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Bridging the complexity of triple negative breast cancer care through multidisciplinary team approach

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Abstract

Triple-negative breast cancer (TNBC) is still associated with a grave prognosis, especially compared to other breast cancer subtypes. TNBC carries a high risk of recurrence and distant metastasis, resulting in lower survival rates. Additionally, TNBC exhibits significant heterogeneity at the histopathological and multiomics levels, further complicating the development of effective treatments. While some TNBC subtypes may initially respond to chemotherapy, resistance frequently develops, increasing the risk of aggressive recurrence. The approach to TNBC management has undergone significant transformations in recent years, recognizing it as a heterogeneous disease with diverse biology and behavior. Chemotherapy remains the cornerstone of treatment for most TNBC cases, with the incorporation of PD-L1 CPS or immune cell (IC) scores and BRCA status being crucial for optimizing patient management. Besides the advancement of TNBC treatment, the multidisciplinary team also plays a key role in TNBC management, enabling improved diagnosis, treatment outcomes, disease monitoring, and management of adverse events.

Keywords: *Breast cancer, multidisciplinary team, treatment, triple-negative breast cancer*

Abstrak

Kanker payudara *triple-negative* (TNBC) dikaitkan dengan prognosis yang buruk, terutama bila dibandingkan dengan subtipe kanker payudara lainnya. TNBC memiliki risiko tinggi terhadap kekambuhan dan metastasis jauh, yang berujung pada angka ketahanan hidup yang lebih rendah. Selain itu, TNBC menunjukkan heterogenitas yang signifikan pada tingkat histopatologis maupun multiomik, sehingga semakin mempersulit pengembangan terapi yang efektif. Meskipun beberapa subtipe TNBC dapat memberikan respons awal terhadap kemoterapi, resistensi sering kali muncul kemudian dan meningkatkan risiko kekambuhan agresif. Pendekatan terhadap penatalaksanaan TNBC telah mengalami perubahan besar dalam beberapa tahun terakhir, dengan pengakuan bahwa penyakit ini bersifat heterogen dengan biologi dan perilaku yang beragam. Kemoterapi tetap menjadi pilar utama pengobatan bagi sebagian besar kasus TNBC, dengan penilaian skor PD-L1 CPS atau sel imun (IC) serta status BRCA yang penting untuk mengoptimalkan penatalaksanaan pasien. Selain kemajuan dalam terapi TNBC, peran tim multidisiplin juga sangat krusial dalam meningkatkan diagnosis, hasil pengobatan, pemantauan penyakit, serta penanganan efek samping terapi.

Kata Kunci: *kanker payudara, tim multidisiplin, terapi, kanker payudara triple-negatif*

Introduction

Breast cancer is the most diagnosed type of cancer worldwide, with an incidence of 2.3 million cases and causing 685,000 deaths annually.[1] In Indonesia, breast cancer is also the cancer with the highest incidence and is the leading cause of cancer-related deaths.[2]

Breast cancer is a heterogeneous disease, classified based on the expression of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 (HER2). Breast cancer cells that express hormone receptors are referred to as hormone receptor-positive breast cancer, cells that express HER2 are referred to as HER2-positive breast cancer, while cells that express none of the three are classified as triple-negative breast cancer (TNBC).[3,4] The molecular classification of breast cancer consists of the luminal A and B subtypes, which overlap with ER+ breast cancer; the HER2-enriched subtype, which overlaps with HER2+ breast cancer and can be TP53-mutated or wild type; and basal-like breast cancer, which overlaps with TNBC, and the claudin-low breast cancer subtype.[5] Shortly the definition of TNBC is the absence of immunostaning for estrogen and progesterone receptors and lack of overexpression or amplification of human epidermal growth factor receptor 2.[6]

Hormone receptor-positive breast cancer accounts for about 70–80% of all breast cancer cases, the HER2-positive subtype makes up around 15–20%, and triple-negative accounts for about 10–15%. Each breast cancer subtype has a different carcinogenesis pathway, resulting in differences in treatment selection and patient prognosis.[7,8] According to data from The Surveillance, Epidemiology, and End Results (SEER), patients with hormone receptor-positive breast cancer have a 5-year survival rate of around 90%, HER2-positive around 80–85%, while triple-negative breast cancer (TNBC) has the lowest survival rate, around 60–70%, highlighting the many treatment challenges that still remain unsolved.[9]

TNBC Classification

Based on genetic expression, TNBC can be classified into various subtypes with distinct clinical characteristics and prognoses, each requiring different therapeutic modalities. Two major classifications of TNBC are the Vanderbilt and Baylor classifications. The Vanderbilt classification divides TNBC into six subtypes: basal-like 1 (BL1), basal-like 2 (BL2), immune-modulatory (IM), mesenchymal (M), mesenchymal stem–like (MSL), and luminal androgen receptor (LAR).[10] However, further observation revealed that most of the IM and MSL subtype markers originate from tumor microenvironment gene expression; thus, they were removed in the revised classification known as TNBCtype-4.[11,12] The BL1 subtype is characterized by increased expression of genes involved in cell replication and DNA damage repair, while BL2 is marked by myoepithelial and cell growth gene markers. The mesenchymal subtype shows increased expression of genes involved in epithelial-to-mesenchymal transition, motility, and cell growth. The LAR subtype is characterized by luminal gene expression derived from androgen receptors.[13] The Vanderbilt classify-cation is the most extensively studied by researchers, both in terms of patient characteristics and therapeutic responses.

The BL1 subtype is associated with younger age at diagnosis, higher Ki-67 index, and more frequent lymph node involvement. BL1 and BL2 subtypes are highly sensitive to platinum-based chemotherapy (pathological complete response [pCR]: 65.4% and 47.7%, respectively). The mesenchymal subtype tends to metastasize to the lungs and shows a poorer response to platinum-based chemotherapy (pCR: 36.4%). The LAR subtype is more commonly diagnosed at an older age, is associated with larger tumor size, more frequent lymph node involvement, and bone metastases, and shows the poorest response to platinum-based chemotherapy (pCR: 21.4%).[14] Unlike the mesenchymal subtype, survival in LAR patients can be improved with the use of androgen receptor antagonists (bicalutamide, abiraterone acetate, and enzalutamide), achieving a clinical benefit rate (CBR) of up to 33%.[15]

The Baylor classification divides TNBC into basal-like immune-suppressed (BLIS), basal-like immune-activated (BLIA), luminal-AR (LAR), and mesenchymal (MES) subtypes.[16] Although not identical, the Baylor and Vanderbilt classifications share similarities in terms of basal, luminal androgen, and mesenchymal features. The BLIS subtype has the best prognosis. It is characterized by decreased expression of B cells, T cells, and natural killer cells. Compared to the Vanderbilt classification, this subtype resembles the BL1 subtype. In contrast to BLIS, the BLIA subtype has the poorest prognosis. It is marked by increased expression of B cells, T cells, and natural killer cells. Compared to the Vanderbilt

classification, this subtype is similar to the immune-modulatory subtype. The LAR and mesenchymal subtypes in the Baylor classification are equivalent to those in the Vanderbilt classification.[17] Unlike the Vanderbilt classification, the Baylor classification has not yet been extensively studied in terms of patient characteristics or treatment response.

Some authors have divided TNBC into AR-positive and AR-negative TNBC based on the expression of the androgen receptor (AR). AR-negative TNBC is also known as quadruple-negative breast cancer (QNBC). There exist differences regarding the tumor biology and molecular profiles between QNBC and TNBC. For instance, expression of epidermal growth factor (EGF) and genes involved in immune response, which results in higher proliferative and immunogenic properties when compared to TNBC, leading to a worse prognosis. For this reason, a distinct subtype classification for QNBC, independent of TNBC, is recommended.[18]

Genetic and Epigenetic in TNBC

Genetically, triple-negative breast cancer (TNBC) is frequently characterized by mutations in key tumor suppressor genes, including TP53, BRCA1/2, PIK3CA, RB1, PTEN, and MYC. These alterations contribute to cell cycle dysregulation, impaired DNA repair, and tumor progression.[19] Many of these mutations have been extensively studied as potential therapeutic targets. For instance, mutations in BRCA1 and BRCA2, which encode essential proteins in the homologous recombination (HR) DNA repair pathway, render cancer cells particularly vulnerable to Poly (ADP-ribose) polymerase (PARP) inhibitors, such as Olaparib.[20] PARP enzymes play a critical role in repairing single-strand DNA breaks via the base excision repair pathway. Inhibition of PARP leads to the accumulation of single-strand breaks, which are eventually converted into double-strand breaks during DNA replication.[21] In cells with functional HR, these lesions can be repaired. However, in BRCA-mutated cells with homologous recombination deficiency (HRD), the inability to repair double-strand breaks results in cell death—a therapeutic mechanism known as synthetic lethality.[22]

Epigenetic dysregulation also plays a significant role in TNBC pathogenesis. Aberrant DNA methylation patterns, such as promoter hypermethylation of tumor suppressor genes such as *BRCA1* and *CDKN2A*, result in gene silencing. Histone modifications and deregulated non-coding RNAs, including microRNAs.[23] MicroRNAs (miR) are small non-coding RNA molecules that regulate gene expression by inhibiting translation or inducing degradation of target mRNAs. In the context of TNBC, miRNAs can function either as oncogenes or tumor suppressors, depending on the genes they regulate. Several miRNAs, such as miR-21 and miR-155, have been identified as oncogenic, promoting cancer cell proliferation, angiogenesis, and metastasis. In contrast, other miRNAs, such as miR-34a and miR-200c, act as tumor suppressors by inhibiting tumor growth and spread.[24,25] Notably, several of these deregulated microRNAs also contribute to the regulation of epithelial-to-mesenchymal transition (EMT), a key process in TNBC progression that facilitates tumor invasion, metastasis, and treatment resistance. In TNBC, EMT is associated with enhanced cellular invasion and migration, as well as resistance to systemic chemotherapy, including platinum-based agents.[26] The main regulators of EMT are believed to include the TGF-β, Notch, and Wnt signaling pathways, and the process is also influenced by tumor microenvironmental factors such as hypoxia and the expression of miR (such as miR- 200c, miR-21 and miR-34a). These combined mechanisms lead to increased expression of transcription factors such as SNAI1, SNAI2 (Slug), Twist, and Zeb1/Zeb2, which drive the mesenchymal transition.[27]

Approved Treatment

The ideal treatment for TNBC includes complete tumor resection and systemic chemotherapy. The commonly used chemotherapy regimen is a combination of anthracyclines and taxanes (AC-T), namely doxorubicin, cyclophosphamide, followed by paclitaxel or docetaxel. Platinum-based chemotherapy is often used in TNBC, particularly in patients with BRCA gene mutations, involving carboplatin or cisplatin followed by paclitaxel or docetaxel.[28] Chemotherapy can be administered either pre-operatively (neoadjuvant) or post-operatively (adjuvant).

Since TNBC lack the expression of ER and PR and have amplification or over expression of HER2, hormonal therapies designed to inhibit ER and PR and anti-HER2 treatment are not effective. Moreover, the high heterogeneity of TNBC tumors makes it very difficult to find a universally useful targeted therapy. Indeed, there is no available biologically effective targeted therapy for TNBC yet.[29]

The management approach to TNBC has undergone significant transformations in recent years, recognizing

it as a heterogeneous disease with diverse biology and behavior.[30-32] Chemotherapy remains the cornerstone of treatment for most TNBC cases, with the incorporation of PD-L1 CPS or immune cell (IC) scores and BRCA status crucial for optimizing patient management.[33]

In patients without targetable molecular expression, determining the intrinsic subtype of breast cancer can help guide the selection of the most optimal systemic chemotherapy regimen.[10-14,16,34-36] Patients with the basal-like subtype (based on EGFR and CK 5/6 expression) tend to respond better to platinum-based chemotherapy, whereas patients with the mesenchymal subtype (based on vimentin expression) may benefit more from non-platinum-based chemotherapy, such as anthracyclines.

Immune checkpoint inhibitors (ICIs) are becoming increasingly relevant in the treatment of TNBC. PD-L1 expression, which serves as a negative prognostic factor in TNBC, has guided the implementation of anti-PD-L1 therapies, such as atezolizumab and pembrolizumab, which have been shown to significantly improve progression-free and overall survival in patients with PD-L1-positive metastatic TNBC.[37,38] However, in early-stage TNBC, the benefit of ICIs is independent of PD-L1 status as stated by ESMO guideline.[39]

The complexity of TNBC treatment is best illustrated by the management of metastatic TNBC. The treatment approach in this setting incorporates both biomarker-driven and pragmatic, region-sensitive strategies. First, PD-L1 testing should be performed to determine patient eligibility for ICIs. Additionally, germline BRCA1/2 mutation testing is recommended—particularly in younger patients and those with a family history of breast or ovarian cancer—to guide the use of PARP inhibitors. For first-line treatment, patients with PD-L1-positive tumors should receive ICIs in combination with chemotherapy. In contrast, for patients who are PD-L1-negative, or in settings where immunotherapy is not accessible, chemotherapy remains the standard of care as suggested by Pan-Asian adapted ESMO guideline. In subsequent lines of treatment, chemotherapy continues to play a central role. However, in patients with BRCA mutations, PARP inhibitors offer an effective targeted therapy option.[38] This level of complexity underscores the need for a multidisciplinary team approach to ensure optimal patient care.

Multidisciplinary Team

A multidisciplinary team (MDT) care policy was developed in the UK in 1995 to enhance the quality of care for cancer patients. MDT comprises a variety of professions, including medical, nursing, and allied workers, as well as diagnostic experts, who work together to identify the best treatment plan for each patient.[40-43] Previous research indicates that MDT care can aid in clinical decision-making. MDT treatment can prevent 98.8% of all drug mistakes and enhance overall care quality.[44] After the introduction of multidisciplinary care in the UK, breast cancer mortality in the intervention region was 18% lower than in the non intervention area.[45]

Various studies have demonstrated the benefits of multidisciplinary management of breast cancer, both in terms of patient outcomes and healthcare costs. A study by Kesson et al. in 2012 showed that breast cancer patients managed through a multidisciplinary approach had better disease-free survival and overall survival.[40] Similar findings were reported by Lu et al. in 2019, where breast cancer patients managed by a multidisciplinary team (MDT) had a 15.6% higher five-year survival rate.[46] Given these findings, it is no surprise that major global organizations such as ESMO, ASCO, and WHO consistently recommend MDT involvement in cancer patient management.[47] Freeman et al. (2015) showed that patients managed through an MDT approach incurred lower healthcare costs compared to those who were not managed through such a team.[48]

At Dr. Sardjito General Hospital in Yogyakarta, the MDT approach has actually been in place for nearly 20 years, initially focusing on the management of nasopharyngeal/head and neck cancers. This MDT program was a collaborative initiative between Dr. Sardjito Hospital, the Faculty of Medicine at Gadjah Mada University (UGM), VUMC Amsterdam, Antoni van Leeuwenhoek Hospital, and supported by the Dutch Cancer Society/Koningin Wilhelmina Fonds and ASIA-Link through the European Commission Programs on Capacity Building in Translational Research from Clinic to Basic Science. Nasopharyngeal cancer—the most common head and neck cancer—was chosen to pilot this effort in delivering adequate care for this specific tumor using internationally recognized protocols, known as the multidisciplinary approach.[49]

As expected, and as widely reported in international literature, patients managed through MDTs show a significantly lower risk of disease progression compared to those without MDT management (59 months vs. 12 months). Similarly, the mortality rate of nasopharyngeal cancer patients was significantly lower in the MDT group—just half that of the non-MDT group. The median overall survival in the non-MDT group was only 13 months, whereas more than half of the patients in the MDT group had not reached median survival at 5 years of follow-up. This study involved 178 nasopharyngeal cancer patients from January 1, 2016 to December 31, 2020.[50]

Various MDT implementations in nasopharyngeal, breast, colorectal, lung, and gastrointestinal tumors have shown improved patient outcomes.[40,51-54] The latest publication from Indonesia is a systematic review and meta-analysis by Pangarsa EA (2023), which included six studies from six countries (China, the UK, Taiwan, Australia, Africa, and France).[55] The review concluded that breast cancer patients who participated in well-organized MDT discussions had better survival outcomes compared to those who did not.

Although the benefits of MDTs have been widely recognized, the implementation of MDTs—particularly for triple-negative breast cancer—still faces many challenges. These include the unequal distribution of human resources in breast cancer management, the willingness of healthcare professionals who should be part of the MDT to engage in multidisciplinary care, the need for strong commitment to adhere to MDT decisions, and the necessity for appropriate regulatory support.

Conclusion

In conclusion, the complex and aggressive nature of TNBC demands a comprehensive and personalized treatment approach. Given its high heterogeneity and poor prognosis, TNBC management should not rely on a single therapeutic strategy. Instead, a multi-modality approach—integrating systemic chemotherapy, targeted therapies based on molecular profiling, and immunotherapy when appropriate—offers the best potential for improved outcomes. Equally important is the role of a MDT, which ensures that treatment planning is collaborative, evidence-based, and tailored to each patient's specific clinical and molecular characteristics. Strengthening MDT implementation, especially in resource-limited settings, is essential to bridging gaps in care and enhancing survival and quality of life for TNBC patients.

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Conflict of Interests

The author declares no conflict of interest.

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