI seemed to be an acceptable alternative for appropriately selected low-risk patients.[39,40] Accelerated partial-breast irradiation (APBI) is also a treatment option for selected early-stage breast cancer patients receiving BCS with reduced recurrence rates (HR = 4.54, 95% CI: 1.78–11.61, p = 0.002) compared with WBI.[41] Brachytherapy also showed a similar breast cancer recurrence rate compared with external radiotherapy (5-year event rate: 4·4%) in the radiation of breast cancer, yet the application of brachytherapy should be cautious due to the lack of sufficient evident data.[42]

For patients receiving mastectomy, whether to irradiate is decided by the number of involved ALNs. Postmastectomy radiation therapy (PMRT) is conventionally used in patients with four or more positive ALNs;[8] however, the administration of PMRT in patients with one to three involved ALNs remains unclear. Current clinical guidelines strongly recommend PMRT for this patient subset, which is based on the result from the meta-analysis published in Lancet 2014 that PMRT had significantly decreased the LRR rate and cancer-related death.[8,43] However, most of the trials enrolled in this meta-analysis were completed before the 1980s, when the RT technique and chemotherapy regimens were much more backward than what it is now, and the LRR rate without PMRT was approximately 30% at that time.[43] Several recent studies showed that there seemed no incremental survival benefits in patients with one to three involved ALNs in the era of contemporary systemic treatment.[44,45] Therefore, it seems to be essential to select high-risk patients for receiving PMRT, such as younger age, a higher burden of breast and axilla, and biological characteristics. Recent studies demonstrated that the 8th American Joint Committee on Cancer (AJCC) pathological prognostic staging integrating molecular markers could guide the RT administration in patients with N1 breast cancer.[46,47] Further studies are needed to explore the value of PMRT in patients with one to three involved ALNs.

For patients with positive regional lymph nodes, there is evidence that chest wall and infra-/supraclavicular regions radiation were beneficial. The MA.20 trial included 1832 patients with LN positive, and randomized to receive breast irradiation with or without full regional nodal irradiation [including internal mammary nodes (IMNs)].[48] Ten-year follow-up showed that additional regional nodal irradiation had improved 24% DFS.[48] Chest wall and infra-/supraclavicular regions are commonly irradiation areas; however, the value of IMNs radiation remains a debate. Several studies demonstrated improved OS and decreased breast cancer mortality in patients receiving regional nodal irradiation including IMNs, but higher heart and lung toxicities, lymphedema, and non-breast cancer mortality risk were observed.[49,50] Another trial evaluated the value of additional IMN irradiation in patients with positive ALNs or central lesions without positive ALNs, and the result showed that there was no survival benefit in any of the groups (10-year OS: 62.6% vs 59.3%, P > 0.5). Therefore, further studies should be conducted to explore the effect of IMN irradiation.[51]

Endocrine Therapy

Endocrine therapy is considered standard as adjuvant therapy for patients with HR-positive (ER or PR staining ≥1%) over the course of 5–10 years. The sensitivity of endocrine therapy is directly associated with the expression of hormone receptors.[52] In premenopausal patients, tamoxifen 20 mg per day for 5 years could reduce about 50% recurrence risk in

the first 4 years, and over 30% during 5–9 years, and a longer duration of tamoxifen resulted in further reduction of recurrence and breast cancer mortality.[53] Another study from the ATLAS trial demonstrated that the administration of 10-year tamoxifen could reduce breast cancer death by 2% (9.6% vs 11.6%) compared with 5-year tamoxifen.[54] Therefore, the duration of tamoxifen should be continued for 10 years. For patients with a high risk of relapses, such as those aged ≤35 years or after chemotherapy, ovarian suppression drugs combined with an aromatase inhibitor (AI) or tamoxifen had improved DFS, but higher toxicity compared with tamoxifen alone.[55,56]

In postmenopausal patients, tamoxifen or AI monotherapy 5 years or in sequence are both alternative treatment strategies. AI monotherapy 5 years had reduced breast cancer mortality than tamoxifen 5 years, thus AI is preferred as adjuvant therapy, especially in high-risk patients and patients with lobular histology.[57,58] However, patients receiving AI therapy had higher rates of bone-related adverse events, such as fractures and osteoporosis; therefore, tamoxifen can be used as an alternative for patients with serious AI-related adverse events. The duration of tamoxifen and AI in post-menopausal patients should be further assessed for the balance of risks and benefits, and multigene assays might be useful in predicting the appropriate duration.[59] In addition, the combination of CDK inhibitors and AI could significantly improve DFS in metastatic breast cancer compared with AI alone; therefore, CDK inhibitors plus AI could be an alternative strategy in endocrine-resistant metastatic breast cancer.[60] Detailed information is presented in Table 1.

The value of neoadjuvant endocrine therapy in early ER-positive breast cancer was unclear. Early studies of neoadjuvant endocrine therapy were focused on elderly postmenopausal patients with locally advanced breast cancer, or unable to receive chemotherapy. The response rate of neoadjuvant tamoxifen was about 50%.[63,64] A recent study showed that neoadjuvant endocrine therapy combined with chemotherapy could increase BCS rates in postmenopausal patients with luminal breast cancer.[61] Moreover, neoadjuvant anastrozole seemed to have a similar anti-cancer effect compared with tamoxifen.[62] AI is more commonly used as neoadjuvant therapy than tamoxifen for better efficacy. Currently, there is no evidence for the optimum duration of neoadjuvant endocrine therapy lacking supporting data. In addition, other ongoing trials use the level of Ki67 after neoadjuvant endocrine therapy to guide the administration of AC.

Targeted Therapy

The appearance of anti-HER2 targeted therapy greatly changed the treatment paradigm and prognosis of HER2-positive breast cancer. Trastuzumab, the first anti-HER2 targeted drug, has been widely used in HER2-positive diseases. American Society of Clinical Oncology (ASCO) Annual Meeting in 2005 firstly reported the benefit of trastuzumab combined with anthracycline/taxane-based adjuvant therapy in HER2-positive breast cancer. A later study showed that

Table 1 Representative Studies of Endocrine Therapy for Breast Cancer

Author	Patients	Intervention	Outcomes
EBCTCG group. 2011[53]	21,457	Tamoxifen 5 years vs no adjuvant tamoxifen	Reduced recurrence rates in the first 10 years, no further gain or loss after 10 year
Davies et al 2013[54]	12,894	Tamoxifen 5 years vs tamoxifen 10 years	10-year tamoxifen could reduce breast cancer death by 2% (9.6% vs 11.6%)
Pagani et al 2014[55]	4,690	Exemestane+ovarian suppression vs tamoxifen +ovarian suppression 5 years	5 years disease-free survival 91.1% vs 87.3%, P<0.001; 5 year breast cancer specific survival 92.8% vs 88.8% P<0.001
EBCTCG group. 2015[57]	31,920	Aromatase inhibitor 5 years vs tamoxifen 5 years	10-year breast cancer mortality: 12.1% vs 14.2%, p=0.009
Gao et al 2020[60]	4200	CDK4/6 inhibitors +endocrine therapy (aromatase inhibitor or fulvestrant) vs endocrine therapy	CDKI plus endocrine therapy had better median progression-free survival (HR 0.59, 95% CI 0.54–0.64)
Alba et al 2012[61]	95	Neoadjuvant chemotherapy vs neoadjuvant hormone therapy	The clinical response rate was 66% vs 48%, p=0.075
Smith et al 2005[62]	124	Neoadjuvant tamoxifen, anastrozole, or the combination of tamoxifen and anastrozole	Anastrozole had similar OR compared with tamoxifen (58% vs 22%, p=0.18) for patients with HER2-positive cancer

adjuvant trastuzumab combined with paclitaxel had low local-regional and distant recurrences and reduced toxicity in HER-2 positive breast cancer patients with tumors ≤2 cm and negative nodes.[65] In addition, trastuzumab combined with other chemotherapy regimens (adriamycin/ cyclophosphamide-paclitaxel, docetaxel, and carboplatin) achieved absolute OS advantage.[66] Based on the above studies, trastuzumab (1 year) incorporating chemotherapy (adriamycin/cyclophosphamide-paclitaxel, docetaxel, and carboplatin) as neoadjuvant and adjuvant regimens is recommended for patients with HER2-positive disease.[8]

Other anti-HER2 drugs, such as pertuzumab and lapatinib, were also assessed in HER-2-positive breast cancer. Recent prospective data showed that additional pertuzumab to trastuzumab plus docetaxel in neoadjuvant therapy could significantly improve pCR compared with trastuzumab plus docetaxel (45·8% vs 29.0%); therefore, neoadjuvant dual-HER2 agents (pertuzumab/trastuzumab) are also an alternative for stage II–III HER2 positive breast cancer.[67] Lapatinib seemed to have higher pCR in the neoadjuvant setting, and a recent phase III study showed that paclitaxel combined with trastuzumab plus lapatinib had better RFS and OS compared with paclitaxel plus lapatinib; thus, chemotherapy plus dual HER2-targeting drugs was still a promising treatment in HER2-positive breast cancer.[68]

For metastatic HER2-positive breast cancer, anti-HER2 therapy should be used as early as possible, docetaxel plus trastuzumab and pertuzumab were recommended as first-line standards based on the CLEOPATRA trial.[69] Trastuzumab emtansine (TDM-1) had a significantly prolonged PFS and OS than lapatinib plus capecitabine in metastatic HER2-positive breast cancer patients previously treated with trastuzumab from the EMILIA trial.[70] Therefore, lapatinib has been approved for the second-line treatment of metastatic HER2-positive breast cancer. Neratinib is another small molecule of HER1/HER2 inhibitors. The addition of neratinib to capecitabine showed improved PFS and lower central nervous system disease compared with lapatinib plus capecitabine in the phase III NALA trial.[71] Another Phase II trial evaluated the value of single-agent neratinib in metastatic HER2-positive breast cancer, but only 8% response rates were observed; thus, the value of neratinib in metastatic breast cancer should be further assessed.[72] Despite the advances in targeted therapy in HER2-positive breast cancer, the resistance to anti-HER2 drugs is still a serious problem and exploring the way to relieve targeted therapy resistance is needed.

Immunotherapy

Breast cancer has impaired activated T cell killing of tumor cells due to the presence of inhibitory factors such as interaction between the PD-1, TIM-3, LAG3, TIGIT, CTLA4 and their ligands on the cancer cells promotes T-cell exhaustion and prevents responsiveness to therapy. Therefore, the use of immune checkpoint blockade as an anti-tumor therapy has demonstrated modest single agent activity in advanced breast cancer.[73,74]

The efficacy of single-agent immune checkpoint inhibitors (ICIs) in metastatic TNBC is low.[75–77] KEYNOTE-012 trial evaluated the value of pembrolizumab in pre-treated PD-L1 positive metastatic TNBC, and an overall response rate (ORR) of 18.5% was observed.[75] KEYNOTE-086 and JAVELIN trials showed an ORR of 21.4% (pembrolizumab) and 5.2% (avelumab), respectively.[76,77] The combination of chemotherapy with ICIs demonstrated better results than ICI monotherapy, with an ORR of 26.4–39.4% in 0–2 prior lines of treatment for metastatic TNBC.[78,79] IMpassion130, a phase III large-scale randomized trial, included 902 previously untreated, locally advanced, or metastatic TNBC patients, and randomized to receive atezolizumab plus nab-paclitaxel or nab-paclitaxel alone.[80] The result showed that patients treated with atezolizumab plus nab-paclitaxel had significantly improved median OS compared with nab-paclitaxel alone.[80] However, another study from the IMpassion131 trial achieved a negative result that atezolizumab combined with paclitaxel could not improve survival compared with paclitaxel.[81] In addition, pembrolizumab plus chemotherapy (nab-paclitaxel; paclitaxel; or gemcitabine plus carboplatin) had increased PFS than chemotherapy alone in untreated locally recurrent or metastatic TNBC.[82] Therefore, atezolizumab and pembrolizumab are approved by the United States Food and Drug Administration (FDA) for the first-line treatment of PD-L1 positive metastatic TNBC. In addition, in patients with metastatic HER2-positive breast cancer, pembrolizumab+trastuzumab showed a 15% response rates in PD-L1-positive tumors; however, atezolizumab combined with T-DM1 did not improve PFS but increased toxicity.[83,84]

The value of ICIs plus chemotherapy was also explored in early-stage breast cancer, and preliminary success was observed.[85,86] The addition of pembrolizumab to chemotherapy (paclitaxel, doxorubicin, cyclophosphamide) in the neoadjuvant setting of stage II–III breast cancer had higher pCR rates in HER2-negative (44% vs 17%), HR-positive

/HER2-negative (30% vs 13%), and triple-negative subtypes (60% vs 22%) than chemotherapy alone.[85] KEYNOTE-522 demonstrated that four cycles of pembrolizumab plus paclitaxel/ carboplatin, then four cycles of pembrolizumab plus anthracycline/cyclophosphamide showed improved pCR rates (64.8% vs 51.2%) and event-free survival (91.3% vs 85.3%) compared with neoadjuvant chemotherapy alone in TNBC.[86] In addition, neoadjuvant durvalumab plus nab-paclitaxel/epirubicin/cyclophosphamide had an increased pCR rate, especially in patients with durvalumab alone before chemotherapy.[87] In Impassion 031 study, atezolizumab combined with nab-paclitaxel+anthracycline also had increased pCR rate (41% vs 58%, $p = 0.0044$) in TNBC patients.[85] However, fewer results were available in luminal and HER2-positive subtypes. A Phase 2 study exploring the effect of pembrolizumab plus neoadjuvant paclitaxel+doxorubicin +cyclophosphamide in HER2-negative patients, and results showed that patients receiving pembrolizumab undergone higher pCR rate (30% vs 13%) in luminal patients.[88] Although promising results were observed in neoadjuvant therapy of ICIs plus chemotherapy, longer follow-up data are needed to confirm the long-term efficacy.

Gene Therapy

Gene therapy is also a promising approach in the treatment of cancers, which defined as sending genetic material through a vector into target cells to edit the gene and change the expression of a gene's product, and achieving the goal of treating cancers.[89] Gene therapy strategies include gene editing, targeting transcription factors, microRNA, and breast cancer cells, DNA or RNA vaccination, and so on. A Phase I clinical trials tested the safety and efficacy of genetic prodrug activation therapy targeted the human HER-2 gene promoter. The study included 12 breast cancer patients, and result showed that the approach was safe and targeted gene expression was detected in up to 90% of the patients.[90] Another phase 2 trial includes 28 patients with metastatic TNBC to explore the value of in situ virus gene therapy (ADV/HSV-tk) plus stereotactic body radiotherapy and pembrolizumab, and the result demonstrated that clinical benefit rate was 21.4%, and patients with clinical benefit had durable responses, with improved median duration on treatment (9.6 months) and OS (14.7 months).[91] Use of microRNA in anti-cancer therapy also showed promising results in inhibiting breast cancer cell proliferation and development. MRX34, to our knowledge, is one of the first miRNA replacement agents (miR-34a), and now in entering clinical trials. It is believed that it will play a vital role in the treatment of breast cancer in the future. Currently, few studies on gene therapy were published, but a lot of strategies have entered clinical trials in breast cancer. We summarized several clinical studies on breast cancer gene therapy in Table 2.

Table 2 Ongoing Trials of Gene Therapy, Vaccine, and CAR-T Therapy of Breast Cancer

Identifier	Patients	Trial phase	Intervention	Endpoints
NCT00849459	mBC	Phase I	Adenovirus-mediated human interleukin-12	Serum antibodies (titer) to adenovirus, toxicity and safety
NCT00880464	Operable BC	Phase Ib	Vaccination with autologous tumor cells engineered by adenoviral mediated gene transfer to secrete GM-CS	Minimum number of vaccine doses, adverse events
NCT00505271	R/M BC	Phase I/II	Rexin-G	Clinical toxicity
NCT00673829	mBC	Phase I	Gene modified T Cells and Interleukin 2	The safety of using modified T-cells, optimal biologic dose of Interleukin 2
NCT01829971	TNBC and other cancers	Phase I	MRX34, micro RNA therapy	Maximum tolerated dose for MRX34
NCT00093834	mBC	Phase I	Allogeneic GM-CSF-Secreting Breast Cancer Vaccine	Toxicity of vaccine
NCT00784524	mBC	Phase II	LMI Vaccination + IL-2	Disease response
NCT04674306	IIA-IIIC TNBC	Phase I	α-lactalbumin vaccine	Treatment cohort maximum tolerated dose of α-lactalbumin vaccine
NCT04430595	III–IV BC	Phase I/II	4SCAR T cells	Number of patients with adverse events
NCT02792114	mBC	Phase I	Mesothelin-targeted T cells	Maximum tolerated dose

Abbreviations: BC, breast cancer; mBC, metastatic breast cancer; R/M, recurrent/metastatic; TNBC, triple negative breast cancer; CAR-T, chimeric antigen receptor T.

Conclusion and Future Perspectives

The value of local and systemic therapies in breast cancer has been well established. For early breast cancer, surgery-based local and systemic treatments are the standard of care. For metastatic breast cancer, chemotherapy-based systemic treatments remain the preferred option, and surgery is only used for palliative therapy in selected patients. However, survival benefits of traditional treatment strategies were limited. The emergence of targeted therapy and immunotherapy further changed the treatment pattern of early and metastatic breast cancer. Atezolizumab or pembrolizumab combined with chemotherapy are approved by FDA for the first-line treatment of PD-L1 positive metastatic TNBC. Neoadjuvant and adjuvant pembrolizumab is approved for early TNBC. Numerous novel ICIs and new ICIs-based combination therapies have entered into clinical trails.

In addition, some innovative therapies are being investigated in breast cancer, such as gene therapy, breast cancer vaccines, adoptive cell therapies, including T cell receptor therapy and CAR-T therapy, and so on. Several phase I/II clinical trails have demonstrated an preliminary improved outcome, and most of them are still ongoing. We summarize some ongoing clinical studies in Table 2. We believe these new therapeutic strategies will gradually be integrated into clinical treatments.

Disclosure

The authors report no conflicts of interest in this work.

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