Current Issues of Targeted Therapy in Metastatic Triple-Negative Breast Cancer

Cornelia Liedtke · Ludwig Kiesel

Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Münster, Germany

Keywords

Triple-negative breast cancer · mTNBC · Clinical trials · PARP inhibitors · Anti-angiogenic agents

Summary

Patients with triple-negative breast cancer are characterized by a poor prognosis compared with patients with other breast cancer subtypes. The angiogenesis inhibitor bevacizumab is effective in the palliative treatment of patients with triple-negative breast cancer as well as in other breast cancer subtypes. PARP inhibitors represent the first group of targeted agents to be developed under the particular aspect of treating patients with hereditary and triple-negative breast cancer. In addition, an increasing number of studies have demonstrated a significant and clinically relevant change in phenotype between primary tumor and metastasis. Consequently, it should be an essential component of the design of modern clinical trials of targeted agents in metastatic breast cancer to determine the relevant tumor phenotype and, depending on the clinical situation, confirm the presence of the therapeutic target in metastatic lesions.

Schlüsselwörter

Triplenegatives Mammakarzinom · mTNBC · Klinische Studien · PARP-Inhibitoren · Angiogenesehemmer

Zusammenfassung

Patienten mit tripelnegativem Mammakarzinom sind charakterisiert durch eine schlechte Prognose im Vergleich mit anderen Mammakarzinomsubtypen. Der Angiogeneseinhibitor Bevacizumab ist eine effektive Behandlungsmethode in der Therapie von Patientinnen mit sowohl tripelnegativem Mammakarzinom als auch anderen Mammakarzinomsubtypen. PARP-Inhibitoren stellen die erste Gruppe zielgerichteter Wirkstoffe dar, die speziell zur Behandlung von Patientinnen mit hereditärem oder tripelnegativen Mammakarzinom entwickelt worden sind. Darüber hinaus zeigt eine zunehmende Anzahl an Studien einen signifikanten und klinisch relevanten Phänotypwechsel zwischen Primärtumor und Rezidiv. Folglich sollte ein wichtiger Bestandteil im Design klinischer Studien für Patientinnen mit metastasiertem Mammakarzinom die Feststellung des Tumorphänotyps und, in Abhängigkeit der klinischen Situation, die Überprüfung desselben in der korrespondierenden metastatischen Absiedlung sein.

Introduction

Triple-negative breast cancer (TNBC) is characterized by the absence of hormone receptor, i.e. estrogen receptor (ER) and progesterone receptor (PR), expression and the lack of overexpression and amplification of the HER2/neu gene [1]. The prognosis of patients carrying this disease phenotype is unfavorable in spite of an increased sensitivity to chemotherapy [2]. With ER, PR, and HER2 not being detectable, essential biomarkers that allow application of endocrine and anti-HER2 therapy are missing. There is a substantial overlap be-

tween the TNBC subtype defined by means of conventional immunohistochemistry / fluorescence-in-situ-hybridization (FISH) and the basal-like breast cancer subtype (BLBC) defined through more complex high throughput gene expression analysis; it has to be acknowledged, however, that this overlap is far from perfect. It is being estimated that about one quarter of TNBC cases do not carry a basal-like gene expression signature while one quarter of BLBC cases do not lack expression / overexpression of hormone receptor and HER2 [3]. Therefore, TNBC may not simply be regarded as a surrogate marker for BLBC.

To date, classical chemotherapy, such as anthracycline- and taxane-containing combination chemotherapy, forms the basis of systemic treatment of TNBC. The first targeted biologic agent that has proven effective in patients with TNBC is the humanized monoclonal antibody bevacizumab that inhibits tumor neoangiogenesis [4]. Recently, 3 issues of potential relevance to the treatment of advanced TNBC have come into scientific focus: i) the use of angiogenesis inhibitors; ii) the use of PARP inhibitors; iii) the correlation between ER, PR, and/or HER2/neu status of the primary tumor and recurrent disease.

Anti-Angiogenic Treatment Concepts in TNBC

Since TNBC are highly proliferative, and growth of blood vessels is needed to maintain tumor proliferation, there may be an increased need of neovascularization for tumor growth, invasion, and metastatic potential among TNBC. Furthermore, elevated levels of vascular endothelial growth factor (VEGF) expression in vivo associated with a TNBC phenotype have been demonstrated [5]. These observations may serve as a rationale for incorporating anti-angiogenic therapy into the treatment of TNBC.

At last year's San Antonio Breast Cancer Symposium 2010, Joyce O'Shaughnessy presented the results of a meta-analysis of the 3 largest independent studies on bevacizumab in the treatment of patients with metastatic breast cancer focusing on the subgroup of 621 patients with TNBC [6]. The objective response rate (ORR) for patients with TNBC in all studies in this combined analysis was significantly higher on treatment with bevacizumab and chemotherapy (42%) compared with chemotherapy alone (23%; $p < 0.0001$), and this benefit translated into significantly prolonged progression-free survival (PFS) (hazard ratio (HR) = 0.65, 95% confidence interval (CI) 0.54–0.79). However, even the meta-analysis did not find a significant overall survival (OS) benefit in the bevacizumab group compared to the chemotherapy alone arm (18.9 vs. 17.5 months) [7]. These results are in line with a recently presented analysis of the ATHENA (Avastin Therapy for Advanced Breast Cancer, MO19391) clinical trial. In this study, patients with HER2-negative metastatic breast cancer were treated with bevacizumab in combination with a taxane-based chemotherapy regimen. Patients with TNBC showed a median TTP of 7.2 months (range 6.6–7.8 months) [8].

In the neoadjuvant setting, results of the neoadjuvant Gepar Quinto clinical trial suggest a particular benefit from the addition of bevacizumab to a chemotherapy backbone particularly among patients with TNBC. The Gepar Quinto trial randomized patients with HER2-negative breast cancer to receive an anthracycline-taxane regimen (epirubicin/cyclophosphamide-docetaxel; EC-Doc) alone or in combination with bevacizumab. While the addition of bevacizumab did not increase the pathological complete response (pCR) rated

significantly in the overall study population, subgroup analysis suggested a particular benefit from bevacizumab therapy among patients with TNBC [9].

The hopes placed in other anti-angiogenic agents for the treatment of breast cancer, however, may not seem to have been justified. For example, 2 studies that compared the efficacy of sunitinib in combination with docetaxel [10] or capecitabine [11] with chemotherapy alone were presented at ASCO 2010. Neither study reached the primary endpoint, defined as a significant prolongation of PFS. However, there was a significant improvement in the secondary endpoint, overall response rate (ORR), for the combination of sunitinib and docetaxel compared to docetaxel alone (51 vs. 39%; $p = 0.0018$), however, at a cost of extensive toxicity (such as grade 3/4 hand-foot syndrome in 17% of patients), which appears hardly acceptable in a palliative setting.

Inhibition of Poly(ADP-Ribose) Polymerase in Patients with TNBC

Hereditary breast cancers are predominantly of the triple-negative subtype and are associated in about 1 in 3 to 4 cases with mutations of the Breast Cancer (BRCA)-1 or -2 genes which are essential for DNA repair. The restricted capability of these tumor cells for BRCA-mediated repair of DNA lesions seems to increase their dependence on other genes or gene products involved in DNA repair, such as poly(ADP-ribose) polymerase (PARP). As a consequence, it is reasonable to assume that in BRCA-deficient breast cancers the pharmacologic inhibition of a second DNA repair pathway, using e.g. an inhibitor of the PARP enzyme, could be exploited for therapeutic purposes (fig. 1). At the ASCO 2009 meeting, Tutt et al. [12] presented data from a multicentre, randomized, phase II trial of 54 patients with metastatic hereditary (i.e. BRCA-1/2-mutated) breast cancer [12]. The patients were randomized to second-line treatment with either 100 or 400 mg doses of the PARP inhibitor olaparib p.o. daily. In the 2 study arms, 64 and 50% carried a TNBC. The intention-to-treat analysis showed an objective response rate of 22 and 41% on treatment with oral olaparib at 100 or 400 mg daily, respectively. Median PFS was 3.8 and 5.7 months, respectively. Treatment was generally well tolerated, although grade 3/4 fatigue and nausea/vomiting reportedly occurred in the 400 mg arm of the trial.

The categories of hereditary breast cancer, triple-negative phenotype, and BLBC – a subtype which has recently been characterized by gene expression profiling – are overlapping with respect to many molecular, clinical, and pathologic features (fig. 2). Although BLBC more often is sporadic rather than associated with germline BRCA1 mutations, BLBCs and hereditary breast cancers share a significant number of common features [13]. This correlation is commonly alluded to as 'BRCAness' and suggests that BRCA1 dysfunction may play

Fig. 1. Rationale for the use of PARP inhibitors in BRCA mutation-associated hereditary breast cancer. In these cancers, the BRCA-dependent DNA repair pathways are dysfunctional, resulting in a dependency on alternative PARP-dependent DNA repair pathways. In this situation, PARP inhibitors are thought to be lethal for the tumor cells because they stop DNA repair completely, which leads to genomic instability and eventually tumor cell death.

Fig. 2. Relationship between the triple-negative (TNBC), basal-like (BLBC), and BRCA mutation-associated (hereditary) breast cancer phenotypes. These categories overlap to an as yet poorly defined extent.

a significant role even in sporadic BLBC [14]. Hereditary breast cancer is not only characterized by a triple-negative phenotype in most cases but also by an overexpression of PARP. This suggests an increased dependence of this subtype on PARP-mediated DNA repair pathways and thus an enhanced sensitivity to treatment with PARP inhibitors. Similarly, TNBC is associated with an increased expression of PARP [15, 16]. Against this background, at the 2009 ASCO meeting, O'Shaughnessy et al. [15] had presented the first results of a randomized phase II trial of the PARP inhibitor BSI-201/iniparib in patients with metastatic TNBC. In this trial, 120 patients were randomly allocated to first- and up to third-line palliative chemotherapy with gemcitabine (1,000 mg/m² intravenously (i.v.), days 1 and 8, every 21 days (q21d)) and carboplatin (area under the curve (AUC) = 2 i.v., day 1, q21d), with or without iniparib (5.6 mg/m² i.v., days 1, 4, 8, 11, q21d). The combination of gemcitabine, carboplatin, and iniparib achieved a significantly higher clinical benefit rate compared to treatment with gemcitabine and carboplatin alone (62 vs. 21%; $p = 0.0002$). Moreover, the objective response rate (48 vs. 16%; $p = 0.002$), median PFS (6.9 vs. 3.3 months; $p < 0.0001$), and even median OS (9.2 vs. 5.7 months; $p = 0.0005$) were significantly improved by the addition of iniparib. Hematological and non-hematological toxicities were not significantly different between the study arms, and the received doses of gemcitabine and carboplatin were similar.

Based on its highly favorable toxicity profile on the one hand and the fact that the addition of BSI-201 to combination cytotoxic therapy resulted in an increase in OS in patients with (in part) heavily pretreated metastatic breast cancer,

BSI-201 has long been regarded one promising agent in this field and has been developed as a potential breakthrough in the treatment of patients with TNBC. Therefore, a phase III multicenter clinical trial was designed to confirm these promising results and has just completed accrual. In this study, patients underwent the same treatment, i.e. gemcitabine/carboplatin with or without BSI-201 as first- to third-line therapy for metastatic TNBC. However, according to preliminary results presented of this trial, the study did not meet its primary endpoint of demonstrating a significant advantage through the addition of BSI-201 regarding PFS and OS (fdanews.com/newsletter/subscribe/options?newsletterId=11; Clinical Trials Advisor, Feb. 3, 2011, Vol. 16, No. 3). Given the promising phase II results, one may argue that the subgroup of patients with breast cancer that do derive significant benefit from this obviously active therapeutic agent still needs to be defined.

PARP Inhibitors at ASCO 2010: Seeking the Optimal Drug, Combination Partner, and Indication

Several PARP inhibitors at various stages of their preclinical and clinical development are currently available (table 1) [17] that show promising activity for patients with distinct subtypes of breast cancer. The relationship between the triple-negative phenotype and hereditary breast cancer with respect to their sensitivity to PARP inhibition remains unclear. Even though a large proportion of BRCA-1/2-associated breast cancers present with a triple-negative phenotype [18, 19], this phenotype actually constitutes a heterogeneous entity consisting predominantly of sporadic tumors. As mentioned above,

Drug name	Company	Administration	Stage of development
AG014699 (PF-0367338)	Pfizer	i.v. (oral)	phase I/II (combination)
Olaparib (KU59436 / AZD2281)	AstraZeneca / Kudos	oral	phase I/II (combination)
Velaparib (ABT888)	Abbott	oral	phase I/II (combination)
Iniparib (BSI-201)	BiPar / sanofi-aventis	i.v.	phase I/II/III (combination)
INO-1001	Inotek	i.v.	phase Ib
GPI21016	MGI Pharma/Eisai	oral	phase I
CEP-9722	Cephalon	oral	phase I
MK4827	Merck and Co.	oral	phase I
BMN-673	Biomarin/LEAD Pharmaceuticals		preclinical

i.v. = Intravenous.

Table 1. Overview of the currently available PARP inhibitors (from [10])

a triple-negative phenotype was present in slightly more than half of the patients in the olaparib trial. Conversely, the BSI-201 trial did not report the proportion of patients with hereditary breast cancer (i.e. with a mutation in the BRCA-1 or BRCA-2 gene region) in the study population. It will be important, therefore, to know whether patients with TNBC display a heterogeneous response to PARP inhibition, depending on their BRCA mutation status. In a study conducted by Gelmon et al. [20], patients with sporadic or hereditary breast or ovarian cancer were treated with oral olaparib at 400 mg twice daily. While patients with hereditary and sporadic ovarian cancer had objective response rates of 41.2 and 23.9%, respectively, there was not a single objective response among 23 patients with breast cancer of whom 8 were carriers of a BRCA mutation and 15 were not. This may be explained by the heterogeneity of this patient subgroup and the fact that olaparib was given as a single agent. Nevertheless, further research will have to demonstrate whether TNBC as a whole may represent the optimal group of patients suitable for PARP inhibition therapy.

In the search for the optimal combination partners for PARP inhibitors, preclinical data compete with clinical rationales. While preclinical studies favor the combination of PARP inhibitors with alkylating agents rather than microtubule-targeting agents such as taxanes, alkylators are not commonly used in the treatment of metastatic breast cancer. On the other hand, taxanes are standard first-line agents in taxane-naïve patients with metastatic breast cancer, but it is unclear whether they can be safely and efficaciously combined with PARP inhibitors. Dent et al. [21] presented the results of a study of first- and second-line therapy (70 vs. 30%) with olaparib in combination with paclitaxel in 19 patients with advanced breast cancer. Despite promising activity, the results were overshadowed by predominantly hematological and gastrointestinal toxicities in more than half the patients. Since neutropenia occurred in 58% of the patients, the protocol had to be amended to allow the addition of hematopoietic growth factors (G-CSF). Another study presented by Isakoff et al. [22] followed the preclinical rationale of combining a PARP inhibitor with an alkylating agent by combining the

PARP inhibitor veliparib with the alkylating agent temozolomide. A total of 41 patients with metastatic breast cancer were treated, of whom 23 were triple-negative and only 3 were BRCA-1 and 5 BRCA-2 mutation carriers. A complete or partial response was seen in 3 patients (ORR 7%). However, activity was limited to BRCA-1/2 carriers as all responses were seen in this subgroup of patients (corresponding to an ORR of 58%). Veliparib was reasonably tolerated without grade 3/4 toxicity. However, the initial dosing of 40 mg twice daily had to be reduced by 25% after grade 4 thrombocytopenia.

Interestingly, PARP expression is not only associated with a TNBC phenotype, but may also predict response to neo-adjuvant chemotherapy independent of phenotype. Loibl et al. [16] presented results of a translational research effort based on 646 patients who were treated with various neo-adjuvant chemotherapy regimens. In this analysis, expression of PARP was associated with pCR. Importantly, while the authors demonstrated an association between expression of PARP and TNBC, expression of TNBC could also be demonstrated in a significant number of cases of other breast cancer phenotypes [16]. This observation could serve as a rationale for evaluating PARP expression in breast cancer subtypes other than TNBC.

Against this background, forthcoming studies on PARP inhibitors should primarily aim to identify and evaluate the most effective cytotoxic agents (i.e. chemotherapy backbone) for combination with PARP inhibitors, to determine the optimal dosage and administration schedules for PARP inhibitors, to identify the subgroup of patients who benefit most from PARP inhibition, and – on the basis of translational studies – to elucidate the mechanisms underlying the *in vivo* efficacy of PARP inhibitors.

Triple-Negative Once and Forever?

Variable discordance rates between primary tumor and its distant metastases have been observed for markers such as the ER (18–56%) or the HER2 oncogene (0–38%) [23]. In

one of the largest studies to date from the University of Texas M.D. Anderson Cancer Center (MDACC) at Houston, TX, USA [24], we demonstrated that 134 tumors (58%) remained non-triple-negative during the course of the disease and 42 patients (18%) had a triple-negative primary tumor and a triple-negative metastatic lesion. A change from triple-negative to non-triple-negative occurred in 22 cases (10%) and a change from non-triple-negative to triple-negative in 33 cases (14%). Importantly, survival after diagnosis of metastatic disease (i.e. post-recurrence survival, PRS) in our study population was significantly worse for triple-negative discordant patients, i.e. those with a change in their triple-negative status, as compared to receptor-concordant patients. Actually, PRS of patients with a triple-negative discordant phenotype was as poor as that for patients with a consistently triple-negative status from primary diagnosis until disease recurrence [24]. In the West German Study Group (WSG), in collaboration with external scientific groups such as the DETECT study group, we have conducted a German multicenter analysis to validate these findings. The results of a systematic comparison of tumor phenotype of primary tumor and disease recurrence site in 436 patients will be presented at the ASCO 2011. Furthermore, a number of studies that examined the phenotype of distant disease or local recurrence in relation to the

primary have been presented recently. In a prospective analysis of 271 patients, Amir et al. [25] found that a biopsy of the secondary lesion and, hence, a possible biomarker discordance, caused a change in clinical management in approximately 15% of patients. Even though some of these discordances were likely to be the result of inaccurate analytical methods, one can still assume that a change in the expression of ER, PR, and HER2 actually takes place in a proportion of tumors, and that this phenomenon will also occur with other therapeutic targets. In an era where new, largely selective targeted therapies are being investigated in increasingly specific subgroups of metastatic patients, it may be essential to determine the relevant metastatic phenotype based on targeted biopsy specimens. At present, this concept should have consequences for the conduct of clinical trials in metastatic breast cancer in that biopsies of metastases should become a routine component of any accompanying translational program, in particular when targeted agents are being used.

Disclosure Statement

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