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Unraveling the Complexity of triple-negative breast cancer: A comprehensive research analysis

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Abstract. TNBC, also known as triple-negative breast cancer, is a predominantly female-targeting and stands out due to its defining attribute. TNBC accounts for a considerable percentage of BC cases, and unfortunately, it is associated with poor prognoses and limited treatment options. In-depth information about TNBC, including its epidemiology, clinical expression, molecular features, and current diagnostic and treatment options, is provided in this research paper. In addition to examining ongoing research projects to better TNBC patient outcomes and treatment options, the report also suggests potential future routes for improved management tactics. The development of effective targeted treatments and individualized treatment plans for such a challenging disease necessitates an understanding of the distinctive characteristics of TNBC. This article contributes to continuing efforts to meet the unmet clinical requirements of patients affected by this aggressive BC subtype by offering insight into the complexity of TNBC.

Keywords: diagnosis, TNBC, treatment, subtype, risk factors, therapy.

1. Introduction

Breast cancer (BC) is a prevalent illness that impacts the mammary glands or tissues. It is ranked as the second most common illness worldwide by the World Health Organization (WHO), with developed countries being particularly vulnerable to its occurrence. In the United States and Europe, BC stands as the primary cause of death, following lung cancer [1]. A comprehensive study conducted across 40 European countries investigated cancer incidence and mortality rates, revealing BC as the third highest in prevalence at 12.8%, trailing behind lung and colorectal cancer [2].

One-half of a million women die yearly due to BC, and 150,000 are considered TNBC cases, like 30% of all BC-related deaths [3]. It is a particular study interest due to medically demanding situations, consisting of low response to remedies and high invasiveness. TNBC, which represents approximately 15-20% of all BC cases, is characterized by the absence of receptors commonly found in other types of BC; specifically, estrogen, progesterone receptors, which are female hormones, and the human epidermal growth factor receptor protein. Doctors can use hormone therapy or other medications to destroy cancer cells by targeting specific receptors. But TNBC does not have any of these tissues, making it difficult to target cancer cells with particular remedies [1, 4].

This paper aims to enhance readers' comprehension of TNBC by diving into various aspects. Readers will first gain knowledge about the distinct molecular subtypes of TNBC. Then, it will explore diagnostic and prognostic markers. Furthermore, it will offer significant insights to minimize the

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likelihood of developing this cancer by explaining various risk factors, existing treatment options, and the potential side effects associated with these treatments. Additionally, the paper will dive into the differences between the male and female TNBC, highlight some major contrasting characteristics, diagnostic approaches, and patient experiences with this cancer.

2. Molecular subtypes of TNBC & specific treatments

2.1. Basal-like 1 & 2 (BL1 & BL2)

The most common subtype of TNBC, Basal-like, displays highly active cellular cycle and DNA damage response pathways, making them susceptible to targeted DNA damage response treatments [5]. Tumors associated with the BL1 subtype exhibit the poorest clinical prognosis. Studies uncovered unique signaling characteristics in this aggressive subgroup of BL1, including heightened RhoA pathway activity, resulting in a more unfavorable prognosis [6]. Research indicates that the BL1 subtype exhibits elevated gene expression levels associated with the cell cycle and DNA damage response. On the other hand, the BL2 subtype is characterized by a stronger association with growth factor signaling and myoepithelial markers [5].

Due to its complex and heterogenous nature, there is no specific treatment for BL1 and BL2 like the other subtypes. Yet, another treatment approach, like standard therapies, will be discussed in the later article [7].

2.2. Mesenchymal (M)

The M subtype exhibits two significant characteristics. Firstly, it is highly likely to acquire resistance to chemotherapeutic medications, making treatment plans difficult. Secondly, the M subtype's tissue features resemble sarcomas or squamous epithelial cells. These distinctive characteristics set the M subtype apart from other BC subtypes and the need for a specialized approach to diagnosis and treatment [5, 8].

If a patient has the M subtype of BC, exploring treatment options involving mTOR inhibitors like NVP-BEZ235 may be beneficial. Frequently, these cancer cells demonstrate activated PI3K/AKT signaling, primarily attributed to mutations in the PIK3CA gene or deficiencies in PTEN. In addition, drugs targeting epithelial-mesenchymal transition (EMT) may also be considered a treatment option [5, 8].

2.3. Luminal androgen receptor (LAR)

The LAR subtype of TNBC has distinctive expression patterns in hormone regulation and estrogen/androgen metabolism pathways. A noteworthy observation is that the LAR subtype of TNBC displays notably elevated mRNA expression of the androgen receptor (AR) compared to other subtypes, with levels approximately nine times higher. This significant AR expression sets the LAR subtype apart from the other subtypes of TNBC [5, 8].

As a result, doctors often suggest anti-AR treatment for this subtype. Targeting the androgen receptor through specific therapeutic interventions can be beneficial in managing and treating LAR subtype BC. It aims to effectively modulate this subtype's dysregulated hormone signaling and metabolic pathways [5, 8].

2.4. Immunomodulatory (IM)

The IM subtype of TNBC presents notable distinctions, particularly with regards to the genetic profile related to immune cell function and the intricate pathways of cellular signaling such as the Th1/Th2 route, dendritic cell pathway, and interleukin-12 & 7 pathways. These findings indicate a robust immune response and notable involvement of the immune system in the IM subtype. Additionally, research studies have established notable similarities between the IM subtype of BC and another distinct subtype known as medullary carcinoma of the breast [5, 8].

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Immune checkpoint inhibitors, including PD1, PDL1, and CTLA-4, are frequently used to treat individuals with BC of the IM subtype. These inhibitors can help regulate immune responses and increase the immune system's capacity to fight tumors. Given its immune-related features and similarities to medullary carcinoma, including immune checkpoint inhibitors in the treatment regimen may be advantageous for patients with IM subtype BC [5, 8].

3. Risk factors

There are two types of risk factors for TNBC: non-modifiable and modifiable. There are specific elements that play a role in increasing the risk of breast cancer, which cannot be modified. These factors include age, biological sex, inherited genetic variations, racial and ethnic background, family history of genetic disorders, breast density, previous exposure to radiation, and past breast conditions. Other factors that can be altered include the use of specific medications, managing body weight effectively, exercising, addressing nutritional deficiencies, avoiding drug use, quitting smoking, and limiting the consumption of processed foods [1].

Approximately 80% of individuals with TNBC are aged 50 and above, making age a non-modifiable risk factor. The incidence of TNBC shows a clear association with age, where the likelihood of developing this type of cancer escalates as individuals grow older. Studies suggest that the risk of TNBC increases by approximately 1.5% at the age of 40, 3% at the age of 50, and exceeds 4% at the age of 70. Gender also plays a role, as estrogen and androgen stimulation and imbalances are more likely to impact female breast cells. TNBC was found in 13% (38,628 out of 295,801) of female patients, while only 6% (185 out of 3,136) of male patients were diagnosed with this subtype of BC. A significant non-modifiable risk factor is the history of breast or ovarian cancer with BRCA mutations in the family [1]. Moreover, there are notable disparities in TNBC prevalence among different ethnic backgrounds. Individuals of African descent have a higher propensity for TNBC compared to those from other ethnic backgrounds. Hispanic women may have a higher incidence of TNBC than white and non-Hispanic white women. Possible reasons for these differences could include a greater occurrence of multiple pregnancies, early-age pregnancies, and higher premenopausal weight in women from non-Hispanic Black, African American, Hispanic, and Latina backgrounds [9]. Breast tissue density and a history of radiation remedies also contribute to the hazard of TNBC. The higher the thickness of the breast, the higher the chances [1].

Modifiable risk factors include using medicinal drugs, such as diethylstilbestrol and selective antidepressants, which may also increase the danger of BC. BMI, physical activity, alcohol consumption, and diet supplements are interchangeable. Obesity and lack of physical activity are linked to a higher chance of developing BC. Additionally, excessive alcohol consumption and poor dietary habits may also contribute to the risk of developing the disease [1]. Over a span of 14 years, a group of 418 patients with TNBC were studied. The findings revealed that among them, 124 individuals (29.7%) were of average weight or underweight, 130 individuals (31.1%) were overweight, and 164 individuals (39.2%) were obese [10]. A study conducted in West Virginia analyzed 620 patients of Caucasian descent who were diagnosed with invasive BC. Of these, 49.6% of the TNBC patients had obesity, compared to just 35.8% of the non-TNBC patients (P=0.0098) [10]. Drug use, smoking, and consumption of processed foods are additional modifiable risk factors for TNBC [1]. The WHO states that meat and other processed foods are group-1 proven carcinogens for gastrointestinal and BC [11].

4. Symptoms

TNBC and other forms of BC share similar signs and symptoms. These symptoms include finding a new lump or thickening in the breast or armpit, noticing alterations to the size, shape, or texture of the breast (which may include swelling, redness, flaking, or pitting), enduring nipple discharge when not pregnant or nursing, and experiencing changes in the position of the nipple (such as nipple turning inward or pulling towards a specific direction). An ulcer on the breast or nipple can also be a sign and sometimes extend to the areola. These symptoms vary from person to person, so it is best to understand how an individual breast generally looks and feels. Non-cancerous breast changes can cause some of these

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symptoms. Breast changes that are not harmful can still cause symptoms such as lumps, discomfort, or nipple discharge. While a mammogram can detect some benign alterations, further tests and examinations are still required to determine whether it is harmless since it is difficult to tell them apart [12, 13].

5. Current diagnosis

One of the diagnostic procedures for TNBC is mammography, an imaging technique that employs a minimal amount of radiation to capture images of the breast tissues, ensuring controlled penetration [12]. Mammograms rely on finding calcifications (white spots), growths, or lumps within the breast to detect BC. Moreover, there are worries about the potential harm of radiation from mammograms, particularly for individuals with high susceptibility to BC, such as those with the BRCA carrier gene or a family history of the disease. Such exposure may increase the likelihood of developing BC [14]. For people who are under the age of 35, ultrasound would most likely be their choice [12]. Sometimes a biopsy is done even if the lump cannot be seen on imaging but can still be felt [14]. To determine if there are any cancerous cells in the breast, a biopsy would involve removing a small sample of tissue for examination. If there is a family history of BC, gene testing may be performed to identify any BRCA cancer gene mutations [12].

6. Future diagnosis approaches

6.1. Blood-based liquid biopsy

Blood-Based Liquid Biopsy is an effective non-penetrating diagnostic technique that involves the collection of a blood sample. Afterward, the collected sample is carefully analyzed to extract pertinent tumor-related data, including circulating tumor cells (CTCs), as well as circulating tumor DNA (ctDNA). By examining these components, valuable insights can be obtained for diagnostic purposes [14]. Liquid biopsy can capture distant metastatic lesions' spatial and temporal heterogeneity, which is difficult with conventional tissue samples. This technology utilizes molecular technology and advanced bioinformatics techniques that are extremely sensitive. With this method, it is possible to discover BC early, screen for it, anticipate how it will advance, identify the minimal residual disease, detect relapses, and track how well it responds to therapy over time. Despite its benefits, liquid biopsy has detection limitations, such as early-stage BC's low quantities of CTCs and ctDNA and some tumors' lack of ctDNA secretion. It is imperative to devise more sophisticated and accurate detection techniques to enhance the precision of liquid biopsy in detecting BC [15].

6.2. Immuno- positron emission tomography (PET)

PET uses a radioactive substance to assess the performance of organs and tissues and has been known for identifying other diseases before other imaging techniques. During this process, a radioactive tracer attaches to biomolecules (such as sugar or protein) and emits positrons. These positrons generate photons as they interact with the surrounding electrons. To study the organ, tissue, or cell, researchers can use data from a PET scanner that detects electrical signals released by photons [14]. It is limited in its inability to detect small tumors, however. PET plays a crucial role in determining the spread of BC to lymph nodes, the presence of metastasis, and the effectiveness of treatment. However, it is only applicable during the initial stages of a cancer diagnosis. Therefore, it is only used explicitly in certain stages of BC and may need to combine with other modalities, such as biopsy and computed tomography imaging, to diagnose TNBC [16].

7. STandard treatment options & side effects

The choice of treatments primarily relies on factors such as the specific location, size, and characteristics of the cancer, along with the overall health condition of the individual [12].

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7.1. Lumpectomy (breast-conserving surgery)

The recommended procedure is a lumpectomy if a biopsy reveals a small and early-stage cancer [17]. In a lumpectomy procedure, a healthcare provider removes the lump from the breast and evaluates the adjacent lymph nodes to assess potential cancer spread. The surgical procedure usually lasts one to two hours, and many women can return home on the same day without requiring an overnight stay [4].

Breast swelling, changes in size and shape, and the development of scar tissue hardness at the incision site are common short-term side effects of breast surgery. There is also a wound infection or bleeding risk following the procedure [18]. If lymph nodes are removed during surgery, it may result in lymphedema, which causes arm swelling due to poor drainage of lymph fluid [4].

7.2. Mastectomy

In some cases, a mastectomy is required instead of a lumpectomy. There are several scenarios where radiation therapy for BC may not be suitable. Some risk factors of developing the second cancer in the breast include having multiple tumors in different areas, experiencing a recurrence of BC, having a gene mutation that increases the risk, or being pregnant and worried about potential harm to the infant [19]. There are various types of mastectomy procedures. The first one is called simple total mastectomy. This procedure requires complete breast removal, including the nipple and areola The modified radical mastectomy involves the removal of the breast tissue, including any visible abnormalities, such as tumors or lesions, as well as the excision of the fascia overlying the chest muscles and the lymph nodes in the axillary region, which are located beneath the arm. In some cases, partial removal of the chest wall may be necessary. The least common is the radical mastectomy. This surgical procedure entails the excision of the breast, including the nipple, areola, and axillary lymph nodes [4, 20].

Tenderness and swelling in the chest region are two possible adverse outcomes of a mastectomy treatment. Additionally, patients may develop shoulder stiffness or soreness in the underarm. In addition, some people may feel uncomfortable or phantom breast discomfort where their breast formerly was. Lymphedema, characterized by arm swelling brought on by impaired lymphatic drainage, is a possibility [20].

7.3. Radiation therapy

Following a lumpectomy, healthcare professionals may recommend radiation therapy as a subsequent treatment option. This therapy involves the use of potent radiation to eradicate any remaining tumor cells, reducing the risk of recurrence. One way to receive treatment is through external radiation, which involves delivering radiation to the breast from outside the body. Another option for radiation treatment is through internal radiation, also called brachytherapy. A device that delivers radiation is temporarily inserted in the affected area to treat BC. There are two radiation therapy options for BC treatment: whole-breast radiation and partial-breast radiation, which is typically recommended for certain early stages of BC. Radiation therapy typically involves daily sessions lasting around 20 minutes each [4]. After a mastectomy, doctors may use radiation therapy. However, this happens after considering whether there are lymph nodes with signs of BC (an indication of cancer cells spreading to other parts), large tumor size (bigger than 5 centimeters), or tissue margins with signs of BC (such as when it is too narrow) [21].

Short-term side effects of radiation therapy for BC commonly occur during or shortly after treatment, typically within six months. These side effects may encompass discomfort, alterations in the skin, inflammation, hair loss in the armpit or chest region, throat soreness, and fatigue. Skin-related alternations are frequent and can manifest as color changes, peeling, tenderness, dryness, itching, soreness, blisters, and increased moisture due to the effects of radiation therapy on the skin. Swelling of the breast or surrounding tissue is also a short-term side effect, but it usually subsides within a few weeks after treatment [4, 22]. Long-term side effects of radiation therapy for BC may manifest months or even years after completing the treatment course. Common long-term adverse effects include brachial plexopathy, lymphedema, and breast changes. Breast changes can result in breast density increasing or decreasing. Radiation therapy can also lead to damage to the nerves in the arm, wrist, and hand, which

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may result in a condition known as brachial plexopathy. This condition can lead to loss of sensation or discomfort in the affected part. Additionally, radiation damage to the nearby lymph nodes can lead to the development of lymphedema, characterized by swelling in the arm, hand, or chest. The accumulation of lymph fluid in these areas contributes to the swelling observed in lymphedema [22].

7.4. Chemotherapy

In many cases, patients undergo a lumpectomy or a mastectomy to remove the tumor or the entire breast [1]. After surgery, chemotherapy is frequently administered to eliminate any cancer cells that may have been undetected, including those remaining in the breast or those that have metastasized to other areas of the body. This form of chemotherapy is referred to as adjuvant chemotherapy. In certain instances, physicians may suggest administering chemotherapy prior to surgery, referred to as neoadjuvant therapy or preoperative chemotherapy, with the aim of reducing the size of larger tumors [1, 23].

Hair loss is an average short-term adverse effect of chemotherapy and generally starts four weeks after chemotherapy begins. Following each chemotherapy treatment, nausea may last for one or two days. Fatigue is also a common side effect; some individuals may have difficulties with memory and concentration after undergoing chemotherapy [1]. One potential long-term side effect of specific cancer treatments, such as chemotherapy, is infertility. This can occur as menstrual periods become irregular or stop altogether (amenorrhea). In addition, women who experience early menopause as a result of chemotherapy may face an increased risk of developing conditions characterized by bone loss, such as osteopenia and osteoporosis [23].

8. Patient perspectives

Ilyasha Hosea, a 24-year-old woman diagnosed with stage III TNBC in the summer of 2017, provided insights into her experience managing the side effects of various therapies such as chemotherapy, surgery, and radiation. Hosea emphasizes that the most distressing side effect that experienced was the radiation burn, which caused her skin to become sensitive and tender, resulting in a raw sensation. Additionally, she expresses that chemotherapy was the most challenging part of her treatment journey. After each infusion, Hosea experienced extreme exhaustion, rendering her unable to engage in daily activities for approximately one week. Despite this, she attempted to combat the fatigue through exercise and gradually regained strength over a few days. After finishing all her treatment by January 2018, there was no evidence of disease in May of that year [24].

9. Conclusion

This paper has expanded the understanding of TNBC by examining various topics, including molecular subtypes, diagnostic markers, risk factors, treatment options, and patient experiences. This article aims to improve readers' comprehension of TNBC to improve outcomes, increase awareness, and provide more efficient targeted treatments for people with this aggressive disease. TNBC poses difficulties for both patients and doctors because of its poor prognosis and few available treatments, which leads to higher death rates when compared to other BC subtypes.

Although TNBC is a deadly disease, there is a solid foundation for its molecular subtypes. Even with molecular subtyping, the disease's inherent heterogeneity may restrict the efficacy of the treatment. As a result, it has become more challenging to create effective customized therapy. Chemotherapy is still the principal therapeutic option for TNBC. However, the emergence of targeted medicines for some TNBC subtypes and targeted therapies are less successful in TNBC than in subtypes with hormone receptors or HER2 amplification. For the development of targeted therapy, further research is vital. Clinical trial trials, which give patients with TNBC access to innovative medicines not available with regular treatment, can offer hope for better results in the interim.

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