International Islamic Medical Journal
Journal Homepage ://journal2.unusa.ac.id/index.php/IIMJ

Treatment Problems in Triple Negative Breast Cancer

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DOI: 10.33086/iimj.v4i2.3951

ARTICLE INFO

Keywords: Chemotherapy, Treatment response, Pembrolizumab, Capecitabine, Olaparib

Submitted: February 25th 2023
Reviewed: April 24th 2023
Accepted: June 15th 2023

ABSTRACT

Background: Breast cancer ranks second on the list of common diseases worldwide. It causes many deaths in the United States and Europe, second only to lung cancer. Triple-negative breast cancer (TNBC) does not express Estrogen Receptor (ER), Progesterone Receptor (PR), and Human Epithelial Receptor (HER2). It represents 24% of new cases of all breast cancer, and its incidence increases yearly. TNBC is a hormone-resistant breast cancer, so no current standard therapy exists. This article aims to explore regimen-resistant and troubleshooting treatment responses in TNBC cases. The method of writing this article is a literature review of studies using the keywords triple-negative breast cancer treatment and regimen, which are limited to only the most recent articles, 2012-2022, using search engines from PubMed, Science Direct, and Google Scholar.
Results: There is no definitive therapy for the triple-negative breast cancer subtype, in which the TNBC type has no target receptor. Chemotherapy is the SOC of TNBC for early stage treatment. For late-stage and relapsed TNBC, however, chemotherapy is no longer the first choice. Currently there is no standard chemotherapy regimen that can be given to patients who experience relapse after chemotherapy because they will have a short response and lead to metastases. Some studies have shown that chemotherapy gives a better response, but the prognosis of TNBC remains poor. TNBC has different responses to therapy. TNBC showed a good response to combination chemotherapy along with pembrolizumab, capecitabine, olaparib, and radiotherapy, compared to chemotherapy by itself. Surgical therapy, such as Breast-Conserving Surgery (BCS), does not improve better prognosis in TNBC patients.
Conclusions: Combining pembrolizumab, olaparib, capecitabine, and radiotherapy with chemotherapy increased survival rates compared to chemotherapy only.

Introduction

Breast cancer ranks second on the list of common diseases worldwide based on World Health Organization (WHO). In the United States and Europe breast cancer is a second rank cause of death, after lung cancer (Almansour, 2022). In 2012, globally, around 1.67 million cases of breast cancer were reported, while in 2020, it increased to 2.2 million cases with 684,996 deaths (International, 2020) (Momenimovahed, 2019).

TNBC is a subtype of breast cancer that does not have Estrogen Receptor (ER),

Progesterone Receptor (PR), and Human Epithelial Receptor (HER2) (Kumar, 2016). It is reported that 24% of new cases of TNBC are diagnosed each year, and the incidence is increasing (Tsai, 2016). In addition, TNBC often affects women of reproductive age under 40 years old (Yin, 2020).

TNBC is classified as an invasive, heterogeneous breast cancer and has a poor prognosis and wide metastatic capabilities (Sukumar, 2021). From the perspective of current therapy, the survival rate for TNBC is around 10.2 months, with and 5-year survival rate of 65% in regional cancer and 11% if cancer has spread to other organs (Kohler, 2015).

TNBC is a hormone-resistant breast cancer, so no current standard therapy exists. TNBC is sensitive chemotherapy, so chemotherapy is one of the therapies of choice, but its effectiveness as a standard therapy is still lacking. This is because residual metastatic lesions of cancer cells can recur after therapy (Kumar, 2016). Chemotherapy has become the Standard Of Care (SOC) for TNBC patients, but it still has weaknesses, such as the possibility of cancer relapses and treatment resistance during treatment (Won, 2020).

The limitations of TNBC therapy cause the death rate from breast cancer to be more significant. The condition is also supported by the characteristics of TNBC, which have a fast growth rate, a very high degree of invasiveness, wide metastatic potential, and poor prognosis.

Methods

The writing of this article uses the method of a literature review or article review, which comes from the results of the analysis and synthesis of various journals. The number at this writing is 27 articles. This article is written using the keywords triple-negative breast cancer, therapy, and resistance. Article search is limited to the latest articles in the last ten years (2012-2022). The selection of journals in this article is full-text related to the topic and published. Journal searches came from PubMed, Science Direct, and Google Scholar.

Results and Discussion

Breast Cancer Emergency

Breast cancer is a malignancy originating from the epithelial cell of the mammary glands, and it causes high rates of hospitalization, mortality, and morbidity. According to the WHO report, breast cancer causes 19.6 million Disability-Adjusted Life Years (DALYs) each year, so the world burden due to this malignant neoplasm is enormous (Lukasiewicz, 2021).

In 2020, breast cancer was the most frequently diagnosed worldwide, with 2.26

million cases. In addition, breast cancer is also the most frequent cause of death for women worldwide, with 684,996 cases (Ferlay, 2020). The trend of breast cancer over the last three decades has increased, i.e., doubling from 1990 to 2016 (Sharma, 2019).

Triple Negative Breast Cancer Case Emergency

TNBC is a subtype that does not have ER, PR, and HER2+ expression on immunohistochemical staining (Kumar, 2016). This cancer develops from basal-like breast cancer cells and is characterized by the loss of some expression of BRCA1 receptors or random (Alluri, 2014). TNBC is a malignant breast neoplasm that represents 12%-20% of breast cancer. TNBC has a higher mortality rate than other breast cancer subtypes due to its aggressive and heterogeneous nature (Brewster, 2014). TNBC has an 8% to 16% lower survival rate than luminal subtype breast cancer and often affects women of African ethnicity (Howard, 2021).

Estimation of around 1 million breast cancer cases worldwide, of which approximately 170,000 cases (12-20%) are TNBC cases (Wahba, 2015). According to the current therapeutic perspective, the survival rate for TNBC patients is about 10.2 months, with five years of survival for people with regional cancer is 65% and 11% if cancer has metastasized to other organs (Kohler, 2015).

Problem of Treatments

Definitive therapy for triple-negative breast cancer subtypes is unavailable, where the TNBC type has no target receptors (Kumar, 2016). So far, surgical therapy also showed unfavorable results.

Several chemotherapeutic drugs have been shown to respond to therapy in TNBC including anthracyclines, alkylation agents (e.g., cyclophosphamide), an anti-microtubule agents taxane, and the anti-metabolite fluorouracil (5-FU). The median Progression-Free Survival (PFS) with chemotherapy ranges from 1.7 to 3.7 months and the median Overall Survival (OS) from the onset of metastasis is 10 to 13 months. (Won, 2020).

Although some studies show that chemotherapy gives a better response, the prognosis for TNBC remains poor. No standard chemotherapy regimen can be given to patients who experience recurrence after chemotherapy because it will have a short response, then recur and be followed by metastases (Won, 2020).

Several things make TNBC more resistant and difficult to treat because TNBC has Tumor Infiltrating Lymphocytes (TILs) in the microenvironment. TNBC is known to be more immunogenic than other breast cancer subtypes. In addition,

chromosomal instability that underlies the pathogenesis of TNBC causes cancer cells' ability to adapt easily and the immune system to become quickly resistant to chemotherapeutic agents (Wein, 2017).

Chemotherapy is the TNBC SOC for early-stage treatment. However, for advanced TNBC and relapse, chemotherapy is no longer the first choice.

Therapy and Regimen in Triple Negative Breast Cancer

Despite its aggressiveness, heterogeneity, and metastatic ability, TNBC is unique in immunogenicity and DNA damage structure. TNBC has a different response toward the therapy as shown in Table 1.

Table 1 Study of Types and Response to Therapy in TNBC Patients

References (Author)	Treatment	Response
Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer (Cortes *et al.,* 2022)	Pembrolizumab was given 200 mg every three weeks plus a chemotherapy regimen	TNBC showed an excellent response to chemotherapy combined with pembrolizumab, capetabine, olaparib, and radiotherapy, compared to just chemotherapy alone. Combination chemotherapy increases survival rates, DFS, and BCSS of TNBC compared to chemotherapy alone. On the other hand, BCS does not show a better prognosis.
Chemoresistance Evolution in Triple-Negative Breast Cancer Delineated by Single Cell Sequencing (Kim *et al.,* 2018)	Administration of anthracycline chemotherapy (epirubicin) and taxane (docetaxel) for 2 cycles then 4 cycles of the same chemotherapy plus an angiogenesis inhibitor (bevacizumab).	Chemotherapy provides optimal effects in TNBC patients with clonal extinction. In contrast, clonal persistence patients still retain large numbers of tumor cells with altered genotypes and phenotypes.
Pathologic Complete Response (pCR) to Neoadjuvant Treatment with or without Atezolizumab in Triple-Negative, Early High-Risk and Locally Advanced Breast Cancer: Neotrip Michelangelo Randomized Study (Gianni *et al.,* 2022)	Intravenous administration of carboplatin and nab-paclitaxel without or with atezolizumab 1200 mg i.v were given 3 weeks for eight cycles.	The analysis revealed that the pCR level after treatment with atezolizumab (48.6%) compared to without atezolizumab (44.4%) was not statistically significant.

Neoadjuvant Atezolizumab in Combination with Sequential Nab-Paclitaxel and Anthracycline-Based Chemotherapy versus Placebo and Chemotherapy in Patients with Early-Stage Triple-Negative Breast Cancer (Impassion031): A Randomised, Double-Blind, Phase 3 Trial (Mittendorf *et al.,* 2020)	Chemotherapy plus atezolizumab or placebo every two weeks. Chemotherapy consisted of nab-paclitaxel followed by doxorubicin and cyclophosphamide followed by surgery.	In patients with early-stage TNBC, atezolizumab treatment combined with nab-paclitaxel-based chemotherapy and anthracycline significantly increased the pathological complete response rate with an acceptable safety profile.
Outcomes after Breast-Conserving Surgery or Mastectomy in Patients with Triple-Negative Breast Cancer: Meta-Analysis (Fancellu *et al.,* 2021)	Meta-analytic research evaluating survival rate in TNBC undergoing Breast Conservation Surgery (BCS) versus mastectomy	TNBC patients with Breast Conserving Surgery (BCS) still have a poor prognosis compared to mastectomy.
Effect of Postmastectomy Radiotherapy on T1-2N1M0 Triple-Negative Breast Cancer (Xia *et al.,* 2022)	TNBC patients undergoing Postmastectomy Radiotherapy (PMRT) and non-postmastectomy radiotherapy.	5-year Breast Cancer-Specific Survival (BCSS) for the PMRT and non-PMRT groups were 79.1% and 74.7%, respectively. The analysis showed that radiotherapy after PMRT in TNBC patients significantly increased BCSS.
A Phase 2 Clinical Trial Assessing the Efficacy and Safety of Pembrolizumab and Radiotherapy in Patients with Metastatic Triple-Negative Breast Cancer (Ho *et al.,* 2020)	TNBC patients were given radiotherapy doses of 3000 cGy in 5 daily fractions followed by administration of pembrolizumab intravenously.	The addition of pembrolizumab and radiotherapy is safe and shows a poor prognosis and metastases.
Combination of Olaparib with Radiotherapy for Triple-Negative Breast Cancers: One-Year Toxicity Report of the RADIOPARP Phase I Trial (Loap *et al.,* 2021)	Olaparib was administered orally starting 7 days before radiotherapy until the end of radiotherapy.	The results of olaparib administration related to breast radiotherapy in TNBC patients showed a very good late tolerance profile. This combination is slightly toxic to the skin and there are no side effects.
Adjuvant Capecitabine with Docetaxel and Cyclophosphamide Plus Epirubicin for Triple-Negative Breast Cancer (CBCSG010): An Open-Label, Randomized, Multicenter, Phase III Trial (Li *et al.,* 2020)	Patients treated with capecitabine (3 cycles of capecitabine with docetaxel and capecitabine, epirubicin, and cyclophosphamide) and patients treated with controls without capecitabine	Capecitabine when added to docetaxel followed by a combination of 3 anthracycline drugs significantly increased Disease Free Survival (DFS) in TNBC without problems.

Suboptimal Therapy Following Breast Conserving Surgery in Triple-Negative and HER2-Positive Breast Cancer Patients (Johnson *et al.*, 2021)	Women ≥ 40 years with TNBC treated with primary and axillary surgery.	7,843 of 11,785 women received optimal therapy. Therapy becomes less and less optimal with age, comorbidities, and characteristics of the cancer.

Conclusion

TNBC showed a good response to combination chemotherapy along with pembrolizumab, capecitabine, olaparib, and radiotherapy, compared to just chemotherapy alone. Combination chemotherapy increases survival rates, DFS, and BCSS of TNBC compare to chemotherapy alone. On the other hand, breast-conserving surgery (BCS) does not show a better prognosis.

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