Theranostics for Triple-Negative Breast Cancer

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Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer with poor prognosis. Current endocrine therapy or anti HER-2 therapy is not available for these patients. Chemotherapeutic treatment response varies among patients due to the disease heterogeneity. Anticancer material conjugated nanoparticles with target-binding ligand and tracer agents enable simultaneous drug delivery and visualization of the lesion with minimal off-target toxicity.

nanomedicine immunotherapy breast cancer

1. Introduction

Traditionally, breast cancer is classified as four molecular subtypes, such as luminal A, luminal B, HER-2 enriched, and triple-negative breast cancer (TNBC). TNBC, which account for 15–20% of all breast cancer, Ref. [1] is defined as lack of the expression of hormones receptors (estrogen receptor (ER) and progesterone receptor (PR)) and lack of amplification of human epidermal growth factor receptor 2 (HER-2). TNBC is known to be an aggressive subtype, which has a higher rate of BRCA1 mutation, recurrence, metastasis, and mortality than other subtypes [2][3]. Precise diagnosis is an essential prerequisite for improving prognosis. However, TNBC diagnostics are still relies on conventional mammography, ultrasonography, magnetic resonance imaging (MRI), and immunohistochemistry (IHC), which are modalities that have limitations in the non-specific contrast agents and possibilities of false-positive findings [4].

Nowadays, “precision” medicine is quite routinely applied in cancer therapy. Precision medicine is defined as the tailoring of treatment using molecular and genomic determinants to classify individuals into specific groups that differ in their susceptibility to a particular disease or their response to a specific treatment [5][6]. Molecular subtyping using multigene array and targeted therapies for breast cancer is a good example of precision medicine. However, TNBC patients cannot benefit from currently available endocrine therapy or anti HER-2 therapy due to their lack of receptors [7]. Chemotherapy with taxanes and anthracyclines is the only systematic treatment option for TNBC. However, the treatment response varies between patients because of the heterogeneity of the disease. High toxicity of chemotherapeutic agents and multidrug resistance are also obstacles to the management of TNBC [4][8]. Recent development of molecular and gene expression analysis has been revealed in the intertumor heterogeneity of TNBC.

“Personalized” medicine means specifically designed treatment for individual patients. The term “theranostics” is defined as the materials that combine both diagnostic and therapeutic capabilities, which was first coined by Funkhouser in 2002 [9]. The concept of simultaneous delivery of drugs and contrast agent to the target site is expected to contribute to the personalization of current medicine. By employing nano-carriers, which were made from various materials such as polymers, lipids, nucleic acid, proteins, carbon, and metals including micelles and liposomes [10][11], theranostics are becoming closer to real-world practice. Anticancer drug conjugated nanoparticles with target-binding ligand and tracer agents enable accurate and efficient drug delivery as well as visualization of the lesion, with minimal toxicity to healthy tissues. Single nanoparticles can be conjugated with various functional materials at same time, such as targeting molecules, therapeutic agents, fluorophores, and/or radioisotopes. The therapeutic agents are not only chemo drugs but also therapeutic genes (e.g., siRNA), photothermal agents, radiosensitizers, and immunostimulants [12].

2. Precision Medicine for Triple-Negative Breast Cancer

2.1. Poly-ADP-Ribose Polymerase (PARP) Inhibitors (PARPi)

Poly-ADP-ribose polymerase (PARP) is an enzyme involved in single-strand break (SSB) DNA repair and genomic stability. The protein encoded by BRCA1/BRCA2 also plays an essential role in DNA repairing by the homologous recombination pathway. As a result, tumor cells with BRCA1/2 mutation present homologous recombination deficiency, which leads to vulnerability to SSB [13]. For these cells, inhibition of PARP results in accumulation of SSBs, which eventually leads to cell death. This mechanism is called synthetic lethality [14]. Gonzalez-Angulo et al. reported a 19.5% incidence of BRCA1/BRCA2 mutations in TNBC patients [15].

Each of the PARPi has various potency and cytotoxic effects. Talazoparib is one of the most potent and cytotoxic PARPi, which has a strong catalytic PARP enzyme inhibition and PARP-trapping potential. EMBARCA was the phase III randomized clinical trial that compared the PFS of talazoparib versus physician’s choice treatment in advanced breast cancer with germline BRCA1/2 mutations. Median PFS was 8.6 months in the talazoparib arm compared to 5.6 months in the standard therapy arm ($p < 0.001$) [16].

2.2. Check Point Inhibitors

Restoring anti-tumor immunity is a mainstay of cancer immunotherapy [17]. Programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) are well-known immune check points, and its ligand negatively regulates the cytotoxicity of anti-tumor effector cells. Several anti-PD-1 and anti-PD-L1 antibodies have been approved by the FDA for refractory melanoma and advanced NSCLC. Since TNBC is highly immunogenic with higher PD-L1 expression and immune-infiltration compared with luminal and HER2-enriched breast cancers, immunotherapy has been represented as a promising treatment strategy for TNBC [18][19]. Pembrolizumab is a human monoclonal IgG4-K antibody blocks the interaction between PD-1 and PD-L1/PD-L2. Pembrolizumab is undergoing clinical trials for TNBC. In a phase 1b KEYNOTE-012 trial, combination neoadjuvant chemotherapy and pembrolizumab for high-risk, early-stage TNBC showed foreseeable toxicity and promising anti-tumor activity with high pCR rates

around 60% [20]. In both previously treated (cohort A) and untreated (cohort B) metastatic TNBC, pembrolizumab monotherapy showed a manageable safety profile and durable antitumor activity in a phase II KEYNOTE-086 study [21][22]. The results of the KEYNOTE-355 phase 3 trial also support adding pembrolizumab to standard chemotherapy for the first-line treatment of metastatic PD-L1-positive TNBC. Pembrolizumab–chemotherapy showed significant prolongation of PFS compared to that of the placebo–chemotherapy group [23]. Based on these data, the FDA approved pembrolizumab in combination with chemotherapy for patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 in 2020. In July 2021, the FDA also granted pembrolizumab for high-risk, early-stage, TNBC in combination with chemotherapy as neoadjuvant treatment and continued as a single agent as adjuvant treatment after surgery.

Another anti-PD-L1 monoclonal antibody, atezolizumab, has been approved by the FDA for combination with nab-paclitaxel in locally advanced or metastatic TNBC with higher expression of PD-L1. In a phase 1 study, atezolizumab's single administration was well-tolerated in metastatic TNBC patients. In the study, the immune cell PD-L1 expression was independently associated with higher objective response rate and longer overall survival [24]. The combination of atezolizumab plus nab-paclitaxel for metastatic TNBC showed acceptable tolerance, with a 39.4% objective response rate in phase 1b trial regardless of previous treatment [25].

2.3. Antibody-Drug Conjugates (ADC)

Antibody–drug conjugates are immuno-conjugate monoclonal antibodies to deliver high-potent cytotoxic small molecules to cancer cells. Sacituzumab govitecan is an anti-trophoblast cell-surface antigen (Trop-2) antibody conjugated with topoisomerase inhibitor. Trop-2 in breast cancer is known to be associated with poor prognosis [26]. Since Trop-2 is expressed in more than 90% of TNBC, the single-arm phase II clinical study proved the efficacy and safety of sacituzumab govitecan in heavily pretreated metastatic TNBC patients. The objective response rate was 30%, and treatment responses occurred early, with a median onset of 1.9 months [27]. Based on the data demonstrated in this trial, sacituzumab govitecan obtained the regular approval of the FDA for patients with unresectable, locally advanced, or metastatic TNBC who have received two or more prior systemic therapies, with at least one of them for metastatic disease.

3. Recently Developing Theranostics for Triple-Negative Breast Cancer

3.1. Lipid-Based Nanoparticles

Lipid-based approaches have been spotlighted due to its hydrophobic characteristics with higher stability and biocompatibility [28]. Liposomes and solid lipid nanoparticles (SLN) are widely investigated for delivering therapeutic agents to the cancer site.

3.1.1. Liposomes

Liposomes are 100–400 nm sized spherical vesicles with phospholipid bilayers encapsulating an aqueous core. Due to their feasibility to encapsulate either hydrophobic or hydrophilic drugs and their high efficacy, stability, non-immunogenic characteristics, and minimal systemic toxicity, Ref. [29] liposomes are versatile nanocarriers for drug delivery. Doxil®, comprised of doxorubicin encapsulated in STEALTH™ liposomes, received the U.S. FDA approval for Kaposi sarcoma or ovarian cancer treatment [30]. Su et al. designed poly ethylene glycol (PEG) engager, which simultaneously binds Doxil® and epidermal growth factor receptor (EGFR) on TNBC cells [31].

The utilization of liposomes has been investigated not only in the chemotherapeutic field but also in the photodynamic therapy (PDT). Liposomes can deliver photosensitizers to the tumor, which can cause cytotoxicity after being triggered by a certain wavelength of light. Ding et al. combined PDT with a hypoxia-activated prodrug to produce a synergistic antitumor effect by using the PDT-induced hypoxic environment. They developed CD44-targeted liposomes encapsulating Photochlor as a photosensitizer and evofosfamide as the hypoxia-activated prodrug. CD44 effectively targeted TNBC cells, and the dual-loaded liposomes exhibited better antitumor activity compared to that of monotherapy groups [32].

3.1.2. Solid Lipid Nanoparticles (SLN)

SLNs are made up of biodegradable physiological lipids with spherical particles ranging in size from 1 to 1000 nm. It is a promising colloidal carrier that can offer wide therapeutic and diagnostic application [33]. SLN has all the advantages of the liposomal system with avoidance of organic solvents use [34].

3.2. Polymer-Based Nanoparticles

3.2.1. Micelles

Polymeric micelles (PMs) are 10–100 nm sized colloidal particles with a hydrophobic core generated by the self-association of amphiphilic block copolymers [35]. PMs have received attention because of their marked stability, nanoscopic size, and biocompatibility arising from their solubility enhancement of hydrophobic drugs [36]. PMs also can increase chemosensitivity in cancer with multidrug resistance (MDR) through various mechanisms, such as inhibition of mitochondrial respiration and enhancing pro-apoptotic signaling in MDR cancer cells [37][38].

3.2.2. Dendrimers

Dendrimers are branched-nanostructure polymers. The unique architecture of dendrimers, comprised of a central hydrophobic core and hydrophilic branched periphery, enables conjugation and attachments of molecules, especially genes such as siRNA [39]. They have high loading capacity of several functional groups simultaneously, which offers benefits for treating cancer. Moreover, rapid solubilization, biocompatibility, high permeability, and bioavailability of dendrimers are suitable features for their use as new drug-delivery agents [40]. Tomalia et al. first reported polyamidoamine dendrimers (PAMAM) in 1985 [41]. Throughout the generations, generation-4 PAMAM dendrimers (G4PAMAM) demonstrated high permeability across the epithelial cell monolayers with high efficiency for gene delivery in vivo [42].

3.2.3. Quantum Dots (QDs)

Quantum dots are semiconductor nanoparticles with a symmetric emission band, long fluorescence lifetime, and strong photostability. QDs have been widely investigated in various biomedical areas, such as cellular imaging, cell trafficking, tumor targeting, and diagnostics [43][44]. Zheng et al. reported the advantages of quantum dot-based molecular pathology and quantitative detection of cancer cells over conventional IHC in breast cancer for the benefits of higher sensitivity and more accurate quantitative analyses. They performed in situ simultaneous imaging and quantitative detection of EGFR and collagen IV in TNBC using a QD-based multiplex molecular imaging algorithm. The EGFR/collagen IV ratio showed prognostic value for 5-DFS in TNBC [45].

3.3. Carbon-Based Nanoparticles

Carbon nanotubes are carbon allotropes with cylindrical nanostructure. They have received attention due to their large surface areas, rich surface chemical functionalities, high penetrating capability, and size stability [46]. CNTs have been used as vectors to deliver anticancer drugs as well as mediators for PTT and photodynamic therapy (PDT). There are three types of CNTs: single-wall carbon nanotubes (SWCNTs), multi-wall carbon nanotubes (MWCNTs), and double-wall carbon nanotubes (DWCNTs) [47].

4. Summary

TNBC remains a challenging subtype of breast cancer with poor prognosis. The lack of expression of triple receptors makes it tough to treat. Systemic chemotherapy remains the standard treatment for TNBC. Anthracycline with cyclophosphamide (AC) followed by taxane (T) therapy is the standard adjuvant therapy for TNBC patients [48]. In relation to neoadjuvant chemotherapy, the INTENS trial reported that AC followed by T showed higher pCR rate and improved 5-year DFS compared to the TAC regimen [49]. The pCR rates vary among TNBC subgroups from 21.4% in the LAR subgroup to 65.6% in the BL1 subgroup [50]. For the recurrent or metastatic, currently available chemotherapies have limitations for treating TNBC due to the heterogeneity of disease. The drug toxicities and resistance are also associated with mortality. Nowadays, overexpression of several druggable target receptors of TNBC has been discovered. The rapid evolution of targeted therapy and immunotherapy is expected to improve the outcomes. A few monoclonal antibodies have been approved for clinical use of metastatic or refractory TNBC, such as PARP inhibitor, anti PD-L1 antibodies, and antibody drug conjugates.

Besides targeting tumor cells itself, induction of anti-tumor immunity via targeting TME is one of the recently identified strategies for treating TNBC. Targeting TME has therapeutic advantage because of its stability and vulnerability compared to the genomic instability of cancer cells [51]. Various components of TME can affect the outcomes of immunotherapy. ECM can promote immunosuppression via impeding immune cell infiltration [52]. The presence of tumor-infiltrating lymphocytes (TIL), such as CD8+ and CD4+ T cells and natural killer (NK) cells, are known to correlate with favorable outcomes [53][54]. TNBC is known to be more immunogenic and immune-infiltrated than luminal or HER-2-enriched breast cancers [18]. According to this property, TNBC is more likely to benefit from immunotherapy. The accumulation of hyaluronan (HA) is associated with tumor growth and reduced overall

outcomes of TNBC [55]. Remodeling the TME via degradation of HA can sensitize cancer cells to anti-PD-L1 immunotherapy [52]. Along with the development of immunotherapy, various attempts to oppose the immunosuppressive microenvironment of TNBC has been made.

Nanotechnology has gained attention for overcoming the limitations of conventional chemotherapy and systemic drug administration. Nanoparticles have been spotlighted in cancer research due to their target specific multifunctional characteristics. Lipid-based nanocarriers including liposomes and SLNs were able to deliver chemotherapeutic agents and photosensitizers with high biocompatibility. Polymeric-based delivery has advantages over lipid-based systems in the aspect of extended circulation time and higher accumulation inside tumor cells. Carbon-based nanoparticles such as CNTs are most versatile. In addition to having the advantages of both lipids and polymers, they possess conductive properties that can contribute to the detection and diagnosis of cancers. Successful designing of nanoparticles can be a promising approach for TNBC theranostics.