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Recent Advances in The Treatment of Breast Cancer

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Abstract

Chemoprevention is a recently established and rapidly developing field of oncology that distinguishes agents with a potential preventive role in malignancy. As early as 40-50 years ago and since the discovery and further regenerative use of tamoxifen, a particular estrogen receptor modulator, the treatment of breast disease has changed into the advancement and realization of tailor-made restorative treatments. Breast cancer is the most common cancer in women worldwide. A woman's genetic background contributes to her risk of breast cancer. Some inherited DNA mutations can dramatically increase the risk of certain cancers and are responsible for many cancers that run in some families. Regarding expanded multigene panels, whole exome sequencing is capable of providing mutational assessment of genetic function for the development of a new strategy in clinical trials. The increasing resistance of breast cancer cells to anticancer drugs is persuading researchers to seek new therapeutic approaches to treat this malignant disease. Brief description of the clinical development of inhibitors of poly(ADP-ribose) polymerase, cyclin-dependent kinases 4 and 6, phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin pathway, histone deacetylation, multi-target tyrosine kinases.

Keywords: Breast Cancer; chemotherapeutic drugs ; new drug ; therapeutic approaches .cyclin-dependent kinases 4 and 6 inhibitors, histone deacetylation.

Introduction

Breast cancer (BC) is the most commonly diagnosed and second leading cause of cancer-related death in women worldwide. One of the main challenges for its treatment is its heterogeneous nature, which determines the therapeutic options . Breast cancer remains one of the most common malignancies in women. This malignancy is the second leading cause of death among women and men. world. In the last 5 years (2012-2016), the prevalence of breast cancer increased slightly by 0.3% per year. However, the death rate from breast cancer continues to decline, falling by 40% from 1989 to 2017. Several risk factors have been found to be associated with the development of breast cancer, including age, hormonal, reproductive, menstrual history, and alcohol. , radiation, hereditary factors, obesity, etc. Among these risk factors, age is the greatest risk factor for developing breast cancer, followed by a positive family history. Previous studies have found based on data reported in the literature several features of inherited mutations in genes. It is estimated that about 10–30% of breast cancer cases are related to hereditary factors, also 5–10% of breast cancer cases have been detected with strong hereditary factors, while between 4 and 5% of these cases have been identified with mutations in genes with high penetrance. Chemotherapy is the use of pharmacological products that prevent the progression of invasive disease either by preventing the DNA damage that initiates carcinogenesis or by arresting or altering the development of premalignant cells in which such damage has just occurred. Recent advances in our understanding of the components of carcinogenesis have prompted the development of new drugs that can suppress tumor development. Approximately two million new cases are analyzed annually. Likewise, it remains a major source of death with approximately 520,000 deaths per year, as revealed by the WHO in the most recent overview of current breast growth in 2015. Breast growth restoration methodologies have changed over the past decades and the use of basic treatment for early and driven infection tailored to each patient individually, is certified to give treatment to those who need it and who could benefit the most. are associated with breast cancer and also how it contributes to the disease.

Current Aspects and Personalized Medicine:

There are several cancer syndromes in which the alleles are located in a predominant autosomal dominant fash-ion and thus lead to a more risk of neoplasm. In addition, non-genetic factors have been shown to be involved in mutation or other genetic changes. Along with genetic changes in tumors, a number of inherited genetic changes in genes are involved in drug metabolism, which are capable of influencing therapeutic responses (eg, increasing drug toxicity). Advances in "pharmacogenomic" science lead to the provision of specific treatments based on individual genetic information. Scientists now realize that changes that occur in a person's cancer may not occur in other people with the same type of cancer, while the same cancer-causing changes can be found in different types of cancer. We are now learning more about genomic alterations (copy number change, deletions, mutations, single nucleotide polymorphisms) and the correlation of these mutations with many types of cancer. These communication studies help determine who is at risk for cancer . Genomic cancer is expected to expand with the use of whole genome sequencing (WGS), DNA sequencing technology and analysis of cancer cells will allow researchers to clearly detect new genetic changes associated with cancer, which is likely to be very beneficial. for the development of

personalized medicine. Providing an integrated analysis and systematic characterization of key genomic mutations in different breast cancer (BC) subtypes may lead to advances in the use of favorable diagnostic, therapeutic and preventive strategies. Cancer can be considered a genomic disease, where each tumor has a set of specific genetic changes. A deep understanding of the genetic changes and molecular mechanisms underlying the regulation of gene expression profiles in BC cells leads to a favorable effective therapeutic approach that is dedicated to each person's genetic profile.

Therapeutic Peptides for Cancer Therapy:

Peptides are short chains of more than fifty amino acids designed by different models. They often have disulfide bond. Peptides are designed with modulation in their sequences and structures to increase their target affinity and interaction with specific molecules such as oncogenic proteins. Therefore, nowadays peptides are considered to be sufficient inhibitors in cancer therapy. Due to the high specificity and biological activity and low toxicity, peptides are considered as candidates for new therapeutic agents and drugs, especially for cancer diseases. Therapeutic peptides in cancer therapy can be divided into three groups, consisting of antimicrobial/pore-forming peptides, cell-penetrating peptides (CPPs), and tumor-targeting peptides. The first group includes small and cationic peptides that are secreted into the aqueous phase and rapidly bind to the target membrane. There are four main classes of cationic peptides, including β-sheet molecules stabilized by two or three disulfide bonds, amphipathic α-helices, elongated molecules. and loops with a single disulfide bond. Antimicrobial/pore-forming peptides affect a variety of gram-negative and gram-positive strains of bacteria, fungi, eukaryotic parasites, and antibiotic-resistant viruses. They can kill microorganisms by disrupting the membrane with sufficient channels and pores . Cationic peptides appear to internalize the outer membrane or cytoplasmic membrane. On the other hand, the mechanism of membrane permeabilization involves disruption of the permeable barrier of the outer membrane lipopolysaccharide (LPS) or the cell wall with subsequent pore formation in the lipid bilayer . Most importantly, mechanisms of action of antimicrobial/pore-forming peptides include the Barrel-Stave model, in which peptides insert into the membrane perpendicularly, the carpet model, and the Toroi-dal pore model. In the carpet model, small areas of the membrane are coated with peptides with the hydrophobic sides facing inward, leaving pores in the membrane. The toroidal pore model is similar to the Barrel-state model; however, the peptides are always in contact with the main phospholipid groups of the membrane . The ability of a peptide to bind to target molecules in the cell membrane and alter lipid organization requires interfacial activity and an appropriate balance in hydrophobic and electrostatic interactions between peptides, water and lipids . Pore-forming peptides can target cancer cell membranes and induce cell death by either necrosis or apoptosis. In necrosis, cationic peptides adhere to negatively charged molecules on the membrane of cancer cells and cause cell lysis; if they can disrupt the mitochondrial membrane and cause cell apoptosis . However, the use of peptides has many limitations, including the low stability of peptides under physiological conditions and the high cost of producing peptides in active pharmaceutical compounds. Moreover, these peptides do not have much potential due to their lack of selectivity.

Current Treatment Regimens and Novel Therapies for Different Subtypes of BC:

Luminal BC (HR+ BC):

Current treatment regimens Luminal BC, which is also hormone receptor positive (HR+), accounts for the vast majority (60–80%) of BC cases in developed countries , and this patient population is increasing in premenopausal women . For HR+ BC, the mainstay of treatment is endocrine therapy, which works by blocking the effects of hormones or reducing hormone levels. Currently available drugs include (i) tamoxifen, a prodrug that blocks ER estrogen uptake; (ii) aromatase inhibitors (letrozole, anastrozole, and exemestane), which suppress the conversion of androgens to estrogens, leading to estrogen depletion; (iii) luteinizing hormone-releasing hormone analogs (goserelin and leuprolide), which suppress ovarian hormone production; and (iv) fulvestrant (selective ER degrader), which is suitable for BC patients refractory to previous hormonal therapy. Sequential administration of endocrine therapy is recommended until a rapid response is required or evidence of clinical resistance, when chemotherapy is indicated . Because endocrine drugs work by different mechanisms, they are generally used in combination for better antitumor efficacy. However, conflicting results have been reported . It is generally believed that patients with endocrine-naïve advanced BC and patients with highly endocrine-sensitive tumors may benefit most from combined endocrine therapy.

Cyclin-Dependent Kinases 4 and 6 (CDK4/6) Inhibitors:

Among emerging therapies, CDK4/6 inhibitors (Palbociclib , ribociclib, and abemaciclib) are attracting the most attention. CDK4/6 regulate cell cycle progression through their reversible interaction with cyclin D1. Amplification of cyclin D1 and CDK4 was found in approximately 29 and 14% of HR+/HER2− BC patients, respectively. Importantly, even when hormone resistance has developed, tumors still depend on CDK4/6-cyclin D1 proliferation . therefore, a more pronounced G1-S cell cycle arrest was observed in HR+/HER2− BC after treatment with a combination of hormonal therapy and a CDK4/6 inhibitor . CDK4/6 inhibitors work by blocking retinoblastoma protein phosphorylation, thereby downregulating E2F response genes to mediate G1-S arrest. They also dephosphorylate the transcription factor Forkhead box protein M1 to inhibit cell proliferation . Palbociclib and ribociclib have received FDA approval for combination with an aromatase inhibitor as first-line treatment of HR+/HER2− advanced BC. They have been shown to significantly improve the median PFS by 10 months and the PFS rate by 20% at 18 months compared to letrozole alone. On the other hand, abemaciclib is still under phase III investigation (NCT02246621). As second-line treatment in combination with fulvestrant in HR+/HER2− advanced BC, palbociclib and abemaciclib have been shown to significantly prolong median PFS by 5 months and 7 months compared with fulvestrant alone. Ribociclib is in phase III investigation (NCT02422615). Although all three CDK4/6 inhibitors acted by a similar mechanism, abe-maciclib showed a higher response rate to monotherapy and induced less neutropenia, which may be related to its superior CDK4 inhibition.

HER2+ BC

Current treatment regimens Several molecularly targeted agents have been approved for use alone or in combination with standard chemotherapy for HER2+ BC. They include (i) trastuzumab (an anti-HER2 monoclonal antibody); (ii) pertuzumab (an anti-HER2 monoclonal antibody with a different HER2 binding site than trastuzumab); (iii) ado-trastuzumab emtansine, an antibody-cytotoxic agent conjugate consisting of trastuzumab linked to a small molecule microtubule inhibitor (emtansine); and (iv) lapatinib, a dual tyrosine kinase inhibitor (TKI) that disrupts both HER2 and the epidermal growth factor receptor (EGFR) pathway. BC patients are tested for HER2 gene amplification or overexpression of the protein to determine whether they would benefit from anti-HER2 therapy.

Neoadjuvant treatment with a combination of chemotherapy and anti-HER2 targeted therapy is currently the standard regimen for early-stage HER2-positive BC . This is followed by surgery, radiotherapy and another 12 months of HER2-targeted therapy. Depending on the specific biology of the cancer, endocrine adjuvant therapy may also be added. With the introduction of HER2-targeted therapies over the past 15 years, the median overall survival (OS) of patients with HER2+ advanced BC has increased substantially from approximately 20 months to the current approximately 5 years.

Monoclonal Antibodies Patritumab (an anti-HER3 monoclonal antibody) has shown promising antitumor activity in a preclinical study through inhibition of HER2/HER3 heterodimer formation. It was found to show favorable efficacy and acceptable tolerability in patients with HER2+ advanced BC. Margetuximab (targeting HER2) was well tolerated and showed promising single-agent activity in a first-in-man phase I study in male HER2+ advanced BC. Additional clinical trials are ongoing to investigate its utility as a single agent (NCT02492711) or in combination with pembrolizumab.

Advances in Breast Cancer Diagnosis and Treatment:

1. **Genomic testing minimizes chemotherapy exposure :**

Many patients have received chemotherapy as part of their breast cancer treatment for years. But a July 2018 study in the New England Journal of Medicine found that chemotherapy would not benefit up to 85% of patients over 50 whose breast cancer was HR+, HER- and had not spread to any lymph nodes.

The study involved a genomic test (or Onco type DX test) that monitored the expression of 21 different genes in the patient's primary tumor. The tumor's gene expression pattern indicates whether or not it will respond to chemotherapy, or whether endocrine therapy alone (such as tamoxifen) would be a better option. The study showed that low- to intermediate-risk patients can safely skip chemotherapy and avoid the hair loss, neuropathy, weight loss and other side effects that often come with it.

"Before this study, we didn't know if it was safe to skip chemotherapy," Lucci says. "Now we know we can achieve the same overall result by doing less." So we minimize over-handling. And it completely changed the way we practice medicine."

2. **The next generation of monoclonal antibodies:**

Trastuzimab (Herceptin) is a monoclonal antibody that has been used to treat patients with HER2+ breast cancer since the 1990s. It works by targeting the HER2 receptor, preventing the cancer from growing. Some breast cancers express too much of the HER2 protein, which triggers the cells to multiply very quickly.

Since then, other monoclonal antibodies (such as pertruzimab/Perjeta) have been developed. Today, this targeted therapy is even more advanced. T-DM1 (Kadycla), an antibody-drug combination, has been approved for use in the treatment of HER2+ breast cancer. Antibody-drug combinations act as a "smart bomb" and deliver chemotherapy directly to cancer cells by attaching to their HER2+ receptors.

"Targeted therapies have changed the way we approach HER2+ breast cancer and offer the opportunity to cure stage four breast cancer in some patients," says Damodaran. "So monoclonal antibodies have changed the game.

3. **An oral option for targeted therapy:**

Until recently, PARP inhibitors were mainly used to treat ovarian cancer. They work by preventing damaged cancer cells with specific genetic mutations from repairing themselves. Today, this targeted therapy is also successfully used to treat breast cancer.

"DNA has several ways to repair itself," Litton explains. "So when someone has a genetic mutation that shuts down one pathway, their DNA uses another instead. PARP inhibitors block these escape routes so cancer cells cannot grow and divide."

Breast cancer is associated with fewer mutations than ovarian cancer, Litton notes, but PARP inhibitors can still take advantage of them. Two phase III clinical trials comparing PARP inhibitors with standard-of-care chemotherapy are currently underway. The OlympiAD trial evaluated olaparib, and the EMBRACA trial, led by Litton, evaluated talazoparib. Both studies demonstrated an improvement in progression-free survival in patients with an inherited BRCA gene mutation and metastatic breast cancer. Both studies also showed an overall improvement in quality of life in patients who received these oral drugs, as opposed to patients who received chemotherapy.

4. **Node preservation reduces lymphedema cases:**

Axillary lymph nodes were routinely removed from the armpit during breast cancer surgery to test for metastases. This caused chronic pain, numbness, and lymphedema in about 1 in 5 patients. However, studies have shown that many of these nodes can be preserved - without compromising long-term survival rates.

Sentinel node mapping allows surgeons to identify which lymph nodes are most likely to be affected by the tumor. Targeted axillary dissection allows surgeons to potentially preserve nodes that once tested positive for cancer but returned negative after chemotherapy or other treatment. In either case, if the tests come back negative for cancer in the first few nodes removed, the remaining nodes can be left alone. This means fewer complications and fewer side effects for our breast cancer patients.

"About 15-20% of patients developed lymphedema when we still routinely collected all the nodes," says Lucci, a surgical oncologist who specializes in breast cancer. "But when the sentinel node mapping is done and the rest of the nodes are left in place, that number drops to 5%. And the chance of recurrence in the axilla is quite small using this strategy. So this is a huge deal. We've really been able to improve the quality of life for patients by suppressing our aggressiveness in routine lymph node removal."

5. **Better identification of hereditary cancer syndromes:**

A number of genetic mutations – such as BRCA1 and BRCA2 – are already known to increase the risk of certain cancers, including breast cancer. But now, next-generation gene sequencing techniques are helping researchers identify other inherited cancer syndromes that can put people at risk.

"We've always known that there are certain families with a strong history of cancer," says Litton, a medical oncologist who specializes in breast cancer genetics. "But by analyzing blood and saliva, we can reach other family members earlier—both to provide preventive care through expanded screenings and to identify existing cancers."

Conclusion

With advances in BC chemotherapy, BC mortality has been decreasing over the past decade. Targeting ER has been shown to be one of the most effective treatment modalities against HR+ BC . In addition, the success of biologics such as the anti-HER2 monoclonal antibody erdsu has also highlighted the feasibility and importance of a molecular targeting approach in BC therapy. However, metastatic TNBC remains a fatal disease with limited treatment options. In recent years, the molecular mechanisms governing the heterogeneous treatment response in BC have been better elucidated. this has encouraged the development of new targeted agents, including PARP, CDK4/6, PI3K/AKT/mTOR, multiple kinase or immune checkpoint inhibitors, for the treatment of specific molecular subtypes of BC. Treatment options should be tailored to the individual patient. Peptides could be used in targeted therapy of various types of tumors, especially in the presence of resistance to antitumor drugs. In this review, we have highlighted the potential of using therapeutic peptides in the treatment of breast cancer. We categorized therapeutic peptides based on their targets in breast cancer cells; peptides that directly target transcription factors, peptides that directly target tumor suppressor proteins of breast cancer cells, peptides that induce apoptosis in breast cancer cells, cytolytic peptides, and also antimicrobial peptides.

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