Chapter

Management of the Triple Negative Locally Advanced Breast Cancer

Amir Iqbal Memon, Ikram Din Ujjan and Aisha Masroor Bhatti

Abstract

One out of eight women is suffering from the breast cancer. 2.3 million New cases is predicted by 2023 worldwide. Triple negative breast cancer (TNBC) is having 10–15% incidence. As categorized with the lack of estrogen, progesterone and human epidermal growth factor receptor 2 neu receptor expression. Though it presents with narrow management opportunities that makes it to be the poor prognostic as well as survival rate. The management of the TNBC includes: neoadjuvant treatment then surgery and the adjuvant treatment or the surgery as the first step and then the adjuvant treatment options accordingly. The discussion are still going on to set a management protocol for the triple negative breast cancers with positive outcome and the good disease free survival. Neoadjuvant or adjuvant chemotherapy decreases the estradiol levels and thus improves the survival. The immune check points and immune modulators are under the research and the trials are still going on to treat the TNBC with the improved outcomes. It has been concluded that the management of the TNBC, still wanting the guidelines as tumor-specific targeted therapies is in trials.

Keywords: triple negative breast cancer (TNBC), locally advanced breast cancer (LABC), modified radical mastectomy (MRM), chemotherapy and immunotherapy

1. Introduction

Breast cancer is the leading cancer globally [1] and when it presents as TNBC, it carries the worst prognosis [2]. As the commonly diagnosed malignancy with the second cause of mortality among women with cancer [3]. Incidence of the breast cancer has been increasing from the western word to the east. It has increased the mental burden to the patients and the families of the affected individual's younger women.

TNBC is described as the lack of the hormone receptor status. As estradiol heights among TNBC patients were considered as favorable outcome [4]. Fortunately the incidence of TNBC is only 15–20% of invasive breast cancers [5], its hostile behavior, comprising prior recurrence with high proliferation and metastasis [6, 7]. International Breast Cancer Conference delivered a novel description of breast cancer molecular subtypes that are: luminal A (ER/PR^+, $HER2^-$, $Ki67^+ < 20\%$), luminal B ($ER/PR^+ < 20\%$, $HER2^-$, $Ki67^+ \geq 20\%$); $HER2^+$ B2 (ER/PR^+, HER2 overexpression), HER2 overexpression (ER^-, PR^-, $HER2^+$) and basal-like TNBC (triple negative) [1]. TNBC is so hostile that it leads to poor survival of the diagnosed cases and makes it

shorter. As the short disease free survival with the death ratio in the initial years of identification. Half of the TNBC patients usually presents with the metastatic disease.

Though molecular phenotype, of the TNBC presents without the receptors expression, proving it most difficult to manage. To control the local disease we have surgical options like modified radical mastectomy (MRM) and lumpectomy or wide local excision (WLE) in breast conserving surgery (BCS) and for the systemic disease add neo-adjuvant or adjuvant chemotherapy. As chemotherapy to these patients can be an option to regress the tumor size and the stage and make it an operable in case of locally advanced disease stage and make the survival considerably good [8].

TNBC has narrow management opportunities that makes it vulnerable. While it is usually known that TNBC that diagnosed timely in its initial stages is responding well to the chemotherapy instead of indistinct management plan. Specifically the inoperable and locally advanced TNBC has a good outcome with the Neoadjuvant therapy.

The residual TNBC lesions ultimately prone to the relapse of the disease. The metastatic disease will get benefit from the neoadjuvant course with platinum-based therapy, combination therapy of paclitaxel per week as adjuvant course will be used [9].

TNBC patients recently receiving FDA-approved regimen of chemotherapy plus immunotherapy [10]. TNBC has the specific features that leads it towards the immunotherapy [11]. As the TNBC tumor has additional tumor-infiltrating lymphocytes (TILs), which correlate to the improved responses to immune check point inhibitors (ICIs), and the high levels of tumor-infiltrating lymphocytes in TNBC proves with better-quality prognosis in initial phase of the TNBC. TNBC also has better PD-L1 expression and making it more useful for the future targeted therapies for ICIs and anti–PD-1 therapies. TNBC has an overexpression of no synonymous mutations, that provide tumor-specific neoantigens for specific T cells to support the targeted behavior towards the tumor reinforced by ICIs [6]. The trials of the immunotherapy with or without the chemotherapy is ongoing to conclude the treatment regimen for the TNBC patients. The blend of ICIs and chemotherapeutic agents has also established the primarily control towards the TNBC. Metastatic progress is more in the favor of liver, chest and brain [12].

Metastatic TNBC has an effect by the Platinum compounds that work by DNA crosslinking and are of better efficiency towards the gBRCA1/2 transformation carriers, while combination therapy with PARP inhibition with veliparib provides the better-quality survival as well [13].

2. Risk factors and pathogenesis

Genetic mutations and the hereditary factors have been the key element for the aggressive behavior of this Cancer with the association of BARCA1 25% BARCA2 75% [5]. Germ line BRCA1 is the most frequently associated with the TNBC but still the debate is going on as there is the variation of the genetics and the ethnicity along with the caner presentation and the prognosis.

The other risk factors are:

- Reproductive history (nulliparity)
- Age
- Dense breasts

- Having cancer or certain benign breast neoplasms
- Breast cancer running in the family
- Contact to radiation
- History for the diethylstilbestrol (DES).

3. Management

TNBC presents with the restricted management options that leads it to the recurrence and metastasis with an unfortunate diagnosis. As it lack the hormone receptors status that target the disease and improves the survival. Chemotherapy looks to be the central approach towards the systemic management of TNBC with the surgery is to control the local disease.

3.1 Chemotherapy

It is the main treatment modality in the TNBC. It can be used as neo-adjuvant as well as the adjuvant setting depending upon the tumor staging.

After the local disease cure by the operative options followed by the adjuvant management by the chemotherapy, the disease free survival (DFS) will be observed. DFS is correlated with the pathological complete response (pCR). Neoadjuvant therapy have more chances to get a high pCR in patients with TNBC and reflected as substitute consequence of the outcome of the disease [12].

3.2 Taxane

Taxel act as the antitumor agent through the macrophages by initiating the apoptosis. The guidelines by national comprehensive cancer network endorse the sandwich of the regimens consists of taxane, anthracycline, cyclophosphamide, Cisplatin, & fluorouracil. Currently, Taxel/Docetaxel + Adriamycin + cyclophosphamide (TAC), Docetaxel + cyclophosphamide (TC), Adriamycin + cyclophosphamide (AC), cyclophosphamide + methotrexate + fluorouracil (CMF), cyclophosphamide + Adriamycin + fluorouracil (CAF), and cyclophosphamide + Epirubicin + fluorouracil + paclitaxel/Docetaxel (CEF-T) are among favored adjuvant therapeutic regimens designed for TNBC. Suitable chemotherapy medications and its optimization for the patients with favorable outcome [1].

3.3 Anthracycline

Anthracycline and anthracycline antibiotics are a group of chemotherapy medications derived from *Streptomyces peucetius* var. *caesius*, having more power to treat the variety of the cancers in comparison to the other regimens. Ongoing clinical educations and studies proved the ideal plans of anthracycline adjuvant to treatment TNBC with dosage of doxorubicin is 60 mg/m^2 and that of Epirubicin is 100 mg/m^2. Anthracyclines that are FEC-100 (100 mg/m^2 Epirubicin), decreases 25–30% danger of relapse as well as mortality. Data currently suggesting that subsequently chemotherapy with anthracycline for the 6 months improves the mortality rate by 38% in

patients of 50 years and below age at the time of diagnosis, whereas the mortality rate in patients with 50 to 69 years at the time of identification, reduced by 20%.

The CREATE-X experimental trial indicated that 6–8 cycles of adjuvant capecitabine (1250 mg/m^2 from days 1 to 14, every 21 days) with better-quality DFS and OS in the TNBC cohort. The significance of aiming adjuvant capecitabine among patients had residual disease was presently emphasized with outcomes of the phase 3 GEICAM/CIBOMA trial. Phase 3 trial of 876 participants diagnosed with initial stage TNBC and accomplished average adjuvant or neoadjuvant chemotherapy was planned towards evaluation the impact of capecitabine (1000 mg/m^2 from days 1 to 14, every 21 days) as an adjuvant therapy irrespective of their pCR status. Though the major transformation was not significant among 5-year DFS and OS between the treatment groups, emphasizing that still there is necessity to select a resistant groups. Outcome among CREATE-X trial currently strength the oncologist and surgeons for management of initial stage TNBC through neoadjuvant chemotherapy and comprehend the group, who ought to have capecitabine. Capecitabine must be considered, ongoing trials are assessing novel agents for the management of the TNBC with residual disease after neoadjuvant treatment [12].

Enhanced markers required to update improved-quality range and managing by the checkpoint inhibitors. Advanced prognosis is observed with checkpoint inhibitors when they are combined with chemotherapeutic agents as an initial therapy. The behavior of malignant tumor is categorizing the possible molecular targets and future researches are also valuing novel small molecule agents for the management of the TNBC with AKT inhibition and numerous others. The management model with chemotherapy agents as "one size fits all" methodology is fluctuating constructed on the behavior and have to be polished more to cover the multiple subtypes [14].

Studies showed that Anthracycline as a single drug up-to-date the pCR rates of 14 to 47%, however consecutive anthracycline and taxane combination therapies had reported pCR of 17 to 39%. Although the research studies are still in the way to express the peak rates of pCR with the chemotherapeutic regimens [12].

3.4 Surgical management

Multiple surgical options are available from the minimal invasive BCS to the MRM and the immediate reconstruction of the breast [5]. Breast and the axilla are the two different entities to treat. Axillary staging and the nodal involvement and the dissection will be done accordingly. As the presentation is usually in advanced stage and the BCS is not A primary treatment for aggressive and advance tumor, so the better option is to start the neo-adjuvant chemotherapy and assess the tumor response to the chemotherapy, again stage the disease and plan the surgery accordingly if possible then the BCS is the best option to the MRM.

Patients with stages I and II TNBC, will be benefited by BCS plus radiotherapy (BCS + RT), mastectomy only (MRM) or MRM plus radiotherapy (MRM + RT), still there is no single point surgical management has been concluded for the TNBC [15]. Disease free survival study revealed that BCS along with the simultaneous RT had considerable predictive effect than MRM and MRM + RT in the early management of the diagnosis. The axilla will be treated as a separate entity with the sentinel lymph node biopsy in case of clinically and radiological impalpable nodes was defined as removal of at least four lymph nodes and axillary node dissection was defined as removal of ≥10 nodes at least up to level-II clearance that is required for the specific staging of the disease [10].

Recent National Comprehensive Cancer Network (NCCN) Guidelines recommend breast surgery (breast conservation surgery or mastectomy) and axillary staging for all TNBC patients diagnosed with the early disease. Study presented that the BCS + RT had better predictive effect than MRM and MRM with RT in the cohort of early staged diagnosed TNBC cases in terms of overall survival. Cox proportional model revealed MRM and MRM along with the RT remained to have unfavorable outcome to the prognosis as related with BCS + RT survival *P* value is 0.006 [15].

3.5 Immunotherapy

It acts on the immune check points.

3.5.1 Immune check point monotherapy

As the outcome results to ICIs are higher in cases with TNBC, but the monotherapy effectiveness is still low and under the research control.

PD-1 inhibitor pembrolizumab, avelumab and atezolizumab established a hopeful (ORR) of 18.5% among 32 cases among PD-L1 + ve TNBC. Though, successive bigger phase II KEYNOTE-086 study (NCT02447003) establish an ORR of 5.3% among 170 participants PD-L1 unselected pretreated cancers. Remarkably, 84 treatment-naïve participants included, ORR observed 21.4%, signifying ICIs had better efficiency with 1st line metastatic malignancy. By the favor of that impression, the phase III KEYNOTE-119 trial (NCT02555657) with cases had metastatic TNBC, not revealed any progress among ORR, PFS, or OS by monotherapy pembrolizumab vs. chemotherapy (monotherapy), while participants had peak PD-L1 impression experienced the tendency for better advantage by pembrolizumab [6].

Two research studies by chemotherapy with or without atezolizumab, presently increasing. The IMpassion131 trial (NCT03125902) have to explore the significances of first line atezolizumab along with paclitaxel compared with paclitaxel only in terms of overall improvement, while IMpassion132 study describe atezolizumab as first line joined by chemotherapeutic agents may progress consequences linked through chemotherapeutic only among participants presenting with recurrence of the disease within the year of adjuvant therapy. Several enduring early-stage disease trials will additional explain the effectiveness of ICIs in TNBC cases as neoadjuvant and adjuvant therapies.

Biomarkers assume advantage to immunotherapy in TNBC are required to sort out the cases with more advantage of ICIs monotherapy, progress blended treatments that overwhelmed the resistance of ICI. Individual with two authenticated biomarkers presently occur, mismatch repair deficiency and manifestation of PD-L1 on immune cells. Nonetheless, mismatch repair deficiency ensues hardly among carcinoma breast and usually among initial stage presentation, those with diagnosed as metastatic TNBC with PD-L1 -ve presently accepted SP-142 assay.

3.5.2 Management of metastatic TNBC by immunotherapy

The II KEYNOTE-086 Cohort A, had appraised Pembrolizumab (inhibitor of PD-1) as it was single arm research, among diagnosed cases of triple negative metastatic breast carcinoma. They had assessed pembrolizumab effectiveness among 170 patients who were kept in this research trial, irrespective of expression of PD-L1. 62% patients enrolled in study had expression of PD-L1 + ve cancers (n = 105).

The response rate 4.7%, seems to be not significant, only one case achieving a complete response and 7 cases with limited response. The overall survival was 8.9 months among all the participants and 8.3 vs. 10 months in the PD-L1 + ve and -ve cohorts separately.

Cohort B of KEYNOTE-086 appraised pembrolizumab as the first line treatment of patients diagnosed by PD-L1 + ve triple negative breast carcinoma. Around 84 participants included in the study, out of that 73 (87%), experienced traditional neoadjuvant or adjuvant chemotherapeutic medications. ORR were 23.1%, three patients achieving a CR and 16 had PR. 12 participants, presently were at data limit. Median PFS 2.1 months and median OS 16.1 months.

Pembrolizumab evaluated by phase III KEYNOTE-119 (NCT02555657) trial. 622 participant diagnosed as TNBC, randomized 1:1 to have pembrolizumab compared with monotherapy chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine) as second- or third-line therapy. But the results are pending and expected to be presented at an future meeting [14].

Impassion130 (NCT02425891), phase III randomized research trial assessing nab-paclitaxel with PD-L1 inhibitor (atezolizumab) vs. nab-paclitaxel with placebo among diagnosed participants as first line management for metastatic or inoperable locally advanced triple –ve breast carcinoma. Neoadjuvant or adjuvant treatment may be permissible if more than 1 year from end of therapy. Participants with PD-L1 + ve when >1% staining is present within immune cells. Co-primary endpoints were PFS and OS in ITT and PD-L1+ participants [14].

4. Follow-up

TNBC progression has exceptional behaviors that leads it towards metastasis and prone to recurrence. As its violent behavior presents it as metastatic cancer even in its primary progress of the disease. The close evaluation is compulsory, at least the first 3-years after controlling the primary disease to control it and make it to be a better disease free survival.

5. Conclusion

The management of the TNBC is the interesting among all cases with breast carcinoma. As TNBC has higher chances of disease relapse, metastasis, and limited survival. The documentation of markers in near future will support the management guidelines in TNBC remains a clinically indolent. Immunotherapy acts in ICIs, promises the pronounced outcomes by immunotherapy agent (ATEZOLIZUMAB). As with unlimited hope and confidence that future ongoing research studies will add more understanding of the progression of the TNBC and will enhance the options for the management that leads towards the better survival.

Novel management options have offered the hope for the improved survival with better outcome by the upcoming period.

Conflict of interest

"The authors declare no conflict of interest."

Acronyms and abbreviations

LABC	Locally Advanced Breast Cancer
TNBC	Triple Negative Breast Cancer
ER	Estrogen receptor
PR	Progesterone receptor
HER2 NEU	Human epidermal growth factor receptor 2 neu
MRM	Modified radical mastectomy
RT	Radiotherapy
BL1	Basal-like 1
BL2	Basal-like 2
M	Mesenchymal
MSL	Mesenchymal stem-like
IM	Immunomodulatory
LAR	Luminal androgen receptor
BCS	Breast conserving surgery
WLE	Wide local excision
NCCN	Current National Comprehensive Cancer Network
ICIs	Immune check point inhibitors
pCR	Pathological complete response
DFS	Disease-free survival
ORR	Overall response rate
TMB	Tumor mutational burden
CR	Complete response
PR	Partial response

Author details

Amir Iqbal Memon*, Ikram Din Ujjan and Aisha Masroor Bhatti
Lumhs Jamshoro, Pakistan

*Address all correspondence to: dramiriqbalmemon@gmail.com

References

[1] Yin L, Duan J-J, Bian X-W, Yu S-c. Triple-negative breast cancer molecular subtyping and treatment progress. Breast Cancer Research. 2020;**22**(1):1-13

[2] Zagami P, Carey LA. Triple negative breast cancer: Pitfalls and progress. NPJ Breast Cancer. 2022;**8**(1):1-10

[3] Garrido-Castro AC, Lin NU, Polyak K. Insights into molecular classifications of triple-negative breast cancer: Improving patient selection for treatment heterogeneity of triple-negative breast cancer. Cancer Discovery. 2019;**9**(2):176-198

[4] Septiani RV, Soewoto W, Budhi IB. Chemotherapy effect on estradiol levels in patients with triple-negative breast cancer: A clinical prospective study from Indonesia. Open Access Macedonian Journal of Medical Sciences. 2022;**10**(B):477-481

[5] Amro A, Newman LA. Surgical management of triple-negative breast cancer. Triple-Negative Breast Cancer. 2018:55-69

[6] Keenan TE, Tolaney SM. Role of immunotherapy in triple-negative breast cancer. Journal of the National Comprehensive Cancer Network. 2020;**18**(4):479-489

[7] Gianni L, Huang C-S, Egle D, Bermejo B, Zamagni C, Thill M, et al. Abstract GS3-04: Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple negative, early high-risk and locally advanced breast cancer. NeoTRIPaPDL1 Michelangelo randomized study. Cancer Research. 2020;**80**(4_Supplement):GS3-04-GS3

[8] Sharma RK, Gogia A, Deo SVS, Sharma D, Mathur S, Sagiraju HKR. Does pathological complete remission after neoadjuvant chemotherapy translate to longer relapse-free survival in patients with triple-negative breast cancer in the Indian population. Journal of Clinical Oncology. 2021;**39**(15_suppl):e12618

[9] Lebert J, Lester R, Powell E, Seal M, McCarthy J. Advances in the systemic treatment of triple-negative breast cancer. Current Oncology. 2018;**25**(s1):142-150

[10] Obeng-Gyasi S, Asad S, Fisher JL, Rahurkar S, Stover DG. Socioeconomic and surgical disparities are associated with rapid relapse in patients with triple-negative breast cancer. Annals of Surgical Oncology. 2021;**28**(11):6500-6509

[11] Zhu Y, Zhu X, Tang C, Guan X, Zhang W. Progress and challenges of immunotherapy in triple-negative breast cancer. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2021;**1876**(2):188593

[12] Bergin AR, Loi S. Triple-negative breast cancer: Recent treatment advances. F1000Research. 2019:8

[13] Eikesdal HP, Yndestad S, Elzawahry A, Llop-Guevara A, Gilje B, Blix ES, et al. Olaparib monotherapy as primary treatment in unselected triple negative breast cancer. Annals of Oncology. 2021;**32**(2):240-249

[14] Lyons TG. Targeted therapies for triple-negative breast cancer. Current Treatment Options in Oncology. 2019;**20**(11):1-13

[15] Wang S, Sun Y, Zhao S, Wei F, Yang G. Breast conserving surgery (BCS)

with adjuvant radiation therapy showed improved prognosis compared with mastectomy for early staged triple negative breast cancer patients: Running title: BCS had better prognosis than mastectomy for early TNBC patients. Mathematical Biosciences and Engineering. 2020;**17**(1):92-105