Present and Emerging Targeted Therapy for Metastatic Breast Cancer

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Abstract: Breast carcinoma is a complex and heterogeneous disease and several different molecular alterations are involved in its pathogenesis and progression. Different growth factor receptor-driven signaling pathways sustain the growth and survival of breast cancer cells. Actually, three targeted agents are available for the treatment of breast cancer: trastuzumab, a monoclonal antibody directed against the human epidermal growth factor receptor-2 (HER2); lapatinib, an oral available dual tyrosine-kinase inhibitor of the human epidermal growth factor receptor-1 (HER1, EGFR) and HER2; bevacizumab, a monoclonal antibody directed against the vascular endothelial growth factor (VEGF). All these agents demonstrated to be synergistic with chemotherapy. In addition, recently concluded clinical trials suggest that signaling inhibitors can prevent or overcome resistance to endocrine therapy in estrogen receptor positive (ER+) breast cancer. Moreover, several other targeted drugs are under investigation in clinical trials. The aim of this review is to give a synthetic but complete picture of various targeted agents for breast cancer therapy that are under clinical trials or currently available in clinical practice.

Keywords: Breast cancer, targeted therapy, EGFR, HER2, VEGF, mTOR inhibitors, PARP-1 inhibitors.

INTRODUCTION

Dates more back than a century the awareness of the estrogen-dependent nature of breast cancer. For this reason, endocrine therapy of breast carcinoma initially was the main strategy of treatment of this tumor and historically represents the first example of "targeted therapy" for breast cancer.

The last decade has witnessed an increasing understanding of the molecular pathways underlying cancer development and metastasis. Within all these pathways, each step of the signal transduction cascade – from outside the cancer cell to its nucleus – represents a potential target to hit, in order to block uncontrolled cancer cells proliferation. Consequently, "targeted therapy" has become a novel approach to anticancer treatment, consisting in targeting specific molecules within the signal transduction cascade, which are crucial for cell-cycle control and apoptosis, tumor invasion and metastasis, tumor-related angiogenesis and metabolism. A new era was born, in contrast to the previous time when the only weapons against tumors were traditional chemotherapy acting through killing any cell in multiplication, or hormone therapy targeting only a few kind of tumors. Targeted therapy offers a real potential to be a "magic" bullet able to kill preferentially only neoplastic cells sparing normal ones. This review aims to provide an overview on current status and future perspectives of target-based therapies in metastatic breast cancer.

TARGETING ESTROGEN RECEPTOR

Dates over than a century the first observation of breast cancer regression after oophorectomy, thus representing the first insight into the estrogen-dependent nature of this tumor [1]. Moving from these data, endocrine manipulation has become the treatment of choice and the first "targeted therapy" for the management of metastatic breast cancer (MBC).

Historically, tamoxifen has until recently been considered the backbone of the first-line endocrine treatment of MBC in postmenopausal women, but the introduction of third generation aromatase inhibitors (AIs) has generated interest in newer form of hormonal therapy.

In the second-line setting, anastrozole, letrozole and exemestane have all been shown to offer efficacy and tolerability advantage over megestrol acetate (previously considered the standard second-line endocrine therapy for tamoxifen-resistant MBC) [2-5]. Subsequently, newer phase III trials were performed in order to compare head-to-head tamoxifen and aromatase inhibitors, thus demonstrating the superiority of the latter [6-10]. For this reason, AIs

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represent the drug of choice in the first-line hormonal treatment of MBC.

Furthermore, a newer molecule has been recently re-evaluated for the treatment in the second-line setting of MBC. Fulvestrant is an estrogen receptor antagonist able to down-regulate breast cancer cell levels of estrogen receptor in a dose-dependent manner [11, 12]. Two phase III trials comparing fulvestrant 250 mg with anastrozole in postmenopausal patients with endocrine-sensitive MBC pretreated with tamoxifen demonstrated similar efficacy and toxicity profile for both treatment [13, 14]. A pooled analysis of these two trials suggested that a dose-dependent effect might exists because they initially included a fulvestrant lower dose arm (125 mg), which was discontinued after a first interim analysis because it failed to reach minimum efficacy results [13-15]. Furthermore, a phase II randomized trial in the neoadjuvant setting [16] comparing two different doses of fulvestrant (250 mg *vs* 500 mg) raised the hypothesis that the higher dose might be related to increased clinical and biological activity.

Moving from these data, a double blind, parallel group, multicenter phase III trial (CONFIRM) was performed aiming to compare two different doses of fulvestrant (500 mg on days 0, 14 and 28 and every 28 days thereafter *vs* 250 mg every 28 days) [17]. Progression-Free Survival (PFS), the primary endpoint of the study, was significantly longer for fulvestrant 500 mg than 250 mg (Hazard Ratio, HR, 0.8; p=0.006), while Clinical Benefit Rate (CBR) and Overall Survival (OS) were 45.6% and 25.1 months for fulvestrant 500 mg and 39.6% and 22.8 months in the 250 mg arm, respectively. Quality of life was similar for both arms.

TARGETING HER2

Trastuzumab

Trastuzumab is a humanized immunoglobulin-G antibody targeting the extracellular domain of the HER2 receptor, thus inducing either G0/G1 cell cycle arrest or apoptosis. Its proposed mechanisms of action include antibody-dependent cellular cytotoxicity (ADCC) [18-20], inhibition of intracellular signaling *via* the mitogen-activated protein kinase (MAPK) and the phosphatidylinositol 3-kinase (PI3K) [21-24], through a high affinity binding to HER2, as well as inhibition of angiogenesis [22, 25-27]. The phase III trial, that has led to the approval of trastuzumab for the treatment of HER2-positive MBC, compared responses in patients who received anthracycline or taxane based chemotherapy plus trastuzumab, with those receiving chemotherapy alone [28]. The results of the study showed that addition of trastuzumab to chemotherapy resulted in longer median PFS (7.4 *vs* 4.6 months; p<0.001), longer median OS (25.1 *vs* 20.3 months; p=0.046) as well as higher Overall Response Rate (ORR) (50% *vs* 32%; p<0.001). In a subsequent study, patients with HER2-overexpressing MBC were randomly assigned to receive docetaxel (with or without trastuzumab) [29]. Trastuzumab plus docetaxel was significantly superior to docetaxel alone, in terms of ORR (61% *vs* 34%; p=0.0002), OS (31.2 *vs* 22.7 months; p=0.0325), median duration of response (11.7 *vs* 5.7 months; p=0.009) and median time-to-progression (TTP, 11.7 *vs* 6.1 months; p=0.0001). Due to these studies, the combination of taxanes plus trastuzumab became the standard first-line therapy in HER2-positive breast cancer. However, the association of trastuzumab with vinorelbine also produced response rates over 60% [30-32]. Recently, the results of a randomized phase III trial (HERNATA), comparing vinorelbine plus trastuzumab versus docetaxel plus trastuzumab were published [33]. In this trial, docetaxel regimen was associated with a significant higher overall incidence of grade 3-4 toxicity. The ORR was 59.3% in both groups, but patients on vinorelbine arm, remained on therapy significantly longer.

Other agents that have been successfully combined with trastuzumab include gemcitabine [34], capecitabine [35], carboplatin-taxane doublets [36, 37], liposome-encapsulated doxorubicin [38] and epirubicin [39].

With regard to hormone-sensitive breast cancer, in the TAnDEM study, postmenopausal women with HER2+ and ER- and/or PR-positive MBC were randomly assigned to receive anastrozole plus trastuzumab or anastrozole alone [40]. Median PFS was longer in the combination arm (4.8 *vs* 2.4 months; p=0.0.0016), as well as TTP (4.8 *vs* 2.4 months; p=0.0007). No significant difference was seen in OS (28.5 *vs* 23.9 months; p=0.325), probably because 70% of patients in the anastrozole alone arm received trastuzumab after progression.

Talking about novel anti-HER2 targeted drugs, the most interesting are trastuzumab-DM1 (T-DM1) and pertuzumab.

T-DM1 consists of trastuzumab linked to an antimicrotubule drug, emtansine (DM1). This is a unique combination of a precise and targeted monoclonal antibody, a stable linker, and a potent cytotoxic, designed to deliver potent anticancer agents to tumors in a targeted manner to limit systemic exposure. A recent preliminary report of a phase II trial [41] in which T-DM1 was administered to patients with HER2-positive MBC progressing upon trastuzumab, lapatinib or both demonstrated an ORR of 25% and a CBR of 34%. In addition, preliminary results of a phase II trial suggest that T-DM1 as single agent is at least as effective as the combination of docetaxel plus trastuzumab [42]. Actually, two randomized phase III clinical trials of T-DM1 are ongoing. The first one (EMILIA trial) aims to evaluate the activity of T-DM1 versus standard second-line therapy with lapatinib plus capecitabine for patients with HER2-overexpressing MBC [43, 44], while the second one (MARIANNE trial) evaluates the efficacy of the association of T-DM1 plus pertuzumab versus standard trastuzumab plus taxane as first-line treatment of HER2-positive MBC [45, 46].

Pertuzumab is an HER2 dimerization inhibitor binding to a different epitope from that recognized by trastuzumab, preventing its linkage to other HER receptor to form heterodimers [47]. Preclinical and preliminary clinical data suggest that these two drugs work synergistically [48, 49]. In this regard, the data of the phase III CLEOPATRA trial have been recently published [50]. It is a phase III randomized, placebo-controlled clinical trial, in which patients with HER2-overexpressing MBC were assigned to receive standard first-line treatment with docetaxel plus trastuzumab or pertuzumab plus docetaxel plus trastuzumab. The association of pertuzumab to standard first-line therapy with docetaxel and trastuzumab resulted in a significant prolongation of PFS (18.5 *vs* 12.4 months, HR 0.62; p<0.001), without increasing cardiac toxicity.

DUAL EGFR/HER2 INHIBITORS

Lapatinib

Lapatinib is an orally active small molecule targeting the TK intracellular domain of HER2 receptor [51], thus blocking receptor phosphorylation and activation. Lapatinib was approved by FDA in 2007, based on the interim results of a phase III trial comparing, in pretreated HER2-positive patients, lapatinib in combination with capecitabine with single-agent capecitabine [52]. Patients treated with combination showed significantly longer TTP (8.4 *vs* 4.4 months, HR 0.49; p<0.001) and ORR (23% *vs* 14%; p=0.113). Furthermore, an update of the results of the trial [53] has confirmed these data, so that the association of lapatinib and capecitabine resulted in a prolonged TTP (HR 0.57; p<0.001) and provided a trend toward increased OS (HR 0.78; p=0.177).

Preclinical studies have revealed promising results from the association of endocrine therapy with HER1/HER2 inhibitors, being lapatinib able to overcome hormonal resistance due to activation of EGFR-family signalling, either in HER2-positive or negative breast cancer [54-57].

Recently, a phase III trial of letrozole plus lapatinib versus letrozole alone, in postmenopausal women with hormone receptor-positive, HER2-positive MBC [58], showed that the addition of lapatinib to letrozole significantly increased median PFS (8.2 *vs* 3 months, HR 0.71; p=0.019), ORR (28% *vs* 15%; p=0.021) and CBR (48% *vs* 29%; p=0.03). Moreover, a phase III randomized trial comparing the association of lapatinib plus trastuzumab *versus* lapatinib alone in trastuzumab-refractory HER2-positive MBC [59], achieved significantly better PFS (HR 0.73; p=0.008) and CBR (24.7% *vs* 12.4%; p=0.01), with a trend toward improved OS (HR 0.75; p=0.106).

TARGETING VEGF PATHWAY

Bevacizumab

Bevacizumab is a chimeric human-murine monoclonal antibody against VEGF-A, the ligand of VEGFR-1 and -2 [60]. This drug is designed to directly bind to VEGF extra-cellular domain to prevent interaction with VEGF receptors (VEGFR) on the surface of endothelial cells. The blockage of angiogenesis induces regression of existing tumor vasculature and inhibition of new and recurrent vessel growth. The clinical result of this biologic activity is tumor regression and inhibition of tumor regrowth. Bevacizumab was approved for MBC under FDA's accelerated approval process in 2008, based on the results of an Eastern Cooperative Oncology Group study which evaluated the efficacy of the association of bevacizumab to paclitaxel in the first-line setting [61]. Patients received paclitaxel +/- bevacizumab until disease progression. PFS – the primary endpoint – was significantly improved in the combination arm compared to paclitaxel alone (11.8 *vs* 5.9 months, p<0.001). The ORR was 36.9% for the combination *vs* 21.2% (p<0.001). A subsequent phase III trial (AVADO) evaluated the efficacy of the association of bevacizumab to docetaxel in patients with HER2-negative MBC [62], revealing an improvement in PFS and ORR for the combination arm. Nevertheless, due to only a sliver of PFS benefit – without an OS benefit – and serious health risks emerged in the updated results of the studies, on November 18th 2011 FDA announced the withdrawal of bevacizumab approval for the first-line treatment of HER2-negative MBC [63].

TARGETING THE PI3K/AKT/MTOR PATHWAY

Everolimus

Everolimus or RAD-001 (40-*O*-(2-hydroxyethyl)-rapamycin) is a rapamycin analog (rapalog) that is being developed as an antitumor agent. Like rapamycin, everolimus binds the cyclophilin FKBP-12, and this complex binds the serine-threonine kinase mammalian target of rapamycin (mTOR) when it is associated with raptor and mLST8 to form a complex (mTORC1) that inhibits signalling downstream through the pathway PI3K/Akt/mTOR. Everolimus has demonstrated antitumor activity in clear cell RCC but also in MBC as single-agent either in daily or weekly administration [64-67]. It also demonstrated activity in combination with tamoxifen in patients with MBC refractory to a previous aromatase inhibitor. In fact, the TAMRAD trial [68] revealed a significant advantage in CBR at six months – the primary endpoint of the study – in favor of the association of everolimus to tamoxifen (61.1% *vs* 42.1%; p=0.045), as well as in TTP (8.6 *vs* 4.5 months, HR 0.53; p=0.0026).

More recently, the interim analysis results of the phase III BOLERO-2 trial [69], comparing everolimus plus exemestane to exemestane alone in hormone receptor-positive MBC progressing on letrozole or anastrozole, were published. PFS – the primary endpoint of the study – was determined either by local investigators and by central assessment. In both cases, the association of everolimus plus exemestane provided a significant advantage in PFS (6.9 *vs* 2.8 months, HR 0.43, p<0.001, according to local investigators; 10.6 *vs* 4.1 months, HR 0.36, p<0.001, according to central assessment).

Finally, moving from the data of a small multicenter phase I trial showing promising efficacy results of the association of everolimus to chemotherapy plus trastuzumab in HER2-overexpressing MBC [70, 71], a phase III trial (BOLERO-1) is actually ongoing [72], aiming to evaluate the efficacy of the association of everolimus to paclitaxel plus trastuzumab as first-line treatment of HER2-positive MBC.

MULTITARGETED AGENTS

Sorafenib

Sorafenib is an orally active TKI, concurrently acting against the neoplastic cells by targeting B-Raf-1 within the RAF/MEK/ERK pathway and the endothelial cells of the tumor vasculature by targeting VEGFR-2 and -3, PDGFR, cKIT and FLT-3 [73]. A recently published phase IIb study [74] revealed a significant increase in PFS from 4.1 to 6.4 months (p=0.0006) for patients with locally advanced or metastatic breast cancer receiving sorefenib plus capecitabine *versus* capecitabine alone. Conversely, the results for the combination of sorafenib with pacliaxel were not as good [75], and the development of the combination of sorafenib with paclitaxel was stopped.

POLY (ADP-RIBOSE) POLYMERASE 1 (PARP-1) INHIBITORS

DNA repair mechanisms are a primary reason because tumors are refractory or become refractory to DNA-damaging drugs. Poly (ADP-ribose) Polymerase 1 (PARP-1) is a member of a superfamily of multifunctional enzymes playing a key role in a DNA repair mechanism known as *base excision repair*, which repairs single-strand breaks in DNA [76].

Iniparib

In a randomized phase II trial, 123 patients with metastatic TNBC were randomized to chemotherapy with carboplatin plus gemcitabine with or without iniparib. The addition of the targeted agent to chemotherapy provided a significantly higher CBR (62% *vs* 21%; p=0.0002), ORR (48% *vs* 16%; p=0.0002), median PFS (6.9 *vs* 3.3 months, HR 0.342; p<0.0001) and median OS (9.2 *vs* 5.7 months, HR 0.348; p=0.0005) [77]. Based on these results, a confirmation phase III trial is ongoing in *naïve* patients [78]. Unfortunately, the preliminary results of this trial did not show any benefit of adding iniparib to carbo-gemcitabine combination.

Olaparib

Olaparib is a PARP-1 inhibitor with antitumoral activity in patients with breast, ovarian and prostate cancer with *BRCA1* or *BRCA2* mutation [79]. In a phase II single-arm trial of olaparib in patients with heavily pretreated *BRCA1*/*BRCA2*-mutated MBC [80], patients were divided in two sequential cohorts receiving 400 mg bid of oral olaparib or 100 mg bid, respectively. The ORR was 41% in the higher dose cohort and 22% in the lower dose, respectively.

Veliparib

Veliparib is newer PARP-1 inhibitor under investigation which showed activity in in a phase II trial in combination with metronomic cyclophosphamide in patients with chemotherapy resistant HER2-negative MBC [81].

CONCLUSIONS

A number of targeted drugs have been identified to treat breast cancer. However, only few of them demonstrated to be really active and were introduced in clinical practice. Among the actually available agents, trastuzumab plays a major role in metastatic as well as in early HER2-positive breast cancer patients, lapatinib is active in patients refractory to trastuzumab and bevacizumab – although active – has a negative balance between cost and benefits. It is important to note that all these agents have negligible activity as single agent, but are synergistic with chemotherapy. Conversely, new and more potent targeted drugs are next to be released, and some of them seem to be as effective as chemotherapy, introducing a new era in which we might finally get rid of chemotherapy and use only targeted agents to treat our patients.

DISCLOSURE

Authors have indicated no financial relationships with companies whose products are mentioned in this article.

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