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Targeted therapy of metastatic breast cancer

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Abstract Breast cancer is a heterogeneous disease characterised by a dysregulation of multiple pathways related to cell differentiation, cell cycle control, apoptosis, angiogenesis and development of metastasis. Acting against these pathways provides therapeutic targets for new targeted biologic therapies, which, in the future, might constitute a key for fighting cancer. The development of molecular technology in recent years has allowed a further comprehension of these mutations and dysregulated pathways leading to oncogenesis. New targeted biologic therapies will block essential functions of cancer cells and tumour stroma. A growing number of therapy options, alone or in combination with background treatments (chemotherapy, hormone therapy, radiotherapy), will allow oncologists a better adaptation of treatment to patients and disease characteristics. Examples of approved targeted agents in breast cancer include agents targeting the human epidermal growth factor receptor 2 (HER2), such as trastuzumab, lapatinib and the anti-VEGF bevacizumab. In addition, there are other therapy classes under evaluation, including novel antiEGFR or antiHER2 therapies; agents fighting other tyrosine kinases, including the Src and the insulin-like growth factor receptor; agents interfering critically relevant pathways, such as PI3K/AKT/mTOR inhibitors; and agents promoting apoptosis, such as PARP inhibitors (for particular breast cancer subtypes, such as basal-like, or breast cancer with BRCA mutations) and others. The better selectivity against malignant cells of these therapies, when compared to conventional chemotherapy, gives, *a priori*, at least two advantages to biologic treatments: fewer side effects and a more individualised treatment of cancer depending on the tumour's molecular characteristics. The ability to identify patients' subgroups and response predicting factors will be crucial in obtaining the greatest benefit with minimal toxicity levels. Unsolved questions remain, such as appropriate patient selection based on the expression of the therapeutic target in the tumour, the study of the efficacy of the drug in not so extensively pretreated populations and with a greater chance of response, the use of new pharmacodynamic models to help to define new response predicting factors for a specific new biologic therapy, the combined and rational use of different biologic therapies having different molecular targets and fighting the same target through a complementary mechanism of action that might improve clinical efficacy.

Keywords Breast cancer · Biologic treatment · Targeted therapies

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Introduction

Breast carcinoma continues to be the most frequent malignancy among women from developed countries and

constitutes an important public health issue [1]. In spite of the progress of systemic adjuvant treatments for primary tumours and the resulting improvement of survival in localised disease cases, 20–30% of patients suffer a systemic recurrence of their disease and approximately 10% show disseminated disease at the time of diagnosis, with a median overall survival ranging between 24 and 36 months.

Breast cancer is a heterogeneous disease consisting of various tumour subgroups with different types of response to treatment and variable prognosis. Clinical practice demonstrates very different clinical outcomes, in terms of survival and response to treatment, of patients with tumours of similar histological characteristics. This variability of breast cancer has been confirmed at the molecular level.

In recent years, new therapeutic strategies have been developed for breast cancer, based on the growing knowledge of the molecular biology of tumours. New targeted biologic therapies block essential functions of cancer cells and tumour stroma. The objective is the design of more individualised treatments, allowing greater efficacy rates, better toxicity profiles, better cost-effectiveness ratios and, definitively, an improvement in the quality of life of patients.

This review introduces some of the new targeted biologic therapies for the future treatment of this tumour, acting on the most relevant oncogenesis pathways and approved for the treatment of breast cancer (trastuzumab, lapatinib, bevacizumab) or currently under development.

Targeting the HER receptor family

The family of the epidermal growth factor receptor (EGFR) consists of 4 members: HER1 (also known as the epidermal growth factor receptor EGFR), HER2, HER3 and HER4. All these EGFR family receptors are closely related. The protein structure of EGFR family members consists of an extracellular domain binding to a ligand (except HER2, for which no natural ligands have been identified, and which is activated through the establishment of a heterodimer with other EGFR family members); a transmembrane domain; and an intracellular tyrosine kinase (TK) domain. The ligand receptor binding at the extracellular domain activates, through phosphorylation, a number of intracellular transduction pathways involving ras/raf-1/mitogen-activated protein kinase, phosphatidyinositol-3-kinase (PI3K) and C phospholipase. This signalling cascade leads to the transcription of genes responsible for proliferation, differentiation, angiogenesis and cell survival.

HER2 inhibition

Combination of trastuzumab plus chemotherapy

Between 20 and 25% of breast cancers show HER2 overexpression, which results in a more aggressive clinical course and lower survival rates [2]. However, the natural history of this disease changed the development of anti-HER2 therapies.

Trastuzumab is a humanised monoclonal antibody against the extracellular domain of HER2 receptor. In patients with HER2+ metastatic breast cancer (MBC) not previously treated, the addition of trastuzumab to chemotherapy (doxorubicin-cyclophosphamide or paclitaxel) improved the response rate (50% vs. 32%), duration of response (median 9.1 vs. 6 months), time to progression (7.4 vs. 4.6 months) and overall survival (median 25.1 vs. 20.3 months) compared to chemotherapy alone. It is interesting to note the increase of overall survival, taking into account that approximately 66% of patients initially treated with chemotherapy received trastuzumab after disease progression [3]. The benefits of adding trastuzumab to docetaxel were also investigated in the M77001 study. Patients were randomised to receive 6 cycles of docetaxel, with or without trastuzumab, until disease progression. The study results revealed a statistically significant improvement of overall response rate (61 vs. 34%), duration of response (11.7 vs. 5.7 months), time to progression (11.7 vs. 6.1 months) and overall survival (31.2 vs. 22.7 months) [4]. The combination of trastuzumab and taxanes is the most recommended. However, there are other effective combinations with chemotherapeutic agents, including vinorelbine, gemcitabine, capecitabine, cisplatin and liposomal anthracyclines. Its use with conventional anthracyclines is not recommended, due to the significant incidence of associated heart dysfunction (up to 27% in combination with conventional anthracyclines vs. 13% with paclitaxel and 4% in monotherapy). The incidence of trastuzumab-related cardiotoxicity is higher in patients previously treated with conventional anthracyclines, over 60 years of age or suffering blood hypertension.

Trastuzumab-DM1 is a novel immunoconjugate that covalently links trastuzumab to the microtubule inhibitor DM1. Unlike other immunoconjugates with cytotoxic agents, the compounds are attached via a nonreducible linker that provides tight binding. Vogel et al. [5] conducted a phase II study of trastuzumab-DM1 in patients with HER2+ MBC who progressed on HER2-directed therapy with previous trastuzumab and/or lapatinib treatment. Trastuzumab-DM1 was administered 3.6 mg/kg every 3 weeks to 112 patients. Trastuzumab-DM1 showed significant activity in this population, with an overall response rate of 25%, a clinical benefit rate of 38% by independent review and a median of progression-free survival of 4.9 months. Trastuzumab-DM1 was well tolerated and no dose-limiting cardiotoxicity was observed. Krop et al. [6] conducted a biomarker analysis correlating HER2 status with efficacy in this study. HER2 assessment by quantitative real-time polymerase chain reaction correlated well with response according to HER2 status as confirmed by other methods (fluorescence in situ hybridisation or immunohistochemistry).

Combination of trastuzumab plus hormone therapy

HER2 overexpression has been related to the development of hormone therapy resistance. A meta-analysis based on 12 studies with 2379 patients retrospectively showed a significant correlation between HER2 overexpression and failure of hormone therapy with tamoxifen and other agents, including megestrol acetate and aromatase inhibitors [7]. In the BIG 1-98 and ATAC randomised trials a benefit of anastrozole and letrozole over tamoxifen was observed, irrespective of the tumour HER2 status. Therefore, the HER2 status does not appear to be a selection criterion for the treatment with aromatase inhibitor vs. tamoxifen in postmenopausal women with endocrine-responsive early breast cancer. HER2 overexpression is related to a high risk of recurrence with either aromatase inhibitors or tamoxifen [8, 9].

The TAnDEM study included 208 patients with HER2+ MBC, and positive hormone receptor, who had not received previous chemotherapy for disseminated disease. Patients were randomised to anastrozole plus trastuzumab vs. monotherapy with anastrozole. The addition of trastuzumab to hormone therapy resulted in an increased median progression-free survival (4.8 vs. 2.4 months) as well as an increased clinical benefit (42% vs. 28%). No differences in overall survival were found, although 70% of patients initially treated with anastrozole received trastuzumab after disease progression [10].

Duration of treatment with trastuzumab

In patients who have progressed on trastuzumab plus chemotherapy, the decision of whether to continue or stop the therapy with trastuzumab is controversial. Preclinical data and retrospective studies exist suggesting to continue trastuzumab therapy after disease progression [11]. However, the only prospective, phase III study supporting this decision is the German study GBG 26/BIG 3-05, in which HER2+ MBC patients who had previously received chemotherapy (primary taxanes) plus trastuzumab were randomised to capecitabine with or without trastuzumab. The combination therapy resulted in improved response rate (48% vs. 27%) and median time to progression (8.2 vs. 5.6 months), and a trend to an improved overall survival rate, without increased toxicity. The study recruited 156 out of the 482 expected patients, due to its early stop after FDA approval of lapatinib in a parallel study [12].

In spite of the good results obtained with trastuzumab, approximately 50% of HER2+ MBC patients do not benefit from this drug, and the median duration of response ranges between 9 and 12 months. Thus, *de novo* and acquired resistances to this drug should be examined [13], and studying the overexpression of the HER2 protein in the tumour is not sufficient.

Patients with HER2+ tumours indicate an increased incidence of brain metastasis. On one hand, HER2+ tumours have a greater tendency to develop visceral metastasis, including the central nervous system; in addition, trastuzumab does not cross the blood–brain barrier and the central nervous system acts as a drug sanctuary; the use of trastuzumab changed the natural history of this disease by providing better control of the disease in other locations, this favouring an increased risk of developing brain metastasis of patients with long-drawn-out survival [14].

Finally, several phase III clinical trials demonstrated a benefit of the addition of adjuvant trastuzumab to the treatment of HER2+ breast cancer both concurrently or sequentially to chemotherapy, increasing disease-free survival and overall survival rates [15–18].

HER1 (EGFR) inhibition

Oral tyrosine kinase inhibitors, including gefitinib and erlotinib, were examined in phase II trials of MBC, as single agents or in combination with hormone therapy or chemotherapy, with disappointing results [19]. In these studies, the lack of response might have been due to inactivity of EGFR inhibition alone, patient selection or the inability to accurately identify EGFR inhibitor-sensitive tumours. High levels of serum EGFR did not predict the response to treatment [20].

Cetuximab is a humanised monoclonal antibody against EGFR. Two randomised phase II trials evaluated the role of cetuximab in triple-negative breast cancer. In the TBCRC 001 study, eligible pretreated women received the anti-EGFR monoclonal antibody cetuximab combined with carboplatin or cetuximab alone, with planned crossover to carboplatin at the time of progression. Monotherapy with cetuximab showed a low response rate and was cancelled early due to the study design, but the combination of cetuximab plus carboplatin indicated a modest activity (17% RR and 31% clinical benefit in this pretreated population) [21]. A similar study examining irinotecan plus carboplatin with or without cetuximab suggested a modestly greater response rate (from 30% to 49%) of the combination in triple-negative breast cancer [22].

Inhibitors of multiple HER receptors

In phase I trials, the dual approach, or panHER inhibitors, showed a synergistic effect in a variety of solid tumours [23]. Lapatinib is a reversible dual oral inhibitor of the TK domain of EGFR and HER2. Lapatinib induces the stop of growth and apoptosis of EGFR- and HER2-dependent cell lines, and is a potent inhibitor of tumour growth. A potential advantage of lapatinib compared to monoclonal antibodies targeting the HER2 extracellular domain, such as trastuzumab, is the inhibition of phosphorylation of the truncated form, known as HER-2p95, which lacks the extracellular domain and maintains the tyrosine kinase activity.

A pivotal phase III trial (EGF10151) evaluated the administration of capecitabine with or without lapatinib in

the treatment of 321 patients with HER2+ MBC who had progressed on anthracyclines, taxanes and trastuzumab (EGF 100151 study). The addition of lapatinib resulted in a prolonged time to progression (median 36 weeks vs. 18 weeks) [24]. A modest but clear activity of lapatinib was observed in the 38 patients with brain metastasis previously treated with trastuzumab, with a 5% response rate. In addition, 8 and 4 patients with brain metastasis remained stable after 8 and 24 weeks of treatment, respectively. This observation, together with the lower number of patients who developed brain metastasis in the lapatinib arm, and the low molecular weight of the drug allowing blood–brain barrier crossing, gives potential to the study of lapatinib in patients with brain metastasis, one of the most frequent metastases of these tumours. The main lapatinib toxicities are diarrhoea, skin rash and asthenia.

Currently, the role of lapatinib in first-line therapy of MBD and for the (neo)adjuvant treatment of breast cancer in combination with trastuzumab (ALTTO study) is being studied. Although these drugs share the HER2 target, their mechanisms of action are complementary and a greater activity of their combination compared to monotherapy is foreseen. The results of a phase III study in patients with HER2+ MBC previously treated with anthracyclines, taxanes and progressing on trastuzumab were reported during the ASCO 2008. The combination of lapatinib and trastuzumab resulted in a modest increase of response rate (10.3 vs. 6.9%) and median time to progression (12 vs. 8 weeks) compared to lapatinib in monotherapy [25].

Pertuzumab is a new humanised monoclonal antibody targeting the extracellular domain of HER2 that binds to a HER2 epitope completely different to the one used by trastuzumab. Pertuzumab inhibits dimer formation, both homo- and heterodimer, and may inhibit the growth of tumours not overexpressing HER2. A phase II study included 66 patients with MBC who had received up to three previous chemotherapy lines and had progressed on trastuzumab at the time of study inclusion. Patients continued their trastuzumab treatment with the addition of pertuzumab and attained an overall response rate of 24% and a clinical benefit of 50% (any response or stable disease ≥6 months) [26]. No cases of significant cardiotoxicity were observed. Pertuzumab as a single agent had poor activity. These results led to the initiation of the ongoing new phase III randomised study in not previously treated patients with HER2+ MBC, randomised to pertuzumab+trastuzumab+docetaxel vs. placebo+trastuzumab+docetaxel.

Neratinib is an orally administered irreversible pan-HER receptor tyrosine kinase inhibitor. A phase II study with 28 patients with advanced HER2+ breast cancer that previously progressed trastuzumab showed a clinical activity with an overall response rate of 28%, a clinical benefit of 35% and a median progression-free survival of 16 weeks. Diarrhoea was the most frequent grade 3–4 adverse effect [27].

Canertinib is an orally available pan-HER tyrosine kinase inhibitor. Its binding to the TK sites is irreversible, which may be an advantage compared to other TK inhibitors, which bind reversibly. This drug was well tolerated in a variety of phase I schedules with some stabilisation in patients with refractory breast cancer [28].

Inhibitors of the PI3K/AKT/mTOR pathway

The PI3K/AKT pathway plays an important role in a variety of cell functions, including proliferation, growth and cell survival. Uncontrolled activation of this pathway through receptors with TK activity, or GTPase Ras proteins, induces genetic and epigenetic changes contributing to the development and progression of tumours, breast cancer among them. The loss of suppressive genes, such as the PTEN, favours its activation as well, and has been related to the resistance to anti-receptor therapies, as occurs in HER2+ tumours with trastuzumab.

Many studies are ongoing with mTOR, PI3K and AKT inhibitors. Everolimus, temsirolimus and deforolimus are potent rapamycin-derived mTOR inhibitors. In non-selected MBC patients, these agents showed response rates of approximately 10% [29]. Thus, there is a need for better defining patients that might benefit from these new drugs. A potential explanation for the limited activity of these drugs is the blockage of the negative mTOR feedback on IGF-1R, increasing PI3K and AKT activation, and counteracting the effect on mTOR inhibition. The inhibition of IGF-1 signalling with antibodies or small molecules inhibiting tyrosine kinase, together with mTOR inhibitors, is a strategy that might improve the efficacy, and positive data were already obtained with the combination of octeotride and everolimus [30].

The temsirolimus and letrozole combination vs. letrozole in monotherapy was explored in a phase II randomised study [31]. The combination indicated a greater time to progression, but a subsequent phase III study was cancelled due to a lack of efficacy. A later phase II randomised study in patients with hormone receptor-positive breast cancer on neoadjuvant letrezole treatment showed greater response rates with the combination compared to letrozole plus placebo (68% vs. 59% by tumour palpation examination and 58% vs. 47% by ultrasound examination); the greater decrease of ki67 with the combination of letrozole and everolimus was a moderate marker of response [32].

src-family tyrosine kinase inhibitors

The src is a non-receptor signalling kinase that functions as a hub of a vast array of signalling transduction pathways influencing cellular proliferation, differentiation, motility and survival. Several mechanisms lead to increased Src activity in cancer. Src is downstream in signalling from a number of growth factors receptors, including PDGFR,

EGFR, IGF-1R and the hepatocyte growth factor. Recent studies suggested an association between Src tyrosine kinase and the development, progression and metastasis of breast cancer.

Dasatinib is a multi-targeted kinase inhibitor that inhibits src and abl, and is approved for imatinib-resistant chronic myelogenous leukaemia. Preclinical evidence suggested that this drug might be effective in cell lines of basal-like breast cancer [33]. These findings provided a scientific rationale for the clinical research of dasatinib in the treatment of patients with basal-like breast cancer, a subtype of tumour characterised by poor prognosis, aggressive behaviour and a lack of targeted therapies.

During the San Antonio Breast Cancer Symposium 2008, data were reported on a study of dasatinib in 44 patients with triple-negative MBC. Single-agent dasatinib showed modest activity [2 patients with partial response (4.7%) and 2 patients with stable disease >16 weeks] [34].

HSP90 inhibitors

Overexpression of heat shock proteins or stress proteins constitutes a protective mechanism against different stressing stimuli, in addition to hyperthermia, which might have a negative effect on cell metabolism. These proteins act as molecular chaperones participating in folding, transport, assembly and even protein degradation processes.

HSP90 belongs to this family of proteins and its function is extensively oriented to cell growth-related processes through its participation in multiple cell transduction pathways, and is required for proper MAP kinase functioning, and for the activity of various tyrosine kinases, proteins of the cell-cycle signalling pathway and steroid receptors. In particular, markedly increased HSP90 levels were found in different human cancers compared to normal cells, favouring the folding and activation of oncoproteins, including HER2 and AKT, or stabilisation of the p53 mutated protein.

Geldanamycin is an anti-tumour drug acting by kinase inhibition through its binding and subsequent inhibition of HSP90, thus affecting the kinase-folding chaperone function of this protein. However, the development of the drug was cancelled due to unacceptable hepatoxicity. 17-Allylaminogeldanamycin (17-AAG) is geldanamycin derived, with lower toxicity levels (significant but transient transaminase elevations). Its activity decreases the expression and function of proteins, such as HER2 and AKT, which was demonstrated in HER2+ breast cancer xenografts.

Initial clinical studies with the HSP90 inhibitor, tanespimycin [35], and the first second-generation HSP90 inhibitor, alvespimycin, have demonstrated their safety and anti-tumour activity when administered in combination with trastuzumab to patients with trastuzumab-refractory HER2+ MBC (RR 25%, SD ≥4 months 4/25 and RR 1/18, SD ≥18 weeks 3/18, respectively) [36].

Antiangiogenic agents

Angiogenesis consists in the development of new blood vessels. This complex process rarely occurs in healthy adult tissues, but is a key factor for continuous tumour growth and the development of metastasis. Vascular endothelial growth factor (VEGF) is an angiogenic factor essential for embryonic and immediate postnatal development. In adults, VEGF functions are limited to injury repair and follicle formation. VEGF cell receptors are almost exclusively expressed in endothelial cells. VEGF stimulates proliferation, migration and survival of endothelial cells, increases vascular permeability, and inhibits apoptosis. Processes intimately related to cancer, including hypoxia, expression of oncogenes and abnormal expression of growth factors may initiate the expression of VEGF genes. In most cancers, there is an increase of VEGF, which is associated with a worse prognosis. Thus, VEGF is a key mediator of tumour angiogenesis and constitutes an important target for the development of new angiogenesis-oriented therapies.

Bevacizumab is a humanised monoclonal IgG1 antibody that blocks the binding of all isoforms of the VEGF to the VEGF receptor (VEGFR). An initial phase I/II study with bevacizumab as a single-agent in women with refractory MBC indicated a 6.7% response rate and 17% stabilisations of at least 6 months [37]. In a first phase III study in previously treated MBC patients, the addition of bevacizumab to capecitabine resulted in a 2-fold increase of response rate (19% vs. 9%); however, no changes were observed in terms of overall survival or time to progression [38]. On the contrary, a later phase III study (ECOG 2100) in patients with MBC not receiving treatment for advanced disease, in which bevacizumab was combined with weekly paclitaxel, showed an improved response rate (36.9% vs. 21.2%) and a 2-fold increase in mean progression-free survival (11.8 vs. 5.9 months), the primary study endpoint, compared to weekly paclitaxel. No significant differences were observed in overall survival (26.7 vs. 25.2 months) [39]. As expected, higher incidence rates of blood hypertension requiring medical treatment, bleeding and grade 3–4 proteinuria were observed in the bevacizumab arm. This study was criticised for the low response rate observed in the control arm with paclitaxel in monotherapy. The main difference between both studies lies in the included patient populations. While in the ECOG 2100 study all patients had received a first-line combination for advanced disease, in the capecitabine study 85% of patients had previously received chemotherapy for advanced disease, mainly taxanes and anthracyclines. This might suggest the hypothesis that the use of antiangiogenic drugs would be more efficient in the initial stages of the disease.

The AVADO study [40] investigated the addition of bevacizumab to docetaxel in HER2+ MBC patients. Patients were randomised to three treatment arms, docetaxel plus placebo in one arm, and different doses of bevacizumab (7.5 or 15 mg/kg every 3 weeks) plus docetaxel in the two remaining arms. With a short duration of follow-up

of 10 months, the study results were positive in terms of response rate (44 vs. 55 vs. 63%, respectively) and median progression-free survival (8 vs. 8.7 vs. 8.8 months, respectively); however, differences were very modest and not as clinically relevant as those in the ECOG 2100 study data. These differences might be explained, at least partially, by the antiangiogenic role of the administration of weekly paclitaxel.

During the recent ASCO 2009 meeting, the results of the RIBBON-1 study [41] were reported. In this randomised, placebo-controlled, double-blind, phase III trial, 1237 patients with previously untreated MBC received a choice of chemotherapy (capecitabine, a taxane or anthracycline-based chemotherapy, all administered on a specified schedule) with or without bevacizumab. Patients were randomised 2:1 in favour of bevacizumab, with progression-free survival as the primary endpoint. In both chemotherapy groups there was a modest and significant improvement in progression-free survival with the addition of bevacizumab but again a lack of overall survival improvement. Among the capecitabine-treated patients, the median progression-free survival was 8.6 months with bevacizumab vs. 5.7 months without bevacizumab. Among patients receiving taxane or anthracycline-based therapy, the median progression-free survival was 9.2 months with bevacizumab vs. 8 months without bevacizumab. The overall response rate was also significantly higher with the addition of bevacizumab to capecitabine (35% vs. 23%) or to taxane/anthracycline therapy (51% vs. 38%). The toxicities were as predicted from previous studies. No major cardiotoxicity was observed in the anthracycline group. In summary, the activity of bevacizumab is clear in the initial treatment of MBC (time to response and response rate), but lack of overall survival improvement remains a limitation.

Currently ongoing studies are evaluating the combination of bevacizumab and hormone therapies, including aromatase inhibitors and tamoxifen. In our experience, an additional problem of therapy with bevacizumab is the lack of efficacy predicting factors that could help to more efficiently select those patients who might benefit from this therapy.

Multiple angiogenic factors play essential roles in angiogenesis. These factors are overexpressed in invasive breast cancer, constituting a rationale for the simultaneous blockade of multiple targets or pathways. Sunitinib is a multi-targeted tyrosine kinase inhibitor that inhibits VEGFR, platelet-derived growth factor receptor, stem cell factor receptor (kit) and colony stimulation factor receptor-1. In a phase II study evaluating sunitinib alone in 64 patients with MBC treated with anthracyclines and taxanes, 7 patients (11%) showed a partial response (median duration of 19 weeks) and three additional patients (5%) remained with stable disease for ≥6 months. Median time to progression and overall survival were 10 weeks and 38 weeks, respectively. Although manageable, dose adjustments were frequently needed to manage toxicities, which included fatigue, diarrhoea, anorexia, hypertension, mucosal inflammation, neutropenia and thrombocytopenia [42].

Sorafenib is an oral drug capable of inhibiting several tyrosine kinase receptors involved in tumour progression and angiogenesis, including vascular endothelial growth factor receptors 1, 2, and 3, platelet-derived growth factor receptors α and β, RET, Flt3 and c-KIT. A phase II trial of sorafenib as a single agent in 23 patients with MBC previously exposed to anthracyclines or taxanes was published. Among the 20 eligible patients for the efficacy analysis, no patient experienced partial or complete response in accordance with RECIST criteria. The trial was stopped at the end of the first stage of the study design due to the lack of activity of sorafenib [43].

Poly ADP-ribose polymerase (PARP) inhibitors

Breast cancer susceptibility genes 1 and 2 (BRCA1 and BRCA2) are important for DNA double-chain rupture repair using a homologous recombination mechanism. After BRCA1 or BRCA2 gene mutation, there is a greater susceptibility to the development of breast cancer and ovarian cancer, among other types of tumour. The poly ADP-ribose polymerase (PARP) pathway is a family of enzymes participating in the repair of DNA abnormalities as well, although using a different mechanism based on the excision of bases in a unique DNA chain. The use of PARP pathway inhibitors would avoid the repair of DNA abnormalities in tumour cells with gene BRCA1 and BRCA2 mutations, thus maintaining the DNA injury in these cells, which would be selectively destroyed. Tumours with mutation and dysfunction of the BRCA1and BRCA2 genes have increased sensitivity to the mechanism of action of PARP inhibitors [44]. An initial phase I study with the oral PARP inhibitor AZD2281 (KU-00594336) demonstrated the safety of this agent in patients with advanced breast cancer or ovarian cancer with mutations of BRCA1 and BCRA2 genes. A 43% response rate was observed in the first 21 patients with inherited ovarian cancer associated to a BRCA mutation, and extensively treated [45]. The promising activity observed in patients with BRCA1/2 mutations led to the conduct of phase II studies evaluating AZD2281 in patients with BRCA1- or BRCA2-positive MBC (ICEBERG 1) and BRCA1- or BRCA2-associated ovarian cancer (ICEBERG 2).

Given that BRCA1-related breast cancers generally have the same phenotypic expression profiles as BRCA-negative basal breast cancers, it has been hypothesised that sporadic triple-negative breast cancers may have a similar DNA repair deficit as BRCA-mutant cases. A randomised phase II trial has evaluated the PARP1 inhibitor BSI-201 in patients with metastatic triple-negative breast cancer [46]. A total of 123 patients were randomised to receive gemcitabine/carboplatin with or without BSI-201. PARP1 expression was significantly upregulated on primary breast cancer samples from 50 patients. In the preliminary efficacy analyses reported in ASCO 2009, the clinical benefit

rate, the primary endpoint, was significantly better with BSI-201 plus gemcitabine/carboplatin compared with gemcitabine/carboplatin alone (62% vs. 21%), as was the objective response rate (48% vs. 16%). There was also a significant survival benefit with the addition of BSI-201 to gemcitabine/carboplatin both in median progression-free survival (6.9 vs. 3.3 months) and in median overall survival (9.2 vs. 5.7 months). There were no significant toxicity differences between treatment arms. A phase III trial will start soon. The design will randomise patients with metastatic triple-negative disease to gemcitabine/carboplatin alone or with the addition of BSI-201. Patients in the chemotherapy-alone arm will be allowed to cross over to add the PARP inhibitor at disease progression.

Tutt et al. [47] conducted a multicentre, phase II trial of the oral PARP inhibitor olaparib in heavily pretreated patients with BRCA1/BRCA2-mutated advanced breast cancer. This small, single-arm study included 2 sequential cohorts of patients. Twenty-seven patients received 400 mg olaparib twice daily and 27 patients received olaparib 100 mg twice daily. This drug showed a remarkable activity with higher dose. The overall response rate was 41% and the median progression-free survival was 5.7 months. Despite the small sample size, these data, combined with those from the BSI-201 trial, suggest substantial activity with the use of PARP inhibitors.

If these preliminary data of the efficacy benefit of PARP inhibitors are validated in larger studies we would start to personalise therapy by giving DNA-damaging agents and PARP inhibitors, at least in patients with BRCA mutations, and perhaps in a subset of patients with phenotypically similar but genetically different tumours.

On the other hand, a significant expression of the PARP-1 pathway was observed in different tumour cell-lines, particularly in negative hormone- and HER2-receptor breast cancer [48], which might favour resistance to therapeutic agents inducing a DNA injury in tumour cells, such as platinum. This drug indicated high activity in this type of tumour.

The future of targeted therapies

In recent years, increased knowledge on cell and molecular biology of breast cancer has allowed the identification of genetic mechanisms responsible for normal cell acquisition of a malignant phenotype. The new biologic therapies targeting relevant specific targets of the oncogenesis of breast cancer will allow maximisation of efficacy and reduction of the toxicities of these new drugs. However, unresolved questions remain. Many of the compounds under research might not have been tested in an appropriate patient population, i.e., no selection of patients whose tumours express the target or the route blocked by this particular targeted therapy had been done. Most studies were conducted on extensively pretreated populations, with a minimal probability of response to potentially active treatments, instead of patients in earlier stages of the disease, with a greater probability of response. Research on new compounds is a priority in the treatment of breast cancer. The neoadjuvant model may validate therapeutic targets earlier, offering an opportunity to study markers that predict drug activity by using seriated biopsies. Last, tumour cells show a redundancy of molecular routes and multiple synchronous abnormalities that make it feasible that the blockade of a unique molecular target might not be sufficient or might have minimal practical consequences. It seems fair to think that a rational combination of different drugs with different molecular targets, or even against the same target but using complementary mechanisms of action, might maximise the inhibition of cell proliferation mechanisms.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

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