The Egyptian Journal of Hospital Medicine (July 2023) Vol. 92, Page 5687- 5691

Updates in the Management of Triple Negative BC: Review article

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ABSTRACT

Breast cancer (BC), which is predicted to impact 1.67 million individuals a year, is the disease with the second highest mortality rate worldwide, the most common cancer in women, and ranks fifth among causes of cancer-related death. BC is the most prevalent form of cancer among Egyptian women.

Objective: This review article aimed to investigate for the updates in the management of triple negative BC (TNBC).

Methods: We searched PubMed, Google Scholar, and Science Direct for relevant articles on: Trible negative breast cancer, updates and management. Only the most recent or thorough studies were taken into account between 2005 and January 2023. The authors also evaluated the value of resources culled from other works in the same genre. Documents written in languages other than English have been ignored due to a lack of translation funds. Unpublished works, oral presentations, conference abstracts, and dissertations were generally agreed upon not to be qualified as scientific research.

Conclusion: Egypt National Cancer Institute (NCI) reported that at the end of 2001, among 10, 556 patients BC represented 18.9% of all cancer cases (35.1% in females and 2.2% in men). Approximately 60%–70% of BC patients are hormone-receptor positive and 20%–25% have amplified HER2. Clinically, ER, PR, and HER2 expression in primary BC tissue is utilised to identify biological subtypes, forecast outcomes, and to determine the optimal course of treatment, particularly for endocrine and HER2-targeted regimens. Targeted treatments targeting one of the aforementioned targets (ER, PR, or HER2) are available for the majority of patients, when patients are identified with tumours that lack ER, PR, or HER2, these therapy options are not available. These BCs are known as triple negative breast cancers. TNBC is a subtype of BC that makes up 15% of all cases. It can be recognised by the loss of ER and PR expression, as well as the absence of HER2/neu oncogene amplification or overexpression.

Keywords: BC, Triple negative, Chemotherapy, Targeted therapy.

INTRODUCTION

Breast cancer (BC), which is predicted to impact 1.67 million individuals a year, is the disease with the second highest mortality rate worldwide, the most common cancer in women, and ranks fifth among causes of cancer-related death. BC is the most prevalent form of cancer among Egyptian women [(1)].

Targeted treatments targeting one of the aforementioned targets (ER, PR, or HER2) are available for the majority of patients, when patients are identified with tumours that lack ER, PR, or HER2, these therapy options are not available. These BCs are known as triple negative breast cancers. TNBC is a subtype of BC that makes up 15% of all cases. It can be recognised by the loss of ER and PR expression, and absence of HER2/neu oncogene amplification or overexpression [(2)].

The idea of a standard approach is incorrect due to the underlying biological variability in TNBC. Without adjuvant therapy, some individuals have favourable outcomes; those who receive adjuvant cytotoxic therapy are cured and those who receive currently available systemic therapy still have poor prognoses. When systemic adjuvant treatment is not used, a fraction of TNBC patients had long-term DFS [(3)].

There were no statistically significant variations in local control between the IHC identified BC subtypes when researchers examined 5-year local regional recurrence, distant metastases free survival (DMFS), and cause specific survival (CSS). However, TNBC was linked to worse DMFS and CSS when compared to non-TNBC. Despite having a worse prognosis overall, some TNBC patients in this study were still clear of the disease after 5 years, which is noteworthy. Surgery and radiation therapy alone resulted in DMFS and CSS for 40 TNBC patients of 82% and 86%, respectively. Even though the majority of these patients had modest (T1) node negative illness, they had positive outcomes [(3)].

According to research studies, some individuals with early TNBC have extraordinarily chemotherapy-sensitive diseases and have great permanent prognoses. This is valid, particularly in the perioperative situation. Patients with TNBC experienced higher pathological complete response (pCR) rates following chemotherapy with neoadjuvant therapy than patients without TNBC [(4)].

Different chemosensibilities within and among BC subtypes in the neoadjuvant setting were identified by prospective gene expression investigations. The HER2-positive subgroup and molecularly identified BL disease were related to elevated pCR. A group of genes with differential expression that are correlated with pCR in BL disease can be utilised to predict pCR within the subgroup [(5)].

Superior OS and DFS over the long run are related to pCR. Due to chemo-resistant micro-metastatic disease, leading to an early, significant resurgence in 3 years of being first diagnosed and with a little window between the remote recurrence and the patient's death (median 13 months), the vast majority of early TNBC

Received: 19/01/2023
Accepted: 22/03/2023

patients have a dismal prognosis despite receiving systemic therapy [6].

Endocrine or anti-HER2 therapy is not a possibility for TNBC patients since they lack the targets for these treatments. Chemotherapy is the current approach in the absence of tailored therapy. The treatment of patients with chemo-sensitive diseases is not standardised. New treatments are urgently required for patients with cytotoxic resistant diseases [7].

1. Chemotherapy

Although there is agreement that TNBC has increased chemosensitivity, there is disagreement on the best cytotoxic drug to use or when to use it. Retrospective subgroup studies with low power and few participants provide the majority of the data. Although a majority of physicians now utilise a strong protocol that combines an anthracycline and a taxane, there is currently insufficient future research supporting such therapies in TNBC populations. Instead, the notion of DNA-harming platinums is gaining ground [8].

2. Anthracyclines

There is no clear advantage to anthracycline-based therapy for TNBC. The use of anthracyclines in cancers with abnormal DNA repair and overexpression of topoisomerase II, a therapeutic target for anthracyclines, would be perfect in theory. While, topoisomerase II gene amplification is extremely uncommon in TNBC, if it does occur at all, topoisomerase II protein overexpression is frequent because of strong proliferative signalling, which governs protein production [9].

In contrast to, for example, HER2, which displays a strong connection among the degree of gene expression and protein, the overexpression as a consequence of complicated multifaceted oversight of transcription, translation, and messenger RNA stability, topoisomerase II demonstrates variable relationship between gene position and proteins levels. The importance of cellular proliferation as a transcriptional regulator is demonstrated by the dependence of topoisomerase II mRNA transcription on cell-cycle phase and the statistically significant association between proliferation indicators and topoisomerase II protein levels [10].

3. Taxanes

The clinical evidence for using taxanes in TNBC is sparse and conflicting. The taxane advantage in TNBC may be explained by a link between p53 mutations and the drug's benefits. A crucial tumour suppressor gene called p53 was altered in more than 80% of cases of TNBC. Intriguing experimental and clinical results indicate taxane benefit yet a mutation in p53 and point to a p53-independent mechanism that works for taxanes, despite conflicting literature that suggests a p53 mutation is a taxane prediction indication [11].

Platinum

The majority of BC patients have not been found to benefit from platinum-based drugs. However, there haven't been many studies that explicitly examined platinums in TNBC. TNBC may be more sensitive to platinum than other BC subtypes and other cytotoxic medications due to the interaction between platinum's inability to repair BRCA-associated DNA damage and the damage that it causes to DNA via double strand cross links [12].

Retrospective analyses back up these preclinical findings. One institution presented the outcomes for the use of platinum in TNBC patients with neoadjuvant, adjuvant, and advanced illness. Patients with TNBC had neoadjuvant clinical response rates of 88% vs. 51%, with a p-value of 0.005 indicating a significant difference when compared to people without TNBC. After neoadjuvant/adjuvant therapy, the 5-year OS was 64% for non-TNBC and 85% for TNBC. PFS for patients with advanced TNBC was 6 months, which was significantly longer than the PFS of 4 months for patients without TNBC ($p = 0.05$). As a result, platinum-based chemotherapy was linked to higher pCR, but lower OS in early BC and higher PFS in late illness [13].

The sole sources of prospective data are a few small-scale trials with a focus on TNBC patients who carry the BRCA mutation. In a neoadjuvant trial, patients with TNBC with a BRCA1 mutation got four rounds of the single drug cisplatin, and nine out of ten (90%) of them achieved pCR; two patients only received two treatments. The only patient, who had a protracted nodal illness, only showed a partial response. Regardless of the inherent molecular grouping, the same trial was expanded to cover a total of 25 women with stage I-III BC and a BCRA1 mutation. They received neoadjuvant cisplatin as a single drug throughout the course of four cycles. Surprisingly, 18 patients (72%) had pCR, demonstrating the high level of success of platinum-based chemotherapy in the treatment of patients with BRCA1-associated BC. The results of a neoadjuvant trial using cisplatin as a single drug in 28 TNBC patients showed that five patients (or 22%) had a pCR [14].

4. Ixabepilone

A brand-new epothilone B counterpart called ixabepilone stabilises microtubules, binds to tubulin, and inhibits the cell cycle in cancer cells via boosting tubulin polymerization [15]. A prospectively planned subgroup analysis was published for 187 TNBC patients from the phase III capecitabine with or without ixabepilone trial, which included 752 patients overall. When ixabepilone was given to TNBC, the response rate rose from 9% to 27% and the PFS rose from 2.1 to 4.1 months (HR 0.68, 95% CI 0.50-0.93). Ixabepilone was the only medication given to 161 participants in a phase II neoadjuvant research trial (080), and pCR was discovered in 19% of those with TNBC versus 8% of those without TNBC [16].

5. Novel therapies

Modern molecular biology platforms are enabling the development of innovative targeted medicines. Targeting the single strand DNA repair enzyme PARP, angiogenesis, EGFR, and tumour necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors are among the promising treatments [17].

a. PARP

The enzyme PARP is necessary for single strand DNA base excision repair. Drugs that target PARP support BRCA-functional cells while synthetically killing homozygous BRCA-deficient ones. The best biological conditions for PARP inhibition are produced in TNBC by PARP-1 overexpression and concurrent BRCA-mediated DNA repair failure. Inhibiting PARP in conjunction with cytotoxic DNA-damaging substances may be beneficial because the PARP enzyme is also involved in the initial repair of DNA damage caused by platinum compounds [18]. In a phase I trial involving refractory cancer patients with a range of tumour types, olaparib was shown to be active and well tolerated, and its effectiveness was increased in patients with BRCA1/2 mutations. Although not all BRCA mutant carriers provided comments, all objective replies were limited to BRCA mutation carriers who had breast, ovarian, or prostate cancer. According to a phase II study, the single agent response rate for olaparib in patients with BRCA1/2 mutations with metastatic BC who were resistant was 38%. Nearly 50% of the patients had TNBC, and the response rate was likewise extremely significant [19].

b. Angiogenesis

TNBC and aberrant microvascular proliferation are related. Glomeruloid microvascular proliferation is seen upon histological inspection, which is associated with a bad prognosis. The crucial function of angiogenesis could be a useful interventional target [20].

Sunitinib, a multikinase VEGF inhibitor, exhibited an 11% single medication response rate in 64 metastatic BC patients who had previously received anthracycline and taxane treatment. The response rate in the subgroup of patients with triple negative tumours was 15% (3 responses in 20 individuals). More information is anticipated from a trial that compares a single agent sutent with the recommended course of treatment for patients with advanced TNBC who have previously received anthracyclines and taxanes [21].

c. EGFR

TNBC and EGFR overexpression are frequently linked. However, there is currently no correlation between EGFR overexpression in TNBC and appreciable clinical benefit from EGFR blocking drugs. Without a doubt, blocking EGFR in the context of overexpressed EGFR has not demonstrated the outstanding efficacy of anti-HER2 medicines in HER2 overexpressing BC [22]. Two recent trials findings were dismal. Cetuximab alone and Cetuximab + Carboplatin were tested in the TBCRC001 multicenter, phase II trial in patients with metastatic TNBC who had already received treatment. Cetuximab, a single drug, shown negligible activity in 102 patients, with an ORR of 6%. It is possible to speculate that the combination's (18%) response was mostly due to the activity of the carboplatin by itself. Additionally evaluated in metastatic illness with carboplatin and irinotecan is cetuximab. The introduction of cetuximab did not improve PFS or OS, however it did increase the RR in TNBC patients from 30% with chemotherapy alone to 49% [23].

d. Trail

Tumour survival requires systems that go beyond common cellular apoptotic processes. The soluble ligand TRAIL must bind to Death Receptor (DR) 4 or 5 in order for the extrinsic apoptotic pathway to work. Recombinant TRAIL or agonist monoclonal antibodies may clinically activate DR4 and DR5. The selective targeting of cancer cells while sparing healthy cells and the synergy that occurs when TRAIL-inducing drugs are combined with chemotherapy are appealing features of TRAIL-induced apoptosis [24].

6. Refined therapy for TNBC

To discover and hone possible therapy targets in this aggressive BC subgroup, extensive preclinical research is now being conducted. Studies with a solid scientific basis should look at how specific medications affect known subgroups with a high response potential. The right choice and timing of chemotherapy and new drugs will be more clearly defined in adequately powered prospective clinical trials in the TNBC group. The outcomes of several trials are eagerly anticipated [25].

Predictive tools

Not every TNBC patient will respond to treatment the same way. The ideal scenario would be for the discovery of pharmacological targets and/or substitute predictive biomarkers to influence the choice of therapy. A certain amount of benefit certainty prior to treatment would be provided by such a strategy. Factors affecting efficacy, in particular the pathways and pathway cross talk that are crucial for cancer survival and proliferation, will reflect the underlying biological variability [26].

TNBC is characterised by high rates of abnormal apoptosis, dysregulated angiogenesis, fluctuating immune response gene expression, defective DNA repair, BRCA mutation or malfunction, and p53 mutation. One day, these characteristics might be used to anticipate a particular therapeutic benefit. Other potential predictive approaches, in addition to TNBC, include overexpressing topoisomerase II alpha protein, a target for anthracycline drugs, to anticipate the benefits of these drugs, or examining the p53 pathway to anticipate p53-independent taxane efficacy [27].

1. DNA damage

2. High genomic instability caused by dysfunctional DNA repair in TNBC may make the cancer more susceptible to treatments that damage DNA. Tools to measure a tumor's potential for DNA repair may help in treatment selection. Even though measuring baseline DNA damage may help in choosing individuals who will benefit from DNA targeted therapy, such as anthracyclines, platinums, and PARP inhibitors, treatment-related DNA damage may suggest success. One such instrument is the comet assay, which measures DNA breakage and break frequency in reaction to a comet's appearance and brightness using single-cell gel electrophoresis. Fluorescence in situ hybridization, which identifies probes to particular DNA sequences for a more in-depth examination, may be used in the comet experiment [(28)].

Using 143 archived TNBC excision samples, a DNA repair profile model based on 4 genes was developed and assessed as a prognostic tool for TMA. The profile's high-risk group had a quicker time to recurrence and a higher risk of doing so. Using gene expression profiles from individuals with familial BRCA1 mutant BC, the "BRCAness" and sensitivity to neoadjuvant anthracycline in 12 patients with sporadic, locally progressed TNBC were assessed. The pCR response to anthracycline therapy was linked with the BRCA1 gene expression pattern. Three genes were part of a panel whose expression varied between sensitive and resistant cancers [(29)].

3. BRCA/ BRCAness

BRCA1 dysfunction/mutation may serve as both a prognostic indicator and a predictor of chemotherapy response. Anthracyclines and platinum chemotherapy may be more effective in patients with BRCA1 dysfunction, according to preclinical research and early clinical assessments. Data on the relationship between taxanes and BRCA1 status are scarce and contradictory. While it could be tempting to apply BRCA1 discoveries to TNBC, functional assays of the BRCA pathway or tests for "BRCAness" would be necessary to determine whether patients will benefit from such applications [(30)]. In a brief research, the effectiveness and safety of the single drug cisplatin were evaluated in 15 patients with metastatic BC and positive BRCA1 tests. Chemotherapy had previously been administered to eleven persons for serious illnesses. Notably, 10 of the patients had TNBC, while 5 of the 15 patients had successful ER or PR outcomes. Impressively, 72% of respondents gave their opinions, with 2 (26% PR) and 7 (46%) CR. To investigate the potential predictive usefulness of BRCA status, more study is needed [(31)].

4. Predictive gene signatures

One biomarker might not be able to accurately predict how well a treatment will work. It can be necessary to use a prediction panel or signature to take into account the variability of disease biology. Predictive gene expression profiling has produced encouraging results. Contrary to popular belief, there is no overlap between the genes linked to pCR for the BL and HER2 subtypes, according to a study assessing the response rates to neoadjuvant chemotherapy among BC subgroups. As a result, a medication's pCR prediction signature can be subtype-specific. This shows that there are a variety of underlying chemosensitivity pathways for the various molecular subtypes. A prognostic signal, on the other hand, might be regimen-specific. In the EORTC 10994/BIG 001 clinical research, for instance, novel tumour gene panels have demonstrated potential for predicting the success of FEC or docetaxel with epirubicin. Using a stromal signature, a 50-gene metagene with anthracycline ties delivers convincing outcomes for chemotherapy benefit prediction [(32)].

The variety of BC subtypes has been further underlined by the research of gene expression modules connected to underlying biological processes. The primary molecular mechanism involved in TNBC prognosis appears to be the immune and complement responses, in contrast to the prognostic significance of proliferation in hormone responsive cancers. ER-negative and triple-negative breast tumours have a good prognosis when immune-related gene signatures are present. Immune gene profiles may be used as prediction tools in new immune response-targeting drugs, potentially enhancing TNBC patients' outcomes [(33)].

DECLARATIONS

- **Consent for publication:** I attest that all authors agreed to submit the work.
- **Availability of data and material:** Available
- **Competing interests:** None
- **Funding:** No fund
- **Conflicts of interest:** no conflicts of interest.

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