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REVIEW

Systemic treatment strategies for triple-negative breast cancer

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Abstract

Triple-negative breast cancer (TNBC) is defined by the lack of immunohistochemical expression of the estrogen and progesterone receptors and human epidermal growth factor receptor 2 (EGFR2). Most TNBC has a basal-like molecular phenotype by gene expression profiling and shares clinical and pathological features with hereditary *BRCA1* related breast cancers. This review evaluates the activity of available chemotherapy and targeted agents in TNBC. A systematic review of PubMed and conference databases was carried out to identify randomised clinical trials reporting outcomes in women with TNBC treated with chemotherapy and targeted agents. Our review identified TNBC studies of chemotherapy and targeted agents with different mechanisms of action, including induction of synthetic lethality and inhibition of angiogenesis, growth and survival pathways. TNBC is sensitive to taxanes and anthracyclins. Platinum agents are effective in TNBC patients with *BRCA1* mutation, either alone or in combination with poly adenosine diphosphate polymerase 1 inhibitors. Combinations of ixabepilone and capecitabine have added to progression-free survival (PFS) without survival benefit in metastatic TNBC. Antiangiogenic agents, tyrosine kinase inhibitors and EGFR inhibitors in combination with chemotherapy produced only modest gains in PFS and had little impact on survival. TNBC subgroups respond differentially to specific targeted agents. In future, the treatment needs to be tailored for a specific patient, depending on the molecular characteristics of their malignancy. TNBC being a chemosensitive entity, combination with targeted agents have not produced substantial improvements in outcomes. Appropriate patient selection with rationale combinations of targeted agents is needed for success.

Key words: Breast cancer; Triple negative; Basal like; *BRCA1*; Poly (ADP-ribose) polymerase 1; Targeted therapy; Chemotherapy

Core tip: Breast cancer is a heterogeneous disease entity with different biological characteristics and clinical behavior. There are no treatment guidelines for triple-negative breast cancer (TNBC). TNBCs are sensitive to taxanes and anthracyclins but there are high rates of local and systemic relapses. Recently there has been great interest in platinum agents, either alone or in combination with poly adenosine diphosphate polymerase 1 inhibitors. Combinations of ixabepilone and capecitabine have shown improved response rates (RRs). Other useful drugs are antiangiogenic agents, tyrosine kinase and epidermal growth factor receptor inhibitors with variable RRs but no survival benefit. In this review, we discuss various systemic treatment strategies available for TNBC and the benefit from each of them.

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INTRODUCTION

Breast cancer is the second most common cancer in the world and the most common cancer among women. However, in the past three decades, the mortality rate has declined as a result of a range of measures, including implementation of screening, improvements in the local management of early breast cancer and most importantly, the introduction of adjuvant systemic treatment and the development of directed therapies for hormone receptor-positive and human epidermal growth factor receptor-2 (HER-2/neu)-positive tumors[1].

Breast cancer is a complex disease entity with different biological characteristics and clinical behavior. Many clinical and pathological features have been defined to predict treatment response and outcome in breast cancer. Classically these include: age, tumor size, axillary node involvement, angio-lymphatic invasion, histological grade, hormonal receptor status (estrogen and progesterone) and HER-2/neu expression. If the last three features are not expressed in breast cancer cells it is called triple-negative breast cancer (TNBC)[2]. Chemotherapy is the only systemic therapy for TNBC patients.

Management of TNBC is challenging because of a lack of targeted therapy, aggressive behavior and relatively poor prognosis. There are no specific treatment guidelines for TNBCs and they are managed with standard treatment. Treatment options are limited as most patients have been treated with adjuvant anthracyclins, taxanes and cyclophosphamide. It has been evidenced by various studies that these tumors are highly chemosensitive[3-7] and in some cases are represented by complete pathological response (pCR), but the results remains unsatisfactory[8-18]. pCR to the neoadjuvant chemotherapy (NACT) is higher in the TNBC subset of patients but the disease free survival (DFS) and OS are still lower than non-TNBC patients[3,5]. Sporadic TNBCs show heterogeneity in response to chemotherapy, with pCR rates ranging from 12% for single-agent to 27%-65% in multi-agent NACT trials[3,5,11,19]. Since the achievement of pCR with primary chemotherapy is of crucial importance in TNBC patients, a maximal effort should be made in selecting the best possible drugs, doses and administration timing. The following are the therapeutic options available in TNBC.

CYTOTOXIC AGENTS

Anthracyclins

Anthracyclins are considered to be among the most active drugs for the treatment of breast cancer. These agents that act by destabilising the DNA through intercalation also prove useful in TNBC due to a degraded DNA repair cascade. Many studies show that TNBC is sensitive to anthracyclin containing regimens[3-5]. The impact of NACT in patients with TNBC was clearly analyzed by Liedtke *et al*[3] and in a retrospective analysis they reported a pCR rate of 22% in TNBCs compared to 11% in non-TNBCs with paclitaxel/5-FU, doxorubicin, cyclophosphamide/5-Fluorouracil, epirubicin, cyclophosphamide (FEC) (Table 1). The 3-year DFS was similar in both the groups (pCR 94% *vs* 98%, $P = 0.24$), while those who failed to achieve pCR had worse 3-year DFS compared to non-TNBCs (68% *vs* 88%, $P = 0.0001$). This was because the rate of early relapse in patients with residual tumor was dramatically higher in TN patients compared with the others.

Table 1 Pathological complete response to triple-negative breast cancer in triple-negative breast cancer and non-triple-negative breast cancer patients

Ref.	Yr	No.	Therapy	PCR (%)	
				TNBC	Non-TNBC
Liedtke *et al*[3]	2008	255	FAC → P	22	11
Chappuis *et al*[4]	2002	9	FEC 3 wk × 3-4	44	4
Skrypnikova *et al*[10]	2011	15	ACC	29.4	NR
Rouzier *et al*[11]	2005	82	P → FAC	45	6

FAC: 5-Fluorouracil, doxorubicin, cyclophosphamide; ACC: Doxorubicin, cyclophosphamide, capecitabine; P: Paclitaxel; PCR: Pathological complete response; TNBC: Triple-negative breast cancer; FEC: 5-Fluorouracil, epirubicin, cyclophosphamide.

In a study by Chappuis *et al*[4] of TNBC patients treated with FEC regimen, pCR was 44%. Carey *et al*[5] showed that the clinical response to doxorubicin and cyclophosphamide was markedly higher among patients with TNBCs than non-TNBCs. pCR to NACT was higher in patients with TNBCs but still these patients had a worse DFS and OS compared to non-TNBCs. An intergroup study (C9741) found differences in favor of dose density with adriamycin and paclitaxel in patients with negative ERs, but not in ER-positive patients (32% *vs* 19%). This study highlights the importance of chemotherapy in hormone-independent tumors[6]. Review of TNBC subgroups in the CALGB 9344 study in node positive patients where they compared the addition of paclitaxel to different anthracyclin doses showed significant benefits for this combination. Although the benefits were independent of HER2 status, ER negative patients derived the greatest benefit in both DFS and OS[7]. In a large cohort of patients with TNBC treated with anthracyclins and taxanes, Hernandez-Aya *et al*[9] concluded that, independently of the size of the tumor, once there is evidence of lymph node involvement, the prognosis may not be affected by the number of positive lymph nodes.

Recently, Skrypnikova *et al*[10] in a prospective pilot trial evaluated the efficacy of a metronomic schedule of doxorubicin, cyclophosphamide and capecitabine in locally advanced and metastatic TNBC. The overall response rate (RR) was 58% with 24% of CR and 34% of PR. Five patients (29.4%) achieved a pCR. In MBC patients, the median progression-free survival (PFS) was 8.3 mo. The most common grade 3 toxicities were hand-foot syndrome (HFS) (28.8%) and mucositis (17.7%), which resulted in discontinuation of doxorubicin in 7 patients. There was 26.4% of grade 3-4 neutropenia. Although the RR was good, this combination is quite toxic.

Table 2 Chemotherapy regimen with their outcomes in triple-negative breast cancer

Ref.	Yr	No.	Therapy	Outcome
Martin *et al*[12]	2010	171	FEC FEC + P	7 yr DFS 56% *vs* 74%
Byrski *et al*[23]	2009	25	Cisplatin + P + GSF	5 yr DFS-76% DDFS-84%
Koshy *et al*[32]	2010	17	Cisplatin + gemcitabine	PFS-5.3 mo TNBC *vs* 1.7 mo non-TNBC
Maisano *et al*[31]	2011	31	Carboplatin + gemcitabine	ORR-32% PFS-5.5 mo

Anthracyclin and taxane pretreated TNBC patients. GSF: Granulocyte stimulating factor; ORR: Overall response rate; PFS: Progression free survival; DFS: Disease free survival; DDFS: Distant disease free survival; TNBC: Triple-negative breast cancer; P: Paclitaxel; FEC: 5-Fluorouracil, epirubicin, cyclophosphamide.

Taxanes

Taxanes produce benefits in TNBC by targeting genomic instability. Many studies reveal the benefits produced by paclitaxel when added to other chemotherapeutic agents. In the neoadjuvant setting, Rouzier *et al*[11] showed that TN and Her2-positive subtypes of breast cancer are more sensitive to paclitaxel and doxorubicin chemotherapy than the luminal and normal-like cancers. pCR was seen in 45% patients with basal like breast cancer (BBC) compared to 6% in luminal subtypes. In a retrospective analysis by Hayes *et al*[8] where paclitaxel was added to cyclophosphamide and doxorubicin in node positive patients, they observed a 5 years DFS and OS of 27% and 32% respectively. The results were similar in TNBC and HER-2/neu positive patients.

In an adjuvant setting, two meta-analyses have shown benefit with taxanes[12,13]. Many studies have demonstrated that taxanes are more effective in receptor-negative patients. Jones *et al*[14] found that docetaxel and cyclophosphamide were equally effective in TNBC and non-TNBC patients. In a study by Jacquemier *et al*[15], there was greater benefit with the addition of docetaxel to the conventional 6 cycles of FEC in BBC patients. A further study (Table 2) showed maximum benefit in TNBC patients when 4 cycles of FEC were followed by weekly paclitaxel for 8 wk compared to just 6 cycles of FEC[16]. Loesch *et al*[17] with the same kind of combination, paclitaxel 3 times weekly *vs* weekly after 4 courses of adriamycin-paclitaxel every 3 wk, showed statistically significant results in 378 TNBC patients treated with weekly paclitaxel. As far as a schedule is concerned, weekly paclitaxel is much more effective than paclitaxel every 3 wk and at least as effective as docetaxel every 3 wk[18]. On the whole, shortening the administration interval from 3 to 2 wk could substantially improve efficacy, at least in TN patients. The role of anthracyclins alone in TNBC is debatable; however, a definite benefit is seen when used in combination with taxanes.

Platinum agents

It has been postulated that TNBC has phenotypic and molecular similarity to *BRCA1* related cancers that would confer sensitivity to cytotoxic agents like cisplatin. The platinum agents act by producing intra and inter strand cross links of double stranded DNA, prevent the replication fork formation and produce double strand breaks and replication lesions, and finally due to *BRCA1* mutation, the DNA repair cascade is non functional and produces cell death[19]. In the last few years, there has been a renewed interest about the role of platinum compounds in the treatment of breast cancer patients. Clinical studies have also suggested that TNBC are more sensitive to DNA damaging agents like cisplatin. In a phase-Ⅱ study, Garber *et al*[20] have shown a pCR of 21% with neoadjuvant cisplatin in patients with TNBC. Among 28 patients, two were *BRCA1* carriers, both (100%) of whom achieved pCR; 4 (15%) of the 26 women with sporadic TNBC also achieved pCR to cisplatin. Overall, 50% of the patients had a good response to cisplatin. In a similar study by Silver *et al*[21] with 4 cycles of single agent cisplatin, a pCR rate of 22% was seen (Table 3). Two patients with *BRCA1* mutation had pCR. They also found a significant association of tumor p53 protein-truncating mutations with cisplatin response. The largest series of *BRCA1* mutation was reported by Byrski *et al*[22]; out of 6903 patients, 102 patients had *BRCA1* mutation. Out of this, 12 patients were treated with neoadjuvant cisplatin and 10 (83%) had pCR. Anthracyclins and taxane based regimens could only produce a pCR ranging from 7% to 22%. In another study which explored role of platins in TNBC with *BRCA1* mutation, out of 25 patients, 72% had a pCR. Projected 5 year DFS and DDFS were 76% and 84% respectively[23]. Ryan and co-investigators found that when VEGF-A inhibitor bevacizumab was added along with cisplatin, a pCR rate of 16% was observed[24]. The results with a single agent or in combination with

Table 3 Response to neoadjuvant platinum based chemotherapy trials in triple-negative breast cancer

Ref.	Yr	No.	Regimen	PCR
Garber *et al*[20]	2006	28	Cisplatin	21%
Silver *et al*[21]	2010	28	Cisplatin 3 wk × 4	22%
Byrski *et al*[22]		12	Cisplatin	83%
[2]Byrski *et al*[23]	2009	25	Cisplatin + paclitaxel + GSF	72%
Ryan *et al*[24]	2009	51	Cisplatin + bevacizumab 3 wk × 4	72%
Frasci *et al*[25]	2009	74	Cisplatin + epirubicin + paclitaxel wk × 8	65%
Sirohi *et al*[26]	2008	62	Platinum[1] + epirubicin + 5-FU (infusion)	88% (cCR)
Sikov *et al*[27]	2007	10	Carboplatin 3 wk × 4 + paclitaxel wk × 16	50%
Leone *et al*[28]	2009	125	Platinum[1] + docetaxel 3 wk × 4	29%
			Platinum + docetaxel → AC 3 wk × 4	40%

[1]Cisplatin or carboplatin; [2]In *BRCA1* mutation carriers. AC: Doxorubicin + cyclophosphamide; 5-FU: 5-Fluorouracil; PCR: Pathological complete response; cCR: Clinical complete response; GSF: Granulocyte stimulating factor.

bevacizumab are somewhat disappointing as the proportions of CRs are significantly less (16%-22%) than that achieved with multiagent NACT (30%-65% in other studies).

Platin and taxane-based primary chemotherapy has also proven to be highly effective in patients with locally advanced breast cancer (LABC). In a study by Frasci *et al*[25] where neoadjuvant cisplatin was used with paclitaxel and epirubicin in a weekly schedule for 8 cycles in LABC patients, a pCR of 65% was achieved. After surgery, patients were treated with 4 or 8 cycles of CMF based on whether lymph nodes were positive at the time of surgery. Patients with pCR had a 5-year DFS of 90% compared to 56% with residual disease. Severe neutropenia and anemia occurred in 23 (31%) and 8 (10.8%) patients, respectively. Thus, lack of achievement of pCR in TNBC is a poor prognostic factor.

Sirohi *et al*[26] found that when platins are used in combination with epirubicin and 5-FU, a very high complete clinical response of 88% was achieved. This may be contributed to by epirubicin and 5-FU which was given as a 24 h infusion for 18 wk. Other investigators[27,28] have observed a pCR from 29% to 50% with platins in combination with taxanes (Table 3). The results are encouraging and merit further validation and testing. At present, platinum agents in the neoadjuvant setting cannot be recommended over established regimens outside of a clinical trial. So, platins should always be used in combination with taxanes or anthracyclins to increase response and survival rates. However, patients with *BRCA1* mutation tend to have maximum benefit in the neoadjuvant setting.

In the metastatic setting, cisplatin or carboplatin have shown an ORR of 20%-40%. Cisplatin is very active in first line chemotherapy in MBC with a RR of 50%, whereas carboplatin is moderately active with an ORR of 30%. In a study by Fountzilas *et al*[29], carboplatin in combination with paclitaxel demonstrated an ORR of 41% in MBC. PFS was better in the paclitaxel and carboplatin arm compared to paclitaxel and epirubicin. However, there was no difference in ORR and OS between the two arms. Gemcitabine (GC) and platinum agents in combination have synergistic antitumor activity that results in inter strand DNA crosslinks and double strand DNA breaks, both of which are preferentially repaired by homologous recombination. Both agents have demonstrated activity in MBC[30], with RR ranging from 26% to 50%. Maisano *et al*[31], in a phase-Ⅱ study with combination of carboplatin and GC in pretreated 31 metastatic TNBC patients, reported a RR of 32%. Median PFS was 5.5 months and median OS was of 11 mo. Many patients required dose reductions. Similarly, in a study by Koshy *et al*[32] in MBC patients, TNBC had a better PFS (5.3 *vs* 1.7 mo) compared to non-TNBC when treated with a cisplatin and GC combination (Table 2).

Lastly, in a retrospective study Staudacher *et al*[33] reported that median OS and median PFS were improved in patients responding to platinum based chemotherapy: 27 *vs* 8 mo ($P < 0.001$) and 10 *vs* 4 mo ($P < 0.001$), respectively. Therefore, combination of platins with taxanes or GC or vinorelbine are good alternatives for patients in whom anthracyclins may pose as toxic or who are already exposed to these in the adjuvant setting. So, once again platins have generated interest among investigators for its role in TNBC. The heterogeneous outcome with platins may be related to the heterogeneity of TNBC. Cisplatin appears to be more effective than carboplatin.

Newer chemotherapeutic agents, antitubulin agents

Ixabepilone is a potent tubulin polymerizer that has recently been added to the armamentarium of drugs available for the treatment of breast cancer. Similarly to taxanes, ixabepilone stabilizes microtubules and causes cell cycle arrest and apoptosis. It is active in taxane refractory and LABC as well as in TNBC. The clinical activity and toxicity profile of ixabepilone are similar to the taxanes, with neuropathy and myelosuppression as dose-limiting toxicities[34,35]. It has the advantage of bypassing the resistance mechanisms associated with drug efflux pumps and specific paclitaxel resistance associated with β-tubulin. In the neoadjuvant setting, a pCR rate of 26% in breast tumor and 19% when there was axilla involvement was seen in 42 patients with TNBC. A low expression of ER gene was identified as a predictor of response to ixabepilone[34].

In patients with anthracyclin and taxane resistant metastatic TNBC, a combination of ixabepilone and capecitabine has an improved RR and PFS compared to capecitabine alone (RR 27% *vs* 9%; PFS 4.1 *vs* 2.1 mo)[35]. Subsequently, in the pooled results of the 046 study (taxane resistant) and the 048 study (population pretreated with anthracyclins and taxanes), benefits were found for the ixabepilone-capecitabine combination in terms of objective responses (31% *vs* 15%) and PFS (4.2 *vs* 1.7 mo), but not for OS (10.3 *vs* 9.0 mo)[36]. These outcomes are comparable to cisplatin combination regimens. So, the ixabepilone and capecitabine combination can be used in patients who do not tolerate cisplatin combinations or when renal function is compromised. The magnitude of benefit also appears comparable to other combinations, such as GC plus paclitaxel or capecitabine plus docetaxel. Another novel mitotic inhibitor currently being studied for the treatment of breast cancer is eribulin. Its activity in TNBC is yet to be seen.

TARGETED THERAPY

Currently, a lot of research is going on to further characterize TNBC with different molecular markers and find targets for therapy in order to improve its outcome.

PARP inhibitors

Poly (adenosine diphosphate ribose) polymerase also plays a vital role in DNA repair like *BRCA*. Unlike *BRCA,* it recognises single strand breaks and repairs by the base excision repair pathway. PARP inhibitors are effective in TNBC because damage to one strand of DNA cannot be repaired by homologous recombination due to *BRCA* mutation and PARP inhibition in synergism creating a state of "synthetic lethality". The inhibition of

Table 4 Clinical outcomes with targeted therapy in metastatic triple-negative breast cancer

Ref.	Line of treatment	Regimen	No.	ORR (%)	CBR (%)	PFS (mo)	OS (mo)
O'Shaughnessy *et al*[40]	First line	Gemcitabine +	61	52	56	5.9	12
		Carboplatin ±	62	32	34	3.6	7.7
		Inipari[2]					
Isakoff *et al*[42]	First line	Veliparib[2] + TMZO	41	37.5	62.5	5.5	NR
Carey *et al*[44]	First line	Cetuxim[1,2] ±	71	18	31	2[2]	12
		Carboplatin[1]	54	6	10		
O'Shaughnessy *et al*[45]	First or second line	Irinotecan +	52	49	NR	5.1	15.5
		Carboplatin ±					
		Cetuxim[1,2]	51	30		4.7	12.3
Finn *et al*[49]	First line	Dasatini[2]	44	4.6	9.2	8.3 wk	NR
Baselga *et al*[46]	First or second line	Cisplatin ±	115	20	NR	3.7[3]	12.9
		Cetuxim[1,2]	58	10		1.5	9.4
Gray *et al*[50]	First line	Paclitaxel ±	122	48	NR	11.8[3]	NR
(E2100)		Bevacizum[1,2]	111	22		5.9	
Miles *et al*[51]	First line	Docetaxel ±	58	64	NR	10[3]	NR
(AVADO)		Bevacizum[1,2]	53	46		8	
Robert *et al*[52]	First line	Tax/Anthr[1]	96	NR	NR	6.5	NR
(RiBBON-1)		± Bevacizum[1,2]	46			6.2	
		Cap ±	87	NR	NR	6.1[3]	NR
		Bevacizum[1,2]	50			4.2	
Brufsky *et al*[53]	Second line	Cap, tax, gem/vinorel, ±	112	41[3]	NR	6.0[3]	17.9
(RiBBON-2)		Bevacizum[1,2]	47	18		2.7	12.6

[1]Cross over to cetuximab + carboplatin arm after progressive disease; [2]For entire cohort; [3]Significant. TMZO: Temozolamide; ORR: Overall response rate; CBR: Clinical benefit rate; PFS: Progression free survival; NR: Not reported; Tax: Taxanes; Cap: Capecitabine; Gem: gemcitabine.

poly (ADP-ribose) polymerase 1 (PARP1) potentiates the effects of ionizing radiation, DNA methylating agents, topoisomerase I inhibitors and platinum compounds[19]. Several *PARP1* inhibitors are at different stages of clinical development. In a phase- I study of olaparib in patients with ABC, 9 (15%) patients had an objective response. Of the 3 patients with *BRCA2* mutation, CR occurred in one and another one had SD for 7 mo[37]. In a phase-Ⅱ study by Tutt *et al*[38] in 54 patients with known *BRCA* mutations in ABC, 27 received olaparib 400 mg twice a day, of which 11 (41%) experienced a response with a median PFS of 5.7 mo. A second cohort of 27 women received 100 mg of per day and 6 patients (22%) experienced a response with a median PFS of 3.8 mo. The majority of patients in the 400 mg dose had *BRCA1* mutation. This agent was fairly well tolerated, with nausea and fatigue being the most common adverse events. A recent phase- I study by Dent *et al*[39] demonstrated that it was not feasible to administer the 200 mg daily dose of olaparib in combination with weekly paclitaxel due to significant myelosuppression, in spite of prophylaxis with growth factor support.

In a phase-Ⅱ randomised study, O'Shaughnessy *et al*[40] found that the addition of iniparib to carboplatin and GC in metastatic TNBC resulted in significant improvements in RR, PFS (Table 4) and OS from 7.7 to 12.3 mo. The addition of iniparib was well tolerated. However, a randomised phase-Ⅲ study by the same investigators failed to prove significant benefit of iniparib in combination with GC in metastatic TNBC in terms of PFS (4.1 *vs* 5.1 mo) or OS (11.1 *vs* 11.8 mo); although, the addition of iniparib did not significantly add to the toxicity profile of GC alone[41].

Another drug, veliparib, is a novel oral inhibitor of PARP1 and PARP2. It has shown a synergistic effect with temozolamide in TNBC[42]. In *BRCA1* and *BRCA2* mutation carriers, ORR was 37.5% and CBR was 62.5% with a PFS of 5.5 mo. Since both the drugs are given orally, they can be good options for patients in whom there is difficulty in accessing a venous line from the above subgroup.

PARP inhibitors have shown clinical activity in *BRCA* mutation carrier breast cancer and TNBC. These drugs are also being evaluated in the neoadjuvant setting but experience is limited and patient selection, combination with other chemotherapy drugs, route of administration, duration of therapy and toxicity of combination therapy are factors that need to be addressed. However, their role in unselected TNBC patients is uncertain and future trials may address these issues.

Epidermal growth factor receptor inhibitors

Epidermal growth factor receptor (EGFR) is over expressed in TNBC and so it is also one of the targets in its treatment. Cetuximab, a chimeric monoclonal antibody, binds specifically to the extracellular domain of the EGFR and inhibits its activation[43]. In a phase-Ⅱ randomised study by Carey *et al*[44] in metastatic TNBC, patients were treated with cetuximab alone or in combination with carboplatin. Patients in the combination arm had a high RR and CBR (Table 4). In patients with cetuximab monotherapy, carboplatin was added at the time of disease progression. However, patients in both arms had a rapid progression, with a median PFS of only 2 mo. In another randomised phase-Ⅱ study, pre-treated patients with MBC (78 patients had TNBC) were randomised to receive carboplatin and irinotecan with or without ce-

tuximab[45]. TNBC patients in the cetuximab arm had a higher RR than the control arm. However, there was no significant improvement in PFS. Patients in the cetuximab arm had more toxicity in the form of neutropenia, thrombocytopenia and diarrhea. The above trials have failed to achieve the expectation of EGFR being a target for treatment in TNBC. In another study by Baselga *et al*[46] in metastatic TNBC with cetuximab alone or in combination with cisplatin, ORR and PFS was better in the combination arm compared to cetuximab alone (Table 4). Several phase Ⅰ-Ⅱ studies with cetuximab in combination with cytotoxic agents or with other targeted therapies, such as trastuzumab, are currently ongoing in metastatic TNBC.

Tyrosine kinase inhibitors

Tyrosine kinase (TK) is also over-expressed in breast cancer and is associated with metastatic disease progression. There are many agents that target the phosphorylation of the receptor by acting at TK, such as imatinib, erlotinib, gefitinib and lapatinib, used for the treatment of many solid tumors. Lapatinib is more effective in HER-2/neu positive breast cancer patients[47]. Cristofanilli *et al*[48] presented data from a small open-label phase-Ⅱ study of 23 patients with newly diagnosed inflammatory breast cancer treated with neoadjuvant lapatinib 1500 mg once daily and paclitaxel 80 mg/m^2 weekly for 12 wk. RR was 95% (20/21) in HER-2-positive and 100% (2/2) in HER-1 positive/HER-2 negative patients. Dasatinib is an oral inhibitor of multiple TKs, including the Src and Abl family, c-kit and platelet derived growth factor receptor (PDGFR)-β. Finn *et al*[49] in a phase Ⅱ trial showed a CBR of 9% in metastatic TNBC, but discontinuation of therapy and dose reductions weakened the results (Table 4). Presently, several studies are evaluating dasatinib as monotherapy or in combination regimens in this setting.

Antiangiogenic drugs

VEGF expression is higher in TNBC than non-TNBC. Targeted therapy against angiogenesis can cause tumor suppression. Bevacizumab is a recombinant humanised monoclonal antibody targeted against VEGF.

The efficacy of first-line bevacizumab-containing therapy for MBC has been proven in three randomized trials[50-52]. The E2100 trial showed that adding bevacizumab to paclitaxel as first-line treatment in TNBC patients doubled RR (48% *vs* 22%) and PFS (11.8 *vs* 5.2 mo)[50]. In the AVADO trial where docetaxel was paired with two different doses of bevacizumab (7.5 and 15 mg/kg) given every 3 wk in 167 patients with TNBC (22%), the addition of bevacizumab at 15 mg/kg led to an improvement in PFS from 6.0 to 8.1 mo[51]. RIBBON-1 offered investigators the choice of capecitabine, once every 3 wk taxane (docetaxel or nab-paclitaxel), or anthracyclin-cyclophosphamide combinations, each given with or without bevacizumab[52]. A subset analysis of patients with TNBC demonstrated an improvement in PFS when bevacizumab was used both with capecitabine (6.1 *vs* 4.2 mo) and taxane/anthracyclin cohort (8.2-14.5 mo). In all three trials, there was statistically significant improvement in PFS and RR with the addition of bevacizumab to chemotherapy but no OS benefit (Table 4). There was also a greater risk of hypertension with any bevacizumab regimen and adverse effects such as headache and nasal congestion, although rarely scored as grade 3 or 4, were also more frequent with bevacizumab. When bevacizumab is paired with taxanes taken once every 3 wk, there is a greater chance of neutropenia. Altogether, between 34% and 57% of patients receiving bevacizumab-based treatment in RIBBON-1 experienced toxicity ⩾ grade 3, suggesting that there may be limitations for adding extra therapy to these combinations. For instance, attempts to add sunitinib, the multitargeted TK inhibitor, to chemotherapy with bevacizumab have proven unsuccessful as a result of extensive toxicity in patients with breast cancer. In further analysis of RIBBON-2 for the role of bevacizumab as second line therapy in metastatic TNBC, there was significant RR and PFS benefit but again no OS advantage[53]. Its cost is also a limiting factor and its toxicity further adds to the overall cost. Currently, its accelerated approval in breast cancer has been withdrawn due to the only modest risk-benefit ratio.

In a recent study by Gerber *et al*[54] where neoadjuvant bevacizumab and anthracyclin-taxane-based chemotherapy was given in 686 TNBC patients, the effect of bevacizumab on pCR was more in patients with TNBC (40.1% *vs* 32.3%). The long term results of this trial will show if this pCR benefit translates to DFS and OS.

Other agents that target VEGF

Sunitinib is a TK inhibitor and inactivates VEGF and PDGFR. Two phase-Ⅲ trials have shown that combining sunitinib with docetaxel or capecitabine does not offer any benefit in prolonging PFS compared to the cytotoxic regimen alone in patients with ABC when used as a first line therapy or in pre-treated patients[55,56]. Sunitinib is currently being evaluated in addition to carboplatin and paclitaxel as adjuvant treatment for TNBC. It should always be used in combination as monotherapy is not recommended.

In the clinical trials so far, sorafenib has not shown any absolute benefit when used as the only therapeutic strategy in breast cancer[57,58]. Median PFS was extended by 2 mo in patients treated with the combination of sorafenib-capecitabine in comparison with the combination sorafenib-placebo, but at the cost of high toxicity (grade Ⅲ HFS 45% *vs* 13%)[57]. The second trial evaluated sorafenib in combination with paclitaxel or placebo as first-line therapy in patients with locally recurrent or MBC. Forty percent of patients had TN disease. The hazard ratio for PFS was 0.78 (P = 0.08), a trend favoring the sorafenib-paclitaxel group[58]. The incidence of grade Ⅲ HFS was 30% *vs* 3% in the placebo group. Such a high incidence of grade Ⅲ HFS is unacceptable and therefore careful monitoring of patients for HFS and timely dose-reduction should be done. The other agents like vandetanib and montesanib are still in the trial stages.

Currently, a lot of research is going on in TNBC. Recently, Melhem-Bertrandt *et al*[59] investigated 1413 patients treated with NACT who used β-blockers (BB), comparing those without BB exposure for pCR, DFS and OS. In 377 TNBC patients, there were significant effects for BB use on both DFS ($P = 0.03$) and OS ($P = 0.05$). Many agents and treatment approaches are under investigation for the treatment of TNBC. Many targets such as αVβ6, cyclin E, c-kit, E-cadherin, O^6MGMT, FOXp3 and mitogen-activated protein kinase pathway need further exploration to dissect TNBC and may possibly identify new targets for therapy.

Future phase-Ⅲ breast cancer treatment trials should endeavour to collect prospective data on relevant medication exposures, weight and weight gain, comorbid conditions, and behaviors that have the potential to influence the microenvironment of the tumor as these may be potent mediators of prognosis and survival and may or may not be effectively accounted for in randomization. Key areas of research should include appropriate patient sub-classification for new and existing treatment options in their rationale combination.

CONCLUSION

TNBC is a heterogeneous disease entity. There are no specific treatment guidelines for TNBC and it is managed with standard treatment. Targeted agents have not produced substantial improvements in outcomes. The result of targeted therapy depends on the existence and level of expression of the target protein. The treatment of TNBC will continue to evolve as we learn more about the heterogeneity of this disease and this will underscore the need for treatments to be tailored for a specific patient, depending on the molecular characteristics of their malignancy. The tumor microenvironment may be a critical target for future cancer treatment and prevention of recurrence.

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