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REVIEW

Characteristics of triple-negative breast cancer

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Abstract
Background Triple-negative breast cancers (TNBC) neither express hormone receptors, nor overexpress HER2. They are associated with poor prognosis, as defined by low five-year survival and high recurrence rates after adjuvant therapy. Overall, TNBC share striking similarities with basal-like breast cancers (BBC), so a number of studies considered them being the same. The purpose of this review is to summarise the latest findings on TNBC concerning its relation and delineation to BBC, discuss the developmental pathways involved and address clinical implications for this complex type of breast cancer.
Methods The recent literature from PubMed and Medline databases was reviewed.
Results Not all TNBC are of the intrinsic BBC subtype (nonbasal (NB)-TNBC), nor are all BBC triple-negative (non-triple-negative (NTN)-BBC). There is increasing evidence that a triple-negative, basal-like breast cancer (TNBBC) subtype develops mainly through a BRCA1-related pathway. Somatic mutations that contribute to NTN-BBC and NB-TNBC development are possibly not related to this pathway, but may occur randomly due to increased genomic instability in these tumours. Several therapeutic options exist for TNBBC, which exhibited promising results in recent clinical trials. Cytotoxic therapies, e.g. combined treatment with anthracyclines or taxanes, achieved good tumour regression rates in the neo-adjuvant setting, but also showed considerable recurrence during the first 5 years after therapy. Targeted therapy options involve PARP1 and EGFR inhibition, although both approaches still need further investigation.
Conclusions TNBC and BBC are not the same disease entity. The TNBBC subtype shows the largest homogeneity in terms of tumour development, prognosis and clinical intervention options.

Keywords Triple-negative breast cancer (TNBC) · Basal-like breast cancer (BBC) · BRCA1 · Adjuvant treatment · Patient outcome

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Introduction

Worldwide, 1.3 million women were estimated to be diagnosed with breast cancer in 2007 (Garcia et al. 2007) Therapeutic options for this type of cancer range from primary surgery to adjuvant chemotherapy, radiotherapy, hormonal therapy or targeted therapy. Breast cancer is a heterogeneous disease, and therefore, no golden standard therapy exists suitable for all tumours of the mammary gland (Early Breast Cancer Trialists' Collaborative Group 2005). For many years, tumours of the breast were characterised by tumour size only. However, this sub-classification proved to be limiting for it was unable to define subgroups sharing similar prognostic and therapeutic aspects. Later on, a histological classification system was developed, dividing breast cancer into subgroups distinguished by the histological appearance of the tumour.

Despite advantages over the system based on tumour size alone, a histo-morphological subdivision also failed to form homogeneous breast cancer subgroups (Weigelt et al. 2008; Page 2003). Currently, the most widely used classification system of breast cancer combines histo-morphological information (such as histological subtype and grading) as well as TNM staging information, i.e. tumour size (T) together with lymph node (N) and distant metastasis occurrence (M) (Elston and Ellis 1993; Sobin et al. 2009). A more recent approach to classify breast cancer subgroups is that of gene expression profiling. Based on transcriptomic similarity, breast carcinomas can be distinguished as part of a group of five distinct breast cancer subtypes, of which the basal-like subtype is characterised by aggressive tumour growth and poorest patient survival (Sorlie et al. 2001, 2003).

Certain breast cancer treatment strategies, like hormonal therapy (e.g. anti-oestrogens) or targeted therapy (e.g. trastuzumab), are only effective when corresponding receptors and targets are expressed by the tumour cell. In breast cancer, a hormonal therapy requires oestrogen (ER) and/or progesterone receptor (PgR) expression to be effective, while trastuzumab therapy applies only to those tumours harbouring overexpression of HER2 due to amplification of its encoding oncogene *ERBB2*. Hormonal therapy and trastuzumab cause less adverse side effects when compared to chemotherapy and prolong disease-free survival (DFS) and overall survival (OS) of the patient (Samphao et al. 2009; Pienkowski and Zielinski 2010). However, some tumours neither express ER and PgR, nor do they overexpress HER2, for why these tumours were termed triple-negative breast cancer (TNBC). The prognosis of patients with this type of tumour is very poor, not only because hormonal therapy and treatment with trastuzumab are ruled out, but also because these tumours seem to be more aggressive than other breast carcinoma subtypes (Nofech-Mozes et al. 2009), similar to those of the basal-like breast cancer subtype.

The objective of this review is to summarise the latest findings on TNBC. It will address the following questions: What is the relation between the basal-like subtype and TNBC? What pathways are involved in the growth of these tumours? Do TNBC have a homogeneous gene expression profile? What is the prognosis of this kind of tumour? and What are the most effective forms of treatment?

Triple negativity and the basal-like subtype of breast cancer

Classically, breast carcinomas can be divided into 18 different subtypes based on histo-morphological characteristics (Tavassoli and Devilee 2003). A large majority of breast tumours (50–80%) is designated as 'invasive ductal carcinoma not otherwise specified' (IDC NOS) (Weigelt et al. 2008). IDC NOS is defined as a tumour that fails to exhibit sufficient morphological features to be categorised as one of the other 17 subtypes (Page 2003; Tavassoli and Devilee 2003; Weigelt et al. 2008). Unfortunately, the histological way of categorising breast tumours fails to divide tumours into different entities of the disease with type-specific prognosis and treatment possibilities. In particular, the largest IDC NOS subtype shows an inhomogeneous prognosis (Weigelt et al. 2008). Moreover, the accuracy of histological classification depends greatly on the pathologist (Page 2003; Weigelt et al. 2008). A new approach to characterise breast tumours using molecular characteristics was first described by Sorlie et al. (2001). This study group clustered breast carcinomas based on similar gene expression profiles, as determined by DNA microarray experiments. The largest overall difference in gene expression was observed between hormone receptor (HR)-positive and HR-negative tumours. HR-positive tumours clustered in two groups with expression patterns similar to luminal epithelial mammary cells. HR-negative tumours clustered in three distinct molecular subgroups: tumours with gene expression similar to basal/myoepithelial mammary cells; tumours with characteristics of HER2 gene amplification; and tumours with expression patterns related to normal mammary stromal cells. The subtypes thus found are referred to as luminal A, luminal B, basal-like, HER2-positive and normal-like breast cancer (Sorlie et al. 2001), all of which are associated with distinct prognosis and treatment possibilities. Interestingly, the normal-like breast carcinomas do not seem to constitute a true subtype. It is assumed that it represents breast cancer samples in which normal breast cells are overrepresented, suggesting that gene expression results reflect a non-cancer cell expression rather than that of the cancerous cells (Sorlie et al. 2001; Morris and Carey 2007).

Basal-like breast cancer (BBC) is associated with triple negativity of an ER/PgR/HER2 status (Sorlie et al. 2001). Therefore, several studies have used the absence of these receptors, sometimes along with cytokeratin 5/6 or cytokeratin 17 expression, as a characteristic feature to define BBC in histological staining (Nielsen et al. 2004). However, a study by Bertucci et al. (2008) showed that TNBC and BBC are not the same entity. Using gene expression profiling, only 123 samples of the 172 triple-negative tumours (71%) were determined to cluster with BBC, suggesting that not all TNBC are of the basal-like subtype. Reversely, only 123 (77%) of the 160 tumours that were defined as BBC by gene expression profiling proved to be triple-negative in histological staining, indicating that not all BBC are triple-negative. In further studies, Morris et al. (2007) and Rakha et al. (2009) showed similar results. In

addition, these studies showed that TNBC do not form a homogeneous group when analysed by gene expression profiling. In contrast, the basal-like subtype does form a homogeneous group of tumours with a similar gene expression profile related to prognosis and therapy response (Bertucci et al. 2008; Rakha et al. 2009). This indicates that the prognosis of TNBC may actually refer to the high percentage of triple-negative tumours that is of the basal-like subtype (Cheang et al. 2008). Indeed, several studies reported a poor disease-specific survival for the basal-like subtype (Sorlie et al. 2003; Nielsen et al. 2004; Carey et al. 2006; Morris et al. 2007). Furthermore, in cases in which metastasis occurred, the disease-free survival interval was found to be significantly shorter (Sorlie et al. 2003). Also, at primary diagnosis, basal-like tumours show adverse characteristics, such as a high nuclear and mitotic grade and unfavourable histological features, like high mitotic index and poor differentiation (Carey et al. 2006).

In conclusion, the triple-negative group of breast cancer is not a homogeneous disease entity. However, a substantial fraction of these tumours belongs to the basal-like tumour type, which does form a homogeneous group. Thus, the overall poor prognosis of TNBC may be a result of this basal-like subgroup, and triple negativity may be seen more as a symptom than as a separate entity of breast cancer.

TNBC expression profiles and pathways leading to the triple-negative or basal-like subtype

Although TNBC and BBC are not the same entity of the disease, there is a large overlap between them. As a consequence, many studies concerning gene expression and cellular pathways in the development of different subtypes of breast cancer do not distinguish between TNBC and BBC. Moreover, evidence is present for a pathway that is related to the BRCA1 pathway that leads to the development of a basal-like, triple-negative subtype (TNBBC). This evidence will be discussed later on in this section. We propose a model in which non-basal-like TNBC (NB-TNBC) and non-triple-negative BBC (NTN-BBC) are possibly not the direct result of this pathway, but receive their distinctive genotype because of random mutations. For example, if a breast tumour develops following disruption of the BRCA1-related pathway, it might turn into TNBBC. However, because of the instable genome, it is possible that genomic changes occur that are not BRCA1 pathway related (Fig. 1). If these genomic changes involve, for example, HER2 gene amplification, the tumour will no longer be TNBBC, but NTN-BBC. Since the tumour benefits from HER2 overexpression, there exists a selective pressure towards HER2 amplification. This could be the explanation for the approximately 20–30% of BBC that are not triple-negative. Likewise, in non-basal-like tumours, a selective pressure is present towards losing HR expression, since this enables the tumour to grow independently from the presence or absence of growth-stimulating factors. This may represent the cause of the approximately 20–30% of TNBC that are not of the basal-like subtype.

The three subgroups of TNBC and BBC show a different prognosis and imply distinct therapeutic options. Especially, NB-TNBC do not behave like TNBBC, for they show better prognosis despite less response to adjuvant chemotherapy (Rouzier et al. 2005; Rody et al. 2007; Tischkowitz et al. 2007). This is why in the remainder of this section of the review we will discuss the TNBBC subtype as defined by Sorlie et al. (2001).

TNBBCs have a specific expression profile that distinguishes them from other breast tumours, e.g. enhanced expression of Ki-67, vimentin, laminin and p53, whereas expression of Bcl-2 is lower than in other subtypes (Rodriguez-Pinilla et al. 2007; Han et al. 2008). Several studies found expression of the tumour suppressor PTEN more frequently lost in TNBBC than in non-TNBC (Perren et al. 1999; Saal et al. 2008; Hu et al. 2009). PTEN plays a role in the phosphatidylinositol 3-kinase pathway, which is crucially involved in many breast cancer subtypes. Interestingly, if this pathway is affected in breast cancer, either PTEN *or* PIK3CA expression is lost, indicating that loss of one gene's activity may relieve the selective pressure on losing the other (Saal et al. 2005). Loss of PTEN expression is associated with a triple-negative phenotype, whereas downregulation of PIK3CA is associated with a triple-positive phenotype (Perren et al. 1999; Saal et al. 2005, 2008). Other genes that tend to be mutated more frequently in TNBBC compared to other breast tumours are the tumour suppressor retinoblastoma gene (*RB1*) and the *KRAS* oncogene, both well known to enhance tumour growth (Hu et al. 2009).

Besides mutations, other genetic changes such as copy number alterations (CNA) occur differentially between distinct subtypes. Hu et al. (2009) observed that globally, CNA occur more often in TNBBC than in any other subtype. However, neither the functional impact of these lesions nor the frequency at which one specific CNA occurred could match those of the HER2 + subtype. In more than 30% of the TNBBC cases, two specific CNA are found, i.e. gene amplification and chromosomal deletion (Han et al. 2008; Hu et al. 2009). A gene that was found to be specifically amplified in TNBBC is nuclear factor 1/B (*NFIB*), residing on the short arm of chromosome 9. The function of this gene in cancer biology has to be defined yet; however, it plays a known role in central nervous system development (Han et al. 2008; Mason et al. 2009). A structural deletion of 80 Mb on chromosome 5q13-14

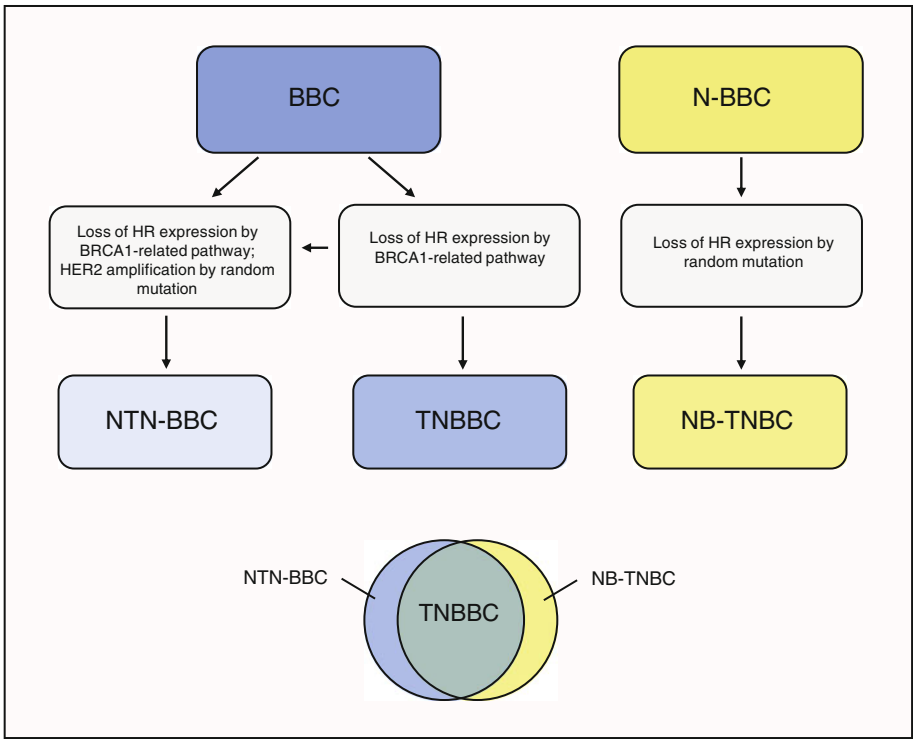

Fig. 1 Origin and related pathways of different types of triple-negative and basal-like breast tumours. The non-basal-like triple-negative breast cancers (NB-TNBC) may originate from non-basal-like breast cancer (N-BBC), and the non-triple-negative basal-like breast cancer (NTN-BBC) as well as triple-negative basal-like breast cancers (TNBBC) may originate from basal-like breast cancers (BBC). Only the TNBBC subtype can be regarded as a homogeneous breast cancer subgroup

that occurs more frequently in TNBC contains the *RASA1* gene. This gene has a function in de-activating RAS, and loss of *RASA1* results in an overactive RAS tyrosine kinase. Since RAS is a stimulator of cell growth, RAS overactivation leads to increased proliferation activity (Hu et al. 2009). *NFIB* and *RASA1* are not the only genes playing a key role in tumorigenesis by CNA. A study comparing gene expression signatures reflecting chromosomal instability with signatures of the different breast cancer subtypes revealed that TNBBC, along with the HER2 + subgroup, displays the most instable genome. They also found that mutations in the *PTEN* and *RB1* gene are associated with this chromosomal instability (Hu et al. 2009).

In search of pathways that lead to the development of TNBBC, several studies have found that BRCA1-related breast cancers are associated with the TNBBC subtype (Foulkes et al. 2003; Lakhani et al. 2005; Diaz et al. 2007), and TNBBC expression profiles resemble those of BRCA1-related breast cancers (Foulkes et al. 2003). This resemblance gave rise to the idea that *BRCA1* mutations could play a role in the development of TNBBC. Further findings support this idea. For example, the earlier mentioned deletion in chromosome 5q found in TNBBC is also associated with BRCA1-related breast cancer, occurring in 71% of cases (Johannsdottir et al. 2006; Hu et al. 2009). Moreover, abnormalities in the inactive X chromosome (Xi) that destabilise its silenced state and activate genes that are inactive in non-cancerous cells are associated with loss of BRCA1 function (Ganesan et al. 2002), and they are also associated with TNBBC (Richardson et al. 2006; Turner et al. 2007). Taken together, these findings support the hypothesis that loss of BRCA1 function may play a major role in TNBBC development (Richardson et al. 2006).

Since not all TNBBC harbour mutations in *BRCA1*, it appears that it is not structural mutations alone to be necessary for the development of TNBBC. Several studies have investigated epigenetic changes, such as DNA methylation, influencing the expression of BRCA1 in TNBBC. However, DNA methylation does not seem to play a supportive role, since *BRCA1* methylation occurs similar frequent in TNBBC and non-TNBBC (Turner et al. 2007; Matros et al. 2005). In contrast, Turner et al. (2007) compared BRCA1 expression in TNBBC to BRCA1 expression in other tumour types and found that expression in TNBBC was twofold lower. In addition, the expression levels of inhibitor of DNA binding 4 (ID4), representing a negative regulator of BRCA1 (Beger et al. 2001), proved to be ninefold higher in TNBBC (Turner et al. 2007). This implies that low BRCA1 expression could also be the result of gene regulatory mechanisms, such as ID4 overexpression in these tumours. Still, the fact that not all TNBBC show loss of BRCA1 expression suggests that further genes related to the BRCA1 pathway are likely to be deregulated in the process of TNBBC development (Richardson et al. 2006).

Several studies linked TNBBC to epidermal growth factor receptor (EGFR) expression, and percentages

ranging from 42 to 71% were found (Nielsen et al. 2004; Nalwoga et al. 2008; Cheang et al. 2008; Meche et al. 2009; Collins et al. 2009). This receptor, like HER2, is a potent stimulating factor of cell-growth-activating pathways and thus stimulates tumour growth when activated (Burgess 2008). EGFR expression in breast cancer is associated with poor disease outcome. Viale et al. (2009) showed worse disease-free survival (DFS), overall survival (OS) and distant disease-free survival (DDFS) for EGFR expressing TNBBC compared to tumours without EGFR expression. Also, response rates of EGFR-positive breast tumours to chemotherapeutic therapy proved to be lower (Nogi et al. 2009). EGFR expression could be one of the causes of the poor disease outcome of TNBBC. Since EGFR can be targeted by newly developed therapies, assessment of EGFR expression, like commonly performed on HER2, could have major therapeutic relevance, as will be described later in this review (Stratford et al. 2007; Hoadley et al. 2007).

Prognostic implications of triple-negative breast cancer

Since most prognostic research is performed as retrospective studies, many of these studies use data collected for diagnostic reasons. Mostly, these studies do not investigate markers for basal-like breast cancer and use triple negativity as an inclusion factor to select their study population. This is why in the following section prognosis is being discussed for TNBC, rather than specifically for TNBBC.

Patients with TNBC suffer from poor prognosis (Nofech-Mozes et al. 2009). Compared to other breast cancer subtypes, TNBC develop earlier in life, and consequently more often in pre-menopausal women (Carey et al. 2006; Rhee et al. 2008). At diagnosis, TNBCs are commonly of high nuclear mitotic grade, of larger tumour size, and they show a more aggressive expression profile with low Bcl-2 but high p53 and Ki67 expression (Foulkes et al. 2004; Fulford et al. 2006; Tian et al. 2008; Dogan et al. 2008; Nishimura and Arima 2008; Chivukula et al. 2008). Taken together, these adverse factors may be a major reason for poorer OS, breast-cancer-specific survival (BCSS) and relapse-free survival (RFS) reported for this disease. Several studies demonstrated significantly lower RFS in patients with TNBC compared to patients with non-TNBC. Rhee et al. found that the four-year survival of TNBC patients was 85.5%, compared to 94.2% in non-TNBC patients (Rhee et al. 2008). Parikh et al. (2008) showed that the frequency of relapse is less favourable in TNBC. Also, the median time to tumour recurrence proved to be 1.2 years shorter in patients with TNBC when compared to non-TNBC patients. Likewise in recurrent breast cancer, those patients with TNBC still had a worse prognosis than non-TNBC. Not only the risk of tumour recurrence was higher, but also the risk of dying as a consequence of this relapse. Mersin et al. (2008) reported a hazard ratio of 4.2 for developing tumour recurrence for TNBC when compared to non-TNBC. Similar results for RFS in TNBC are widely reported (Sorlie et al. 2003; Rakha et al. 2007; Dent et al. 2007; Tian et al. 2008; Nishimura and Arima 2008; Kaplan and Malmgren 2008). Overall five-year survival was determined to be 81% for TNBC compared to 91% for triple-positive breast cancer, and 94% for HR-positive/HER2-negative (HR+/HER2−) breast cancer (Kaplan and Malmgren 2008). Like RFS, shorter OS in TNBC is widely reported (Dent et al. 2007; Tian et al. 2008; Nishimura and Arima 2008; Chivukula et al. 2008). There is only one breast cancer subtype that has a prognosis comparably poor as TNBC. This is the HR-negative, HER2-positive (HR−/HER2+) subtype. BCSS of this subgroup is reported as 86%, compared to 88% in the TNBC subgroup and 95% in the triple-positive group (Kaplan and Malmgren 2008). However, it should be noted that the recently published long-term studies on breast cancer survival mostly included patients during the pre-trastuzumab era. The introduction of trastuzumab as therapy regimen significantly improved the prognosis in the HR−/HER2+ subgroup (Pienkowski and Zielinski 2010). Interestingly, it seems that the higher risks of recurrence and tumour-related death diminish over time. After 5 years of therapy, each type of risk is lowered and almost equals those of the non-TNBC subtypes (Dent et al 2007; Hergueta-Redondo et al. 2008). This suggests that the poor prognosis of TNBC may be due to effects that occur during the first 5 years after surgery.

Therapeutic options of triple-negative breast cancer

In general, adjuvant therapeutic options for TNBBC can be divided into two groups, cytotoxic agents and targeted therapies. Cytotoxic agents confer a DNA-damaging effect to generally all dividing cells. Fast dividing cells, like cancer cells, are more susceptible to cytotoxic therapy, but so are other fast dividing normal cells, like blood cells. This is why cytotoxic agents often result in numerous adverse side effects. In contrast, targeted therapies interfere with a specific biomolecule to which their effect is directed. This target is a specific characteristic of the cancerous cell, e.g. an overexpressed receptor, providing certain selectivity against malignant cells, thereby being ineffective or less effective on normal cells (Tan and Swain 2008).

The short-term effects of cytotoxic agents are greater in TNBBC than in any other breast cancer subtype (Carey et al. 2007). Patients with TNBBC have increased pathologic complete response (pCR) rates compared to non-TNBC patients, especially to taxanes and anthracycline

agents (Carey et al. 2007; Hugh et al. 2009). Wang et al. (2009) found a pCR of 38% in TNBBCs, compared to 14% in non-TNBBCs when treated with taxane in combination with anthracycline agents. Similar results were found by Liedtke et al. (2008). In spite of the better response to chemotherapy, the prognosis of TNBBC is still worse than that of other breast cancer subtypes, due to a higher likelihood of relapse in patients with residual disease (Rouzier et al. 2005; Dent et al. 2007; Carey et al. 2007).

Another group of cytotoxic agents showing good results in TNBBC are the platinum-containing agents, such as cisplatin and carboplatin (Tan and Swain 2008). To date, only few studies on the effect of these platinum-containing agents in TNBBC have been completed. One study by Sirohi et al. (2008) reported a clinical response rate of 88% in TNBBC after neo-adjuvant treatment with platinum-containing cytotoxic agents, compared to 55% clinical complete response rate in other breast tumours. However, the overall five-year survival was still worse for TNBBC compared to tumours of other subtypes.

Targeted therapies are currently being developed or evaluated for TNBBC, including inhibition of Poly [ADP-ribose] polymerase 1 (PARP1) and EGFR, the latter also known as HER1. However, none of these therapies have yet reached approval level by the US. Food and Drug Administration (FDA) (Tan and Swain 2008). PARP1 is an enzyme that has an important function in the repair of DNA single-strand breaks (SSB) as a part of the base excision repair pathway (Dantzer et al. 2000). In this pathway, PARP1 binds to the exposed ends of the corrupted DNA strand and recruits essential enzymes needed to repair SSBs. When PARP1 is inhibited, the base excision repair pathway fails, which leads to accumulation of SSBs. In a replicating cell entering the S-phase, replication is arrested at a SSB site, leading to a DNA double-strand break (DSB).

Inhibition of PARP1 leads to more single-strand breaks in all cells, so why is it a targeted therapy? In healthy cells, DSBs lead to the activation of a repair mechanism referred to as homologous recombination. Since homologous recombination uses an intact DNA strand as a template, this mechanism is accurate and error-free. An important mediator in this pathway is BRCA1. In the absence of BRCA1, DSBs cannot be repaired by homologous recombination, and cells activate an alternative repair pathway termed non-homologous end joining (NHEJ). Intriguingly, NHEJ is highly error-prone. Thus, in BRCA1-deficient cells, the damage executed by PARP inhibitors leads to accumulation of structural DNA lesions, which results in genomic instability and finally apoptotic cell death. Since BRCA2 operates in the same pathway like BRCA1, deficiency of this protein renders the cell vulnerable to PARP inhibitors as well (D'Amours et al. 1999; Tutt and Ashworth 2002). Preclinical in vivo models investigating the effectiveness of PARP inhibitors in the triple-negative/basal-like setting have shown significant tumour regression, longer DFS and OS in mice (Rottenberg et al. 2008). When applying a dose non-cytotoxic for healthy cells in mouse models carrying a *BRCA2* mutation, similar effects were achieved (Kyle et al. 2008; Hay et al. 2009). Recently, several phase I and phase II trials of PARP inhibitors have been performed with *BRCA1* mutation carriers, showing promising anti-tumour activity and only few adverse side effects. For instance, in a phase I trial, the PARP inhibitor olaparib (AZD2281) showed selective activity against *BRCA1/2*-mutated breast cancer, whereas BRCA-unrelated tumours remained unaffected (Fong et al. 2009). Based on this finding, Tutt et al. (2010) demonstrated in a phase II trial on efficacy, safety and tolerability employing solely *BRCA1/2* mutation carriers that olaparib at a higher dose was also associated with an improved objective response rate, while toxicity in *BRCA1/2* mutation carriers was similar low to that reported for patients without BRCA mutations. In a further randomised phase II trial, another PARP inhibitor, BSI-201, showed significantly increased OS in combination with gemcitabine and carboplatin when compared to the standard regimen alone, in heavily pre-treated patients. Importantly, this trial recruited TNBC only and showed in parallel that TNBC also exhibited significantly elevated PARP1 expression levels in contrast to normal breast tissue (O'Shaughnessy et al. 2008). An important question here is that of how to select the right patient population among TNBC subtypes most likely to respond to inhibition of PARP. Addressing this question, several scenarios have recently evolved. As previously mentioned, *BRCA1/2* genotyping may be beneficial, as these tumours affected by mutation show large overlap with the TNBC phenotype. In another study, TNBC were shown to express PARP1 more frequently than other breast cancer subtypes (von Minckwitz et al. 2010). High levels of PARP1 expression also correlated with improved response to chemotherapy, so it is intriguing to see whether levels of PARP1 expression may also predict response to olaparib or BSI-201 in combination with conventional chemotherapy, a trial that is currently being initiated by the respective study group (von Minckwitz et al. 2010). Third, other disruptions of DNA damage repair may also contribute to PARP inhibitor sensitivity. For instance, gene inactivation by promoter methylation of *BRCA1* is a common lesion among sporadic breast tumours (Esteller et al. 2000). Interestingly, *BRCA1*-methylated and *BRCA1*-mutated breast cancers exhibit similar transcriptional profiles (Hedenfalk et al. 2001). A recent study revealed that the frequency of *BRCA1* methylation is elevated among TNBC, and the inhibition of PARP in *BRCA1*-methylated breast cancer cell lines is similar effective as in *BRCA1*-

mutated cell lines (Veeck et al. 2010), altogether suggesting that also *BRCA1*-methylated sporadic breast cancers might be susceptible to PARP inhibitors. In summary, further parameters may become valuable biomarkers of PARP inhibitor response among patients with TNBC. These parameters should be assessed in current and ongoing future trials as stratifying biomarkers of response among TNBC in order to identify the population with the greatest benefit of this kind of treatment. Despite these promising findings, Edwards et al. discovered resistance to PARP inhibitors developing in tumour cells as a result of a deletion in *BRCA2*, reactivating the disabled gene (Edwards et al 2008). Besides from using PARP inhibitors as (neo)adjuvant therapy, it has been suggested as a preventive strategy. In patients with an inherited *BRCA1/2* mutation, preventive use of PARP inhibitors may eliminate any cell developing a second *BRCA1/2* hit, before it advances further to cancer (Helleday et al. 2005). More research on the long-term effects of PARP inhibitor use needs to be performed before preventive use of PARP inhibitors can be considered.

As described earlier, TNBBC is more likely to express EGFR than other breast cancer subtypes (Nielsen et al. 2004; Cheang et al. 2008; Meche et al. 2009; Collins et al. 2009; Nalwoga et al. 2008). The EGF receptor stimulates cell replication similar to HER2. If targeted, the stimulating effect of EGFR could be diminished, resulting in tumour growth arrest or even tumour regression. EGFR can be targeted by two types of agents, monoclonal antibodies (mAbs) and small molecule tyrosine kinase inhibitors (TKIs). MAbs target the extracellular domain of the receptor, inhibiting its function by blocking ligand binding and receptor internalisation. Possibly, they can also trigger an immune reaction against the EGFR expressing cell. TKIs target the intracellular domain of the receptor, inhibiting its tyrosine kinase activity and rendering the receptor impotent (Harari 2004). Corkery et al. (2009) evaluated the effect of the TKI gefitinib in combination with docetaxel on TNBC cell lines and found higher effectiveness of the combined therapy scheme. However, as a monotherapy gifitinib seems to be ineffective, since phase II studies showed very little benefit from gifitinib monotherapy in hormone resistant breast tumours (Green et al. 2009; von Minckwitz et al. 2005). Unfortunately, results for another TKI, lapatinib, were as disappointing by showing very little clinical benefit, except for HER2-positive tumours (Burris et al. 2009). Other phase II studies addressing the effectiveness of the monoclonal EGFR antibody cetuximab are currently being performed. It seems that inhibition of EGFR as a monotherapy is ineffective, but it can increase the effectiveness of adjuvant chemotherapy (Oliveras-Ferraros et al. 2008). Cetuximab has already been approved for use in metastatic colon cancer. However, results in breast cancer are not yet convincing for either TKIs or mAbs (Burness et al. 2010); thus, more research is needed to study their potential benefits and improve their effectiveness.

Conclusions

Triple-negative breast tumours show high recurrence and poor survival rates. Often, TNBC and BBC are assumed to represent similar entities. In fact, TNBC and BBC share certain similarities but are clearly not identical entities of breast cancer. There is increasing evidence that points towards a BRCA1-related pathway leading to the development of a TNBBC subtype. Possibly, TNBBC develops due to aberrations in this BRCA1-related pathway, whereas mutations that are not related to this pathway may occur randomly because of the genomic instability of the tumour and may lead to NTN-BBC and NB-TNBC subtypes. TNBBC shows a good initial response to chemotherapeutic agents, especially to anthracyclines and taxanes. However, in the neo-adjuvant setting, recurrence rates after pathologic complete response are high. Targeted therapies, like PARP inhibitors and EGFR targeting agents, might represent further promising therapeutic options, but still need to be evaluated in appropriate phase III clinical trials.

Conflict of interest The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

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