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Perspective

Progress in targeted therapy for breast cancer

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Abstract

Breast cancer is a multistep, multifactorial, and heterogeneous disease. Significant transformations have occurred in the systemic management of breast cancer in the past decade. Due to the further understanding of pathogenesis, scientists have found plenty of signaling pathways and correspondingly therapeutic targets in breast cancer, such as hormone receptor, human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), phosphoinositide-3-kinase (PI3K), v-akt murine thymoma viral oncogene homolog (AKT), mechanistic target of rapamycin (mTOR), cyclin-dependent kinase 4/6 (CDK4/6), poly(adenosine diphosphate-ribose) polymerase (PARP), and programmed death-1 (PD-1). Targeted therapy, which optimizes the accuracy of antitumor activity and minimizes toxicity to normal tissues, plays a crucial role in breast cancer treatment in the era of precision medicine. In this review, we aimed to summarize the latest developments in targeted therapy for breast cancer and discuss the existing problems.

Keywords: Breast cancer; Targeted therapy; Precision medicine

Introduction

Breast cancer is the most commonly diagnosed cancer among women worldwide; it is a great threat to women's health and puts a heavy burden on patients and the society. Although there have been several breakthroughs in the treatment of breast cancer in the past few decades, the high incidence of relapse and progression after conventional therapies is deeply concerning and indicates a great need for developing new therapeutics for breast cancer. Recently, molecular targeted therapy has been considered a milestone in precision medicine for breast cancer. Distinctive biological processes and diverse genetic mutations are intimately related with the progression of different subtypes and sensitivity to various drugs, such as hormone receptor, human epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), mechanistic target of rapamycin (mTOR), and cyclin-dependent kinase 4/6 (CDK4/6). Moreover, there is still no specific therapy for triple-

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negative breast cancer (TNBC), but poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors have shown promising activity in breast cancer associated with breast cancer 1 (BRCA), the expression of which is commonly observed in TNBC. This article will mainly focus on the following aspects: HER2 inhibitors [such as trastuzumab, pertuzumab, lapatinib, and trastuzumab emtansine (T-DM1)], phosphoinositide-3-kinase (PI3K)/v-akt murine thymoma viral oncogene homolog (AKT)/mTOR inhibitors (such as everolimus, buparlisib, and ipatasertib), PARP inhibitors (such as veliparib, talazoparib, olaparib, and iniparib), CDK 4/6 inhibitors (such as palbociclib, abemaciclib, and ribociclib), VEGF inhibitors (such as bevacizumab), and immune checkpoint inhibitors (such as pembrolizumab and avelumab). Through this review, readers will be able to understand the latest developments in major targeted therapies for breast cancer and apply them in clinical practice as soon as possible.

HER2 inhibitors

Several predictive factors are correlated with the risk of metastasis in breast cancer, such as the hormone receptor, HER2, and Ki-67 proliferation index.[1] Overexpression of *HER2*, which is observed in about 20% of breast cancer cases, is associated with an aggressive type, a poor prognosis, and a high mortality rate.[2] The *HER2* oncogene, first discovered in 1985 by Schechter et al,[3] is localized to chromosome 17q and encodes a transmembrane tyrosine kinase receptor protein belonging to human epidermal growth factor receptor (HER) family. Besides HER2, there are three other core members of the HER family, HER1, HER3, and HER4. All of them play vital roles in signal transduction for normal cellular growth and division and are closely related to the tumorigenesis and progression of breast cancer. HER2, which is regarded as the first therapeutic target in breast cancer, is still being tested in various clinical trials Table 1 summarizes the important trials targeting HER2 in breast cancer.[4−8]

Trastuzumab

Trastuzumab, a humanized monoclonal antibody of the immunoglobulin G1 (IgG1) type, was the first monoclonal antibody to revolutionize the treatment strategy for both early and advanced breast cancer. It binds to the extracellular domain IV of HER2 and thereby inhibits the downstream signal transduction that participates in the proliferation, motility, and antiapoptosis of normal cells, and in the invasiveness and angiogenesis of tumor cells.[9]

In 1998, the US Food and Drug Administration (FDA) approved trastuzumab as the first targeted agent for breast cancer. Thereafter, a body of international multicenter clinical trials, including the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, North Central Cancer Treatment Group (NCCTG) N9831, Breast Cancer International Research Group (BCIRG) 006, HERceptin Adjuvant (HERA), and Protocol for Herceptin as Adjuvant therapy with Reduced Exposure (PHARE) trials, have been initiated to determine the efficacy and safety of trastuzumab in postoperative patients with HER2-positive breast

Table 1
Trials targeting HER2 in breast cancer.

Study	Treatment schedule	*n*	Results
CLEOPATRA[4]	Docetaxel plus trastuzumab and pertuzumab *vs.* placebo plus docetaxel and trastuzumab	404 *vs.* 404	PFS: 18.5 *vs.* 12.4 months, $HR = 0.62$, $P < 0.001$
CALGB 40601[5]	Lapatinib plus paclitaxel and trastuzumab *vs.* paclitaxel plus trastuzumab *vs.* lapatinib plus paclitaxel	118 *vs.* 120 *vs.* 67	pCR rate: 56% *vs.* 46% (the paclitaxel plus lapatinib arm was closed in July 2011, based on reports of inferiority and greater toxicity of lapatinib-only regimens), $HR = 0.35$, $P = 0.013$
EMILIA[6]	T-DM1 *vs.* lapatinib plus capecitabine	495 *vs.* 496	PFS: 9.6 *vs.* 6.4 months, $HR = 0.65$, $P < 0.001$ OS: 30.9 *vs.* 25.1 months, $HR = 0.68$, $P < 0.001$
TH3RESA[7]	T-DM1 *vs.* physician's choices (chemotherapy, endocrine therapy or HER2-directed therapy)	404 *vs.* 198	PFS: 6.2 *vs.* 3.3 months, $HR = 0.528$, $P < 0.0001$
MARIANNE[8]	T-DM1 *vs.* T-DM1 plus pertuzumab *vs.* trastuzumab plus taxane	367 *vs.* 363 *vs.* 365	PFS: 14.1 *vs.* 15.2 *vs.* 13.7 months; $HR = 0.91$, $P = 0.31$ (T-DM1 *vs.* trastuzumab plus taxane); $HR = 0.87$, $P = 0.14$ (T-DM1 plus pertuzumab *vs.* trastuzumab plus taxane)

HER2: human epidermal growth factor receptor 2; CLEOPATRA: Clinical Evaluation of Pertuzumab and Trastuzumab; PFS: progression-free survival; pCR: pathologic complete response; *HR*: hazard ratio; OS: overall survival; CALGB: Cancer and Leukemia Group B; T-DM1: trastuzumab emtansine.

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