



SYSTEMIC TREATMENT OF TRIPLE NEGATIVE BREAST CANCER

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ABSTRACT

Triple negative breast cancer (TNBC) is a complex and aggressive subtype of breast cancer which lacks estrogen receptors, progesterone receptors and HER2 amplification, thereby making it difficult to target therapeutically, in addition, TNBC has the highest rates of metastatic disease and the poorest overall survival of all breast cancer subtypes. Optimal chemotherapy regimens have yet to be established; however, there have been advances in the systemic treatment of triple-negative breast cancer in the neoadjuvant, adjuvant, and metastatic settings. In this review, we discuss evidence for the potential benefit of neoadjuvant platinum-based chemotherapy, adjuvant combination chemotherapy with weekly paclitaxel, and BRCA mutation-directed therapy in the metastatic setting.

Keywords: Triple negative breast cancer, Neoadjuvant, Adjuvant Setting

INTRODUCTION

Breast cancer (BCa) is the commonest female cancer worldwide, with 1.7 million new cases and over 520,000 deaths recorded in 2012 [1]. Therapeutic approaches for breast cancer have changed over the past few decades, and the use of systemic therapy for early and advanced disease tailored to the individual patient holds the promise of delivering treatment to those in need and who could benefit the most. Triple negative breast cancer (TNBC) is a subtype of BCa defined classically by its lack of estrogen receptor, progesterone receptor and HER2 overexpression, thereby making it difficult to target. Triple-negative breast cancer (TNBC) accounts for approximately 10%–15% of diagnosed breast cancers [2]. Compared with the hormone receptor-positive breast cancers, TNBC has a worse prognosis, with an aggressive natural history and it is more commonly seen in younger and obese women, the average age of onset being 53 years. The prevalence of TNBC is higher in premenopausal African American women [3-7]. Approximately 70% of TNBCs fall into the basal-like subtype, and most basal-like cancers are triple-negative; however, those characteristics are not mutually exclusive [8].

In a recent genomic analysis of TNBC, four subtypes were described: luminal androgen receptor, mesenchymal, basal-like immunosuppressed, and basal-like immunoactivated [9]. Of those subtypes, basal-like immunoactivated is associated with the best prognosis [9], which is in keeping with prior research showing that prognosis is better for TNBC tumors with lymphocytic infiltration [10]. The *BRCA*-mutated cancers tend to be triple-negative and generally fall into the basal subtype [11]. Tumors that do not have germline mutations in *BRCA1/2*, but that display the characteristics of *BRCA* pathway deficiency are described as having “*BRCAness*” [12]. Those tumors are proposed to behave potentially more similarly to *BRCA*-mutated cancers in terms of natural history and response to systemic therapy. Molecular characterization of TNBC is an area of active research, but the application and relevance of that research to clinical practice has yet to be established. At diagnosis, TNBC tumors are more likely to be T2 or T3, to be positive for lymphovascular invasion, and to have already metastasized to lymph nodes [3]. The pattern of spread is distinct from that for hormone receptor-positive tumors: TNBC has a greater propensity for brain and lung metastases, and a lower prevalence of bone metastases [6]. In a large observational prospective study of women with stages I–III breast cancer, women with TNBC were found to have worse overall survival (OS) compared with those having hormone receptor-positive, HER2-negative tumors [hazard ratio (HR): 2.72; $p < 0.0001$] [6]. The difference was most pronounced in the first 2 years, the HR for OS being 8.30 [6].

Management option	Organization	Recommendation	Evidence
Screening and supportive care			
	ASCO	In patients with triple-negative or luminal metastatic BCa, genetic counselling and possibly <i>BRCA</i> testing should be discussed with the patient, if the results can affect the treatment decision or clinical trial entry (or both).	Expert opinion
		Risk evaluation and genetic counselling should be offered if hereditary risk factors are suspected [for example, women with a strong family history of cancer (breast, colon, endometrial) or for those 60 years of age or younger with triple-negative BCa.	II,A
	NCCN	In an individual with triple-negative BCa diagnosed at 60 years of age or younger, consider referral to cancer genetics professional.	II,A
Neoadjuvant treatment			
	ESMO	The addition of a platinum compound (carboplatin) to neoadjuvant chemotherapy allows for an increase in the pCR rate in triple-negative tumours, particular those carrying deleterious <i>BRCA</i> 1/2 or <i>RAD51</i> mutations or those occurring in patients with a family history of breast or ovarian cancer. But the effect of those compounds on long term outcomes is unknown.	I, B
	NCCN	The NCCN panel does not recommend the addition of carboplatin to neoadjuvant standard chemotherapy for patients with triple-negative BCa outside a clinical trial setting.	
Adjuvant treatment			
	ESMO	Triple-negative tumours benefit from adjuvant chemotherapy with the possible exception of low-risk “special histologic subtypes” such as secretory juvenile, apocrine, or adenoid cystic carcinomas.	I, A
	ASCO/CCO	When considering lymph node-negative tumours with T > 5 mm, these features should be considered high-risk (and thus the patient should be considered a candidate or chemotherapy): <ul style="list-style-type: none"> • Grade 3 • Triple negative • Lymphovascular invasion positive • An Oncotype DX recurrence score that is associated with an estimated relapse risk of 15% or more at 10 years • HER2 positivity 	
In patients who can tolerate it, use of an anthracycline-taxane regimen is considered the optimal strategy for adjuvant chemotherapy, particularly in patients deemed to be high risk.			
Advanced or metastatic disease			
	ESMO	For triple-negative locally advanced BCa, anthracycline-taxane chemotherapy is recommended as initial treatment.	I, A
		In triple-negative advanced BCa patients (regardless of <i>BRCA</i> status) previously treated with an anthracycline with or without a taxane in the neoadjuvant or adjuvant setting, carboplatin (compared with docetaxel) demonstrated comparable efficacy and a more favourable toxicity profile. It is therefore an important treatment option.	I, A
		In patients with <i>BRCA</i> -associated triple-negative or endocrine-resistant metastatic BCa previously treated with an anthracycline with or without a taxane (in the adjuvant or metastatic setting, or both), a platinum regimen, if not previously administered, is the preferred option when no suitable clinical trial is available.	I, A
	ASCO	Tumour type should not be used to dictate the choice of first-line treatment. That choice should be based on efficacy, prior treatment, risk of life-threatening disease, relative toxicities, performance status, Comorbid conditions and patient choice.	

*Refer to the original guidelines for their definitions of level of evidence.

Excerpts from current guidelines by major organizations for the management of triple-negative breast cancer (BCa)[13-18]

ASCO = American Society of Clinical Oncology; NCCN = U.S. National Comprehensive Cancer Network; ESMO = European Society for Medical Oncology; pCR = pathologic complete response; CCO = Cancer Care Ontario.

SYSTEMIC TREATMENT FOR TNBC

Neoadjuvant setting:

Neoadjuvant chemotherapy is a type of chemotherapy used in the treatment of localized early-stage breast cancer with a goal of breast-conserving surgery, or for patients for whom surgery is not possible temporarily [14, 19]. The use of chemotherapy in the neoadjuvant setting allows for a direct assessment of the *in vivo* response by clinical examination or imaging evaluation

Neoadjuvant chemotherapy results in higher rates of pathologic complete response (pCR) in TNBC than in hormone receptor-positive, HER2-negative disease [20]. The rate of pCR varies according to the subtype of TNBC, with the basal-like 1 subtype having the highest frequency of pCR (52%) and the basal-like 2 and luminal androgen receptor subtypes having the lowest frequency [21]. In a prospective database analysis, response to neoadjuvant therapy and long-term survival were compared in patients with TNBC and non-TNBC [22]. In that study, the rate of pCR was found to be higher in TNBC than in non-TNBC however, TNBC was associated with a decreased 3-year progression-free survival (PFS) and a decreased 3-year OS [22]. Patients who achieved a pCR showed the strongest association with positive long-term outcomes [20, 22, 23].

The optimal chemotherapy regimen for the neoadjuvant treatment of TNBC has not been established. Platinum-based regimens have been suggested to possibly be more active in TNBC [24]. In the Cancer and Leukemia Group B 40603 (Alliance) study, the rate of pCR was compared in patients receiving carboplatin or bevacizumab (or both) in addition to weekly paclitaxel, followed by dose-dense doxorubicin and cyclophosphamide [25]. Rates of pCR were significantly improved with the addition of either carboplatin or bevacizumab in breast-confined disease. In locally advanced disease involving both breast and axilla, only carboplatin resulted in improved rates of pCR.

Adjuvant Setting:

The use of adjuvant systemic therapy is responsible for much of the reduction in cause-specific mortality from breast cancer seen in almost every Western nation [26].

Adjuvant chemotherapy refers to the use of cytotoxic chemotherapy after breast cancer surgery, administered with the goal of eradicating microscopic foci of cancer cells that, if untreated, could grow and recur as metastatic cancer. In general, similar chemotherapy regimens are used as adjuvant chemotherapy regardless as to whether tumors are estrogen (ER) or progesterone (PR) receptor positive or negative. Treatment directed against the human epidermal growth factor receptor 2 (HER2) is incorporated for those patients with HER2 overexpression. As of February 2018, European Society for Medical Oncology guidelines do not recommend further adjuvant systemic treatment if residual disease is present after completion of neoadjuvant chemotherapy [14]. However, that principle has recently been challenged in the CREATE-X trial [27]. In that study, patients with HER2-negative disease who did not achieve a pCR with neoadjuvant chemotherapy were randomized to receive either standard of care, which included hormonal therapy or radiation therapy if indicated (or both), or the addition of oral capecitabine (1250 mg/m² twice daily for 14 of 21 days) for 6–8 cycles. The study included patients with both hormone receptor-positive and -negative

tumors. In contrast to the European Society for Medical Oncology guidelines, the U.S. National Comprehensive Cancer Network guidelines were updated in February 2018 and incorporate the consideration of using capecitabine in this setting

For patients who do not receive neoadjuvant chemotherapy (with the possible exception of those having rare histologic subtypes), the European Society for Medical Oncology guidelines suggest treatment with adjuvant chemotherapy [14]. Some controversy surrounds the choice of systemic chemotherapy for small tumors (≤ 0.5 cm) that are node-negative and that decision must therefore be individualized [14-16]. The optimal adjuvant regimen for TNBC has not been established, but current guidelines support the use of regimens that contain an anthracycline and a taxane, if feasible [14, 16].

The GEICAM 9906 trial compared adjuvant fluorouracil–epirubicin–cyclophosphamide (FEC) with FEC-P (FEC followed by weekly paclitaxel) in lymph node–positive breast cancer [28]. That study found a 23% reduction in the risk of relapse and a 22% reduction in the risk of death with the addition of paclitaxel. On subgroup analysis, patients with TNBC were found to experience improved DFS when treated with FEC plus weekly paclitaxel compared with FEC alone.

The role of weekly paclitaxel was also studied in the E1199 phase III trial [29]. In that study, women with stages II–III breast cancer were treated with 4 cycles of doxorubicin–cyclophosphamide followed by paclitaxel or docetaxel every 3 weeks for 4 doses or weekly for 12 doses in a 2×2 design [29]. At the 10-year follow-up, significant improvement in DFS and OS was observed for the TNBC subgroup treated with weekly paclitaxel compared with paclitaxel every 3 weeks or with docetaxel in either schedule. Those findings suggest that a benefit might accrue to the addition of weekly paclitaxel to adjuvant chemotherapy in TNBC; however, that regimen was not the primary objective of the study, and thus it is difficult to base recommendations on the subgroup analysis alone

The addition of bevacizumab to chemotherapy was studied in the adjuvant setting in the BEATRICE study [30]. No invasive DFS or OS benefit was demonstrated in that setting.

Although studies supporting the role of neoadjuvant and palliative platinum-based chemotherapy in TNBC have been published, no data in the adjuvant setting are currently available. Clinical trials investigating the role of platinum-based adjuvant chemotherapy are ongoing

Metastatic Setting:

Triple negative breast cancer usually has very high risk of distant recurrence, which happens usually within first 2 years of diagnosis [3, 6]. The biopsy of the site of distant disease should be attempted to assess for discordance in hormone receptor and HER2 status when metastases occur because retrospective analysis found that 8% of tumors that were initially estrogen receptor–negative had converted to estrogen receptor–positivity when the metastatic tumour deposit was assessed for hormone receptor status but there was no statistical discordance in HER2 status [31, 32].

The choice of initial systemic chemotherapy should be individualized based on a number of factors, including tumor burden, rate of disease progression, performance status, previous chemotherapy exposure,

and patient preferences [17, 18]. In palliative setting combination therapy are usually avoided due to increased side effects but TNBC often results in visceral involvement so more aggressive course and combination chemotherapy is more frequent choice[33]

Platinum-based chemotherapy has been suggested to potentially be more effective than non-platinum-based chemotherapy in metastatic TNBC.

Future directions:

Although multiple targeted therapy approaches are being explored in clinical trials, cytotoxic chemotherapy continues to be the mainstay of treatment for TNBC. Understanding the role of BRCA1 in DNA repair and its overlap with TNBC has led to reconsideration of platinum agents and development of PARP-1 inhibitors. Similarly, identification of EGFR overexpression as a common marker in basal-like tumors and recognition of common mutations in downstream effector pathways has led to multiple targeted approaches. As a greater understanding is obtained about the mechanisms driving this aggressive phenotype, new targeted strategies for TNBC should continue to evolve over the next 5–10 years.

SUMMARY

Triple Negative breast cancer is a heterogeneous disease that is both frustrating and confusing for all party involved such as researchers, physicians and patients due to its poor prognosis and fewer treatment options, with a lack of targeted use of therapies which are reflected with high mortality in comparison to other subtypes of breast cancer. Chemotherapy is mainstay treatment of TNBC and to date there are multiple approaches attempting to improve care of TNBC but still optimal chemotherapy regime is yet to be established. 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. As molecular research advances an understanding of the driver mutations in this disease, more targeted treatments could become available. A number of investigational therapies hold promise, including PARP inhibitors, AR pathway inhibitors, and immunotherapy.

Conflict of interest: None

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