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Recent advances in treatment of Triple-negative breast cancer

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Abstract
Triple-negative breast cancer (TNBC), a specific subtype of breast cancer that does not express estrogen receptor (ER), progesterone receptor (PR), or human epidermal growth factor receptor 2 (HER-2), has clinical features that include high invasiveness, high metastatic potential, high risk of relapse, and poor prognosis. Because TNBC tumors lack ER, PR, and HER2 expression, they are not sensitive to endocrine therapy or HER2 treatment, and standardized TNBC treatment regimens are still lacking. Therefore, development of new TNBC treatment strategies has become an urgent clinical need. This paper aims to provide recent treatment options and their future prospects for TNBC treatment.

Keywords: Breast cancer, human epidermal growth factor receptor 2, poly (ADP-ribose) polymerase inhibitor, programmed cell death protein 1, triple negative breast cancer

Introduction

Breast cancer is the most common malignancy in women in India and worlwide. Breast cancer is a highly heterogeneous disease. Clinical treatment and prognosis varies greatly between patients. New definition of breast cancer molecular subtypes is luminal A (ER/PR^+, $HER2^-$, $Ki67^+ < 20\%$, with the percentage indicating the immunohistochemical staining results for patient samples), luminal B ($ER/PR^+ < 20\%$, $HER2^-$, $Ki67^+ \geq 20\%$); $HER2^+$ B2 (ER/PR^+, HER2 overexpression), HER2 overexpression (ER^-, PR^-, HER2 overexpression), basal-like TNBC (ER^-, PR^-, $HER2^-$) and other special subtypes [1].

Triple-negative breast cancer (TNBC) is defined as a type of breast cancer with negative expression of estrogen (ER), progesterone (PR), and human epidermal growth factor receptor-2 (HER2) [2]. Gene expression profiling analysis often classifies TNBC as a subtype of basal-like breast cancer (BLBC).

Epidemiological data show that TNBC mostly occurs in premenopausal young women under 40 years old, who account for approximately 15–20% of all breast cancer patients [3]. Compared with other subtypes of breast cancer, the survival time of TNBC patients is shorter, and the mortality rate is 40% within the first 5 years after diagnosis [4]. TNBC is highly invasive, and approximately 46% of TNBC patients will have distant metastasis. The median survival time after metastasis is only 13.3 months, and the recurrence rate after surgery is as high as 25%. The metastasis often involves the brain and visceral organs. Distant metastasis mostly occurs in the 3rd year after diagnosis [5]. The average time to relapse in non-TNBC patients is 35–67 months, while that in TNBC patients is only 19–40 months. The mortality rate of TNBC patients within 3 months after recurrence is as high as 75% [6, 7].

TNBC is not sensitive to endocrine therapy or molecular targeted therapy. Thus, chemotherapy is the main systemic treatment, but the efficacy of conventional postoperative adjuvant chemoradiotherapy is poor. The residual metastatic lesions eventually will lead to tumor recurrence [8]. Bevacizumab has been used in combination with chemotherapeutic drugs to treat TNBC in some countries, but the survival time of patients did not increase significantly [9]. Therefore, it is urgent to develop new treatment regimens and targets.

Current drugs for treatment of TNBC

Triple negative breast cancer is more aggressive and difficult to treat than HR+ and HER2+ BC. For TNBC, standard chemotherapy remains the mainstay of treatment. Compared to other types of breast cancer, TNBC has limited treatment options, is prone to recurrence and metastasis, and has a poor prognosis. The main reason is that the expression of ER, PR, and HER2 are all negative, making specific endocrine therapies and targeted therapies ineffective. Therefore, chemotherapy has become the main approach for the treatment of TNBC.

Taxanes

Taxanes act mainly through the inhibition of microtubule depolymerization, and thus, cells cannot form spindles and spindle fibers during mitosis, forcing the cells to stop in prometaphase, thereby inhibiting cell division. In addition to its antimitotic effect, taxel also has the antitumor function mediated by activated macrophages. The antitumor toxicity of taxel is also associated with its induction of apoptosis. Gene profiling analysis of TNBC molecular subtypes showed that the BL subtype has active expression of proliferation-related genes and DNA repair genes, suggesting that the BL subtype may be sensitive to antimitotic drugs (e.g., taxel or docetaxel). After the application of taxane-based chemotherapy in TNBC patients, the basal-like subtypes (BL1 and BL2) have four times higher clinical remission rates than the MSL subtype and LAR subtype [10, 11].

Anthracyclines

Anthracyclines are a class of chemotherapeutic drugs derived from *Streptomyces peucetius*. They are broad spectrum anticancer drugs and can treat many types of cancer [12]. Through a large number of clinical studies, researchers have obtained optimal dosing schedules of anthracycline adjuvant therapy for breast cancer: the optimum dose of doxorubicin is 60 mg/m^2 and that of epirubicin is 100 mg/m^2 [13]. According to the existing clinical data, after 6 months of chemotherapy with anthracyclines, the mortality rate decreased by approximately 38% in patients younger than 50 years at the time of diagnosis, whereas the mortality rate in patients aged 50 to 69 years at the time of diagnosis decreased by approximately 20%. The efficacy of anthracycline chemotherapy showed no significant difference between breast cancer subtypes [14].

Cyclophosphamide

Cyclophosphamide does not have antitumor activity in vitro. After entering the body, cyclophosphamide is first converted to aldophosphamide by the microsomal mixed-function oxidases in the liver. Aldophosphamide is unstable and is activated by cytochrome P450 in tumor cells to produce nitrogen mustard and acrolein with alkylating activity. Nitrogen mustard has cytotoxic effects on tumor cells. Currently, TC is commonly used as the standard neoadjuvant chemotherapy regimen for HER2-negative breast cancer. Nakatsukasa et al. enrolled 52 breast cancer patients. Of them, 94.2% (49/52) patients completed 4 TC cycles and had an overall pCR rate of 16.3% (8/49); patients with luminal A-like breast cancer (ER$^+$, Ki67 index < 20%, HER2 negative) had a pCR rate of 0% (0/12); patients with luminal B-like breast cancer (ER$^+$, Ki67 index > 20%, HER2 negative) had a pCR rate of 4.3% (1/23); patients with TNBC had a pCR rate of 50.0% (7/14); almost all of the pCR occurred in TNBC breast cancer patients [34]. The results showed that neoadjuvant chemotherapy with TC was more suitable for the treatment of TNBC but had limited efficacy in treating other subtypes of breast cancer. Wu et al. found that adjuvant cyclophosphamide, methotrexate, and fluorouracil chemotherapy effectively reduced the locoregional recurrence rate and prolonged the DFS of patients with node-negative TNBC, especially in patients with a tumor diameter greater than 2 cm and in patients who had undergone partial mastectomy [15].

Platinum agents

The cis-structured platinum compound, cisplatin, has inhibition effect on cancer cells [16]. Zhang et al. conducted a phase II study (NCT00601159) to evaluate the efficacy and tolerability of cisplatin and gemcitabine (GP) as the first-line treatment regimen of metastatic TNBC (mTNBC). The results showed that the combination regimen had significant activity and favorable safety for mTNBC patients, particularly patients with basal-like subtypes [17].

Fluorouracil

5-Fluorouracil (5-Fu) itself does not have any biological activities. Under the action of orotate phosphoribosyltransferase, 5-Fu can be converted into active metabolites, fluorouridine monophosphate and fluorodeoxyuridine monophosphate, in vivo. Capecitabine is a cytotoxic agent that has selective activity against tumor cells. Capecitabine itself has no cytotoxicity and is highly effective after transforming into cytotoxic 5-Fu in vivo. This process is catalyzed by the large amount of thymidylate phosphorylase in the tumor, resulting in the production of more 5-Fu in the tumor, with stronger (better than 5-Fu) antitumor efficacy. Capecitabine is suitable for the further treatment of advanced primary or metastatic breast cancer with an ineffective paclitaxel or anthracycline chemotherapy. With the widespread application of anthracyclines and taxanes in the treatment of breast cancer, an increasing number of patients develop resistance to anthracyclines and taxanes, which has become an urgent problem in clinical practice. As a new-generation oral fluorouracil drug, capecitabine selectively acts on tumor cells with a high expression of thymidine phosphorylase. Capecitabine has high effectiveness, low toxicity, and convenient administration. [18].

Novel Therapies

TNBC has the fewest therapeutic options among all BC subtypes due to the lack of well-defined molecular target(s). Identification of new therapeutic targets and development of effective targeted agents is urgently needed. Table 1 and Figure 1 summarize the promising agents currently in clinical development for TNBC.

Poly (ADP-ribose) Polymerase (PARP) Inhibitors

The most important advancement toward understanding the complex heterogeneity of TNBC is probably the discovery of a subgroup of sporadic TNBC that shares the homologous repair deficiency characteristic with BRCA1/2-mutated BC. Drug combination regimens are

thus proposed by incorporating PARP inhibtors or the DNA-targeting platinum drug (carboplatin) (19, 20) to standard chemotherapy (21, 22). The PARP enzyme repairs DNA single-strand breaks whereas the BRCA1/BRCA2 genes encode tumor-suppressor proteins that repair DNA double-strand breaks through homologous recombination. PARP inhibitors have showed promising clinical activities in patients bearing germline BRCA1/BRCA2 mutation (gBRCA+), presumably by synthetic lethality from unresolved DNA damage and by replication arrest caused by physical obstruction of DNA replication forks (23). Olaparib has proceeded the furthest in clinical development. In a phase III trial, it improved median PFS by 2.8 months and lowered the risk of disease progression/death by 42% compared to standard chemotherapy (21). Talazoparib, in phase III trial (NCT01945775), has the greatest preclinical potency due to its strong binding to DNA by trapping PARP–DNA complexes (24). It demonstrated encouraging antitumor activities as a single agent in advanced gBRCA+ BC (25). Veliparib combined with carboplatin and paclitaxel, though failed to prolong PFS in gBRCA+ BC (26), in phase III trial (NCT02163694) in advanced gBRCA+ BC (27). Niraparib (phase III, NCT01905592) and rucaparib (phase II, NCT02505048) are investigated in gBRCA+ advanced BC patients as monotherapy and also in combination with chemotherapy (niraparib: phase I/II, NCT02657889; rucaparib: phase II, NCT01074970). The use of PARP inhibitors or carboplatin in TNBC is usually determined by three DNA-based homologous recombination deficiency scores, which are highly correlated with genetic defects in BRCA1/2 (28). However, none of these agents is effective in treating all TNBC because TNBC can be further divided into at least six subclasses [basal-like (BL1 and BL2), an immunomodulatory, a mesenchymal, a mesenchymal stem-like, and a luminal androgen receptor subtype], each of which has its own molecular features and unique drug sensitivity (29–31). The identification and characterization of clinically relevant molecular biomarkers of drug responsiveness is needed to further refine this treatment strategy.

Anti-Angiogenic Agents

The intra-tumoral expression of VEGF, a key angiogenic factor, is known to be remarkably higher in TNBC than in non-TNBC BC (32). Bevacizumab (anti-VEGF monoclonal antibody) suppresses tumor neovasculature growth and inhibits metastasis. In metastatic TNBC (phase III), the addition of bevacizumab to first-line chemotherapy (docetaxel) has been shown to increase response rate (placebo plus docetaxel: 46% versus bevacizumab plus docetaxel: 64%) and median PFS (placebo plus docetaxel: 8.1 months versus bevacizumab plus docetaxel: 10.0 months) (HR, 0.67; P (HR, 0.67; P< 0.001) [33, 34] Importantly, combination of bevacizumab with docetaxel did not affect significantly the overall safety profile of the regimen.

EGFR Inhibitors

Epidermal growth factor receptor is overexpressed in TNBC. Numerous phase II studies have evaluated the efficacy of cetuximab (anti-EGFR monoclonal antibody) in combination with cisplatin in metastatic TNBC (35, 36). While only modest objective response rate (ORR) was observed (ORR = 20% for cisplatin plus cetuximab versus 10% for cisplatin alone), cisplatin plus cetuximab resulted in longer median PFS (3.7 versus 1.5 months) and median OS (12.9 versus 9.4 months) compared with cisplatin alone. Favorable response may be correlated with lower expression of alpha-crystallin B chain, higher expression of PTEN, and lack of KRAS expression in the tumors (37).

SRC Inhibitors

SRC is a non-receptor signaling kinase downstream of several growth factor receptors (EGFR, IGF-1R, PDGFR, and HGFR), which is/are deregulated in TNBC. Dasatinib (inhibitor of multiple tyrosine kinases including SRC), when tested as a single agent for TNBC in a prospective, open label, phase II trial (CA180059), has shown disappointing result. Objective response rate (ORR) was only 4.7%. Median PFS was 8.3 weeks. Higher dose (100 mg BID) was associated with treatment interruption, dose reduction, and serious adverse events (38). However, in cell line studies, when dasatinib was combined with cetuximab (antiEGFR monoclonal antibody) and cisplatin, synergistic anticancer activity in a panel of TNBC cell lines was observed (39). Therefore, clinical studies may be warranted to investigate the use of dasatinib-containing combinations in TNBC patients whose tumors co-overexpressed both EGFR and c-Src.

Monoclonal Antibodies

Glembatumumab vedotin is a monoclonal antibody-cytotoxic drug conjugate designed to target glycoprotein NMBoverexpressing (gpNMB+) TNBC (40). gpNMB is a transmembrane protein associated with tumor invasion and metastasis and it is overexpressed in 40% of TNBC (41). On gpNMB+ advanced TNBC patients (phase II trial), a significantly improved PFS and OS by glembatumumab vedotin was observed compared to the treatment of physician's choice (42).

Immunotherapies

Pembrolizumab is a human monoclonal IgG4-κ antibody against the programmed cell death 1 receptor (PD-1). It demonstrated clinical efficacy and safety in patients with advanced TNBC. PD-1 prevents autoimmunity by suppressing T cells and thus preventing the immune system from killing cancer cells. While patients with PD-L1 (a ligand of PD-1)-positive advanced TNBC were selected for investigation in a phase Ib study (43), the antitumor activity of pembrolizumab appeared to be independent of PD-L1 expression according to a phase II study (44).

Conclusion

The selection and optimization of chemotherapy regimens are important for ensuring good treatment outcome and prognosis of TNBC patients. With the advancements in the chemotherapy for BC, the mortality rate from BC is decreasing with time. Targeted therapy has been proved one of the most useful treatment modalities against HR+ BC. Metastasizing TNBC remains a deadly disease with limited treatment options. In recent years, the molecular mechanisms driving the heterogeneous treatment response in BC are better elucidated. This has fueled the development of novel targeted agents, including inhibitors of PARP, CDK4/6, PI3K/AKT/mTOR, multiple kinases, or immune checkpoint, for the treatment of specific molecular

subtypes of BC. Further exploring of treatment options should be done for better options.

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