Breast Cancer: Targets and Therapy

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REVIEW

Triple-Negative Breast Cancer on the Rise: Breakthroughs and Beyond

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Abstract: Triple-negative breast cancer (TNBC) represents a particularly aggressive and heterogeneous subtype of breast cancer, associated with poor prognosis and limited treatment options. This review delves into the rising incidence of TNBC, particularly among younger women, and explores the significant demographic disparities that contribute to variations in incidence, treatment access and survival outcomes. We provide a discussion of TNBC's molecular and genetic landscape, including key pathways revolving around TP53, BRCA1/2 mutations, and PI3K/AKT signaling, which have informed the development of targeted therapies. Recent practice-changing studies are highlighted, which have resulted in the integration of immune checkpoint inhibitors in both early-stage and metastatic settings, the application of PARP inhibitors for BRCA-mutated TNBC and the introduction of antibody-drug conjugates as valuable new therapeutic options. We also review the role of neoadjuvant chemotherapy, novel biomarkers such as tumor-infiltrating lymphocytes, and advancements in diagnostic tools, including machine learning-based imaging and spatial transcriptomics, which are all driving shifts towards personalized approaches. This review synthesizes emerging research and major changes in clinical practice to provide a concise overview of the recent innovations and upcoming trends in TNBC diagnosis and therapy.

Keywords: TNBC, oncology, diagnosis, therapeutics, medicine, genomics, immunotherapy

Introduction

Breast cancer remains one of the most common malignancies affecting women worldwide, representing a major portion of cancer-related morbidity and mortality.[1] Among the various subtypes, triple negative breast cancer (TNBC) stands out due to its aggressive behavior and poor prognosis. The American Society of Clinical Oncology and College of American Pathologists guidelines define TNBC as cancers where estrogen receptor (ER) and progesterone receptor (PR) are less than 1% by immunohistochemistry (IHC), and human epidermal growth factor receptor 2 (HER2) is either 0 to 1+ by IHC, or IHC 2+ with negative fluorescence in situ hybridization (FISH).[2,3] These cancers represent approximately 10–15% of all breast cancers.[4] Localized or early-stage cancers of all subtypes can be approached with curative intent by surgical resection and postoperative radiation if lumpectomy is performed, typically followed by systemic therapy. Metastatic breast cancer is treated with systemic therapy according to subtype, with the goal of preventing further growth or spread. Unlike other subtypes that can benefit from hormonal or HER2-directed therapies, TNBC lacks these specific targets, which for many years made conventional chemotherapy regimens the only practical treatment options. This aggressive subtype is associated with lower rates of cure and poorer overall survival compared to ER/PR-positive or HER2-positive breast cancers.[5,6] The heterogeneity of TNBC also contributes to its complexity, with varying molecular subtypes influencing prognosis and treatment response.[7,8] Advancements in the understanding of TNBC's unique biology have brought about promising new treatment strategies. Molecular profiling has revealed distinct subtypes within TNBC, opening opportunities for more personalized approaches.[9] Targeted therapies and immunotherapies have in recent years emerged as practice-changing avenues, offering new hope for patients with this daunting subtype. This review will explore the genomic and epidemiologic landscapes of TNBC, examine recent breakthroughs, highlight disparities in incidence and treatment outcomes and discuss future directions in research and clinical practice.

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Rising Incidence of TNBC

Despite improvements in rates of breast cancer survival, recent epidemiologic evidence points to a concerning increase in the incidence of multiple forms of breast cancer, including TNBC. This recent surge is notable among younger women, reflecting broader trends in cancer incidence in adolescents and young adults.[10–14] Studies highlight that women born after 1980 have higher rates of breast cancer, and that a higher proportion of these represent TNBC, compared to those born before 1950.[15,16] TNBC thus constitutes a larger proportion of breast cancers among younger women as compared to other age groups, emphasizing the need for targeted prevention and consideration of alternative early detection strategies in this demographic. International trends also show a rise in breast cancer among adolescents and young adults worldwide.[12,17–20]

Genotypic Associations and Racial Disparities

Genetic and molecular heterogeneity of TNBC present major challenges for suitable therapeutics. Genomic studies have identified several key mutations and pathways associated with TNBC, including alterations in TP53, BRCA1 and BRCA2 genes, as well as cellular pathways including PI3K/AKT, MYC and DNA repair mechanisms.[21–24] These genetic insights have fueled the development of targeted therapies and personalized approaches that have reached clinical practice and remain under investigation in clinical trials, as discussed below. A particularly striking aspect of TNBC is that significant racial and ethnic disparities exist in its incidence and outcomes. Black women are disproportionately affected by TNBC, exhibiting incidence rates nearly double that of White counterparts.[4] This disparity is thought to be driven by a complex interplay of genetic, socioeconomic and healthcare access factors. Genetic studies have revealed that certain mutations, such as those in the BRCA1 gene are more prevalent in Black women.[24] Another recent study revealed a distinct DNA methylation pattern present in Black women diagnosed before age 50, suggesting a distinct epigenetic profile among this group.[25] Regardless of these genetic factors, a robust body of work underscores that Black women experience higher breast cancer mortality rates due to later stage diagnosis, limited access to adequate screening, and financial barriers to completing optimal treatment.[26–33] Consequently, survival rates are lower among Black women at every stage and every breast cancer subtype as compared to White women. Addressing these gaps is a critical health priority that demands urgent multidisciplinary advocacy and action. The medical and scientific communities must extend opportunities for patient education and engagement, facilitate accessible screening for all, and actively involve minoritized populations in medical research studies, and support the inclusion of specialized race-congruent staff at all levels.[34]

Therapeutic Advances in Early-Stage TNBC

Remarkable progress has been made in the management of early-stage TNBC with the addition of neoadjuvant chemotherapy and immunotherapy. Neoadjuvant therapy, which is administered before surgical resection, has become a cornerstone in the treatment of this aggressive subtype. This approach not only helps reduce tumor size, making surgery more effective, but also provides an early indication of how the tumor responds to systemic therapy, which is crucial for tailoring subsequent treatment strategies. Neoadjuvant chemotherapy has become a standard treatment pathway in eligible patients with triple-negative tumors that measure 2 cm or greater or involve lymph nodes, and can also be employed for early HER2-positive and advanced ER/PR-positive tumors.

The advent of immune checkpoint inhibitors marked a major breakthrough in the treatment of early-stage TNBC. The Phase 3 KEYNOTE-522 trial assessed the efficacy of pembrolizumab, a programmed death-1 (PD-1) inhibitor, versus placebo in combination with neoadjuvant chemotherapy. This trial showed that addition of neoadjuvant and adjuvant pembrolizumab to sequential neoadjuvant chemotherapy significantly improved pathological complete response (pCR) rates (64.8 vs 51.2%).[35] This also yielded the benefit of avoiding morbid complete axillary lymph node dissections in more patients. Subsequent analysis also demonstrated benefits in 3-year event-free survival (EFS, 84.5 vs 76.8%) and 5-year overall survival (OS, 86.6 vs 81.7%).[36] This regimen has been widely accepted into clinical practice with follow-up studies generally supporting its use in this setting.[37–39] Some groups have observed significant limitations in implementing this regimen into practice, often related to significant immune toxicity or disparities in access to care.[37–43] The ongoing phase 3

OptimICE-PCR trial aims to assess whether 1 year of adjuvant pembrolizumab significantly influences outcomes after obtaining a pCR, and this may help avoid unneeded exposure to immunotherapy in this group.[44] Patients with residual disease after neoadjuvant therapy and surgery can continue on 6 to 8 cycles of adjuvant capecitabine, based on results of the CREATE-X trial, which found PFS and OS benefits over control in patients who did not achieve a pCR after neoadjuvant chemotherapy.[45] These patients are often offered to complete 1 year of pembrolizumab concurrently with capecitabine, though data are limited regarding combined treatment.

Targeted therapy has also made a recent stride in the treatment of early-stage TNBC. The phase 3 OlympiA trial randomized patients with HER2-negative early breast cancer and BRCA1 or BRCA2 germline pathogenic variants to receive adjuvant olaparib.[46] Treatment with the poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor, which targets defective homologous recombination repair of DNA damage, resulted in an increase in invasive disease-free survival of 85.9 vs 77.1%. The Phase 2–3 PARTNER trial later found no significant difference in pCR, EFS or OS in TNBC patients with wildtype germline BRCA1 and BRCA2 randomized to receive neoadjuvant olaparib or placebo in addition to chemoimmunotherapy.[47] Results for the germline mutated BRCA1/2 cohort are still pending.

Surgical Management in Early-Stage and Recurrent TNBC

Surgical strategies for triple-negative breast cancer (TNBC) are increasingly guided by tumor biology, treatment response, and recurrence patterns. Evidence supports that breast-conserving surgery (BCS), when combined with adjuvant radiotherapy, is a safe and effective option for many patients with TNBC. A meta-analysis involving over 19,000 patients demonstrated that BCS with radiotherapy provides comparable or better outcomes than mastectomy, with significantly lower odds of locoregional recurrence (LRR), distant metastasis (DM), and all-cause mortality.[48] Notably, patients with smaller tumors were more likely to undergo BCS, highlighting the importance of careful patient selection at this stage. Similarly, a retrospective study found that BCS with radiotherapy achieved oncological outcomes equivalent to mastectomy across various tumor and nodal risk subclasses, even in cases with larger tumors where oncoplastic techniques were utilized to optimize local control.[49] Emerging work has also explored alternatives to traditional surgical approaches. A phase 2 trial evaluated the omission of surgery in patients achieving a pathological complete response (pCR) to neoadjuvant systemic therapy, confirmed by vacuum-assisted core biopsy. Among the 50 enrolled patients (42% with TNBC), no ipsilateral breast tumor recurrences were observed in the 31 patients who achieved pCR and thus received radiotherapy alone.[50] In cases of ipsilateral breast cancer recurrence (IBCR), salvage mastectomy has traditionally been the standard approach. However, a recent retrospective study indicates that a second BCS may yield better distant disease-free survival (DDFS), OS, and breast cancer-specific survival (BCSS) compared to mastectomy for patients with small recurrent TNBC tumors.[51] These results are largely in line with a systematic review including patients with various breast cancer subtypes, which demonstrated that repeat BCS for IBCR is associated with a higher rate of second local recurrence compared to salvage mastectomy but offers a small overall survival benefit.[52] Together these studies all support the expanding role of BCS in TNBC and highlight the importance of careful patient selection, with tumor biology and response to prior treatment serving as critical determinants of the surgical approach.

Metastatic TNBC

In patients who experience a recurrence of their cancer after surgery/radiation or distant spread is noted at diagnosis, single-agent chemotherapy regimens incorporating anthracyclines or taxanes have been the mainstay of first-line therapy for many years. Incorporation of immune checkpoint inhibitors as initial treatment for metastatic TNBC came with results of KEYNOTE-355. This phase 3 trial found an overall survival benefit with addition of pembrolizumab to chemotherapy for patients with PD-L1 combined positive score (CPS) of 10 or greater, whereas the benefit was not seen for tumors with lower PD-L1 expression.[53] This strategy and PD-L1 testing has now become standard practice as first-line therapy for metastatic TNBC. Pembrolizumab monotherapy did not show a statistically significant improvement in metastatic TNBC outcomes over single-agent chemotherapy in the phase 3 KEYNOTE-119 trial.[54] In cases where PD-L1 CPS is less than 10 with a germline BRCA1/2 mutation, PARP inhibitors olaparib and talazoparib have shown benefits in progression-free survival and can be recommended as first-line therapy.[55,56]

The other notable advance in this setting came with the antibody-drug conjugate sacituzumab govitecan, which was studied in the phase 3 ASCENT trial. This agent is composed of an antibody targeting trophoblast cell surface antigen (TROP)2 coupled to

the irinotecan active metabolite SN-38, essentially facilitating targeted chemotherapy delivery.[57] TROP2 is a protein present in high levels in various cancers, including over 90% of breast cancer cells. Delivery of the cell-permeable drug SN-38 has also been shown to elicit antitumor effects on neighboring tumor cells through a process termed bystander effect. Similarly, the phase 3 DESTINY-Breast04 trial advanced trastuzumab deruxtecan as another second-line option for patients with triple-negative HER2-low disease.[58] Unfortunately, despite these advances, survival outcomes remain quite limited for metastatic disease and further investigative efforts are needed for this vulnerable population.

Emerging Diagnostics and Future Directions

Preclinical and clinical phase investigations continue to identify potential new avenues to diagnose, treat and predict response to therapy in TNBC. Imaging tools play a critical role in the initial detection of cancer and ongoing refinement in modalities, including optimal screening and clinical course prediction, will be essential to maximize benefit to the most patients. Ultrasound, magnetic resonance imaging (MRI) and positron emission tomography (PET) are the most widely employed imaging modalities in breast cancer diagnosis, and significant interest has developed in understanding features of TNBC as an adjunct to traditional pathologic analysis or even independently.[59] With recent advances in machine learning algorithms and applicability, these models are more commonly being applied to provide highly accurate predictions of outcomes such as likelihood of pCR and are likely to provide significant insights in the realms of TNBC and oncology at large.[60–62]

The notion and potential of tumor-infiltrating lymphocytes (TILs) in various cancers have been postulated for several years, however their applicability as a prognostic or therapeutic has been unclear. Retrospective studies have recently provided evidence that TIL abundance can predict overall survival in early-stage TNBC.[63,64] Similarly, multiple preclinical and early-stage clinical investigations are underway studying the suitability of various forms of intratumoral immunotherapy, including viral vector-based, antibodies or innate immune agonists.[65] Technical progress in single cell RNA sequencing and spatial transcriptomics have also enormously expanded our ability to visualize and probe gene expression shifts in fascinating multi-dimensional representations, and gain mechanistic understanding behind treatment response or unresponsiveness.[66,67] These studies will propel oncologic diagnosis and treatment towards a much needed, highly personalized approach for patients with TNBC. Developments in molecular profiling and gene signature assays can also provide indications of likely tumor trajectories and responses to therapy.[68,69] Likewise, deeper basic science interrogations of the genomic and epigenomic landscapes of various cancers including TNBC and viral infections have dissected intricacies of chromosomal instability, DNA damage sensing and interferon signaling, which may provide explanations for responsiveness to immunotherapy and other new lines of treatment.[70–74]

Finally, the following phase 2 trials modeled as components of I-SPY2.2 engaged a novel neoadjuvant sequential therapy platform, previously employed in I-SPY2,[75] as a means to efficiently identify therapies likely to succeed in phase 3 trials.[76] Randomization was stratified into 8 subtypes, defined by receptor status and a 70-gene signature based on a commercially available assay. The trials evaluated efficacy of datopotamab-deruxtecan (Dato-DXd), an antibody-drug conjugate targeting TROP2, both alone[76] and in combination with durvalumab,[77] a PD-L1 inhibitor, in patients with high-risk stage 2/3 breast cancer. The results showed that Dato-DXd alone did not meet the prespecified criteria for advancing to phase 3 trials in any breast cancer subtype, but the combination treatment graduated in the "immune-positive" subtype. Dato-DXd is now recommended as an option for second-line treatment of patients with metastatic ER/PR-positive HER2-negative breast cancer based on results of the TROPION-Breast01 trial but has not yet received an indication in TNBC.[78] Additional trials are ongoing to assess the use of Dato-DXd in locally recurrent inoperable or metastatic TNBC (TROPION-Breast02), in conjunction with durvalumab for residual TNBC after neoadjuvant therapy at time of surgery (TROPION-Breast03) and as neoadjuvant therapy for TNBC in conjunction with durvalumab (TROPION-Breast04).[79–81] Perhaps most notably, the I-SPY2.2 trial design incorporates up to 3 blocks of distinct treatments, allowing real-time adjustments based on MRI and biopsy results to optimize patient outcomes and minimize exposure to ineffective agents.[82]

Conclusion

The landscape of TNBC is rapidly evolving with significant advancements in both our understanding of its molecular underpinnings and the development of novel therapeutic strategies. Integration of immune checkpoint inhibitors and targeted therapies has opened new avenues for treatment, offering hope for improved outcomes in this challenging subtype. However, the persistence of health disparities and real-world challenges in treatment administration underscore

the need for a more personalized and equitable approach to care. Future molecular insights, such as deeper understanding of tumor heterogeneity, dynamic genomic changes and immune microenvironment interactions, have the potential to revolutionize TNBC treatment algorithms. Ongoing research into mechanisms of immune interactions with the use of single-cell sequencing, epigenomic profiling and spatial transcriptomics could enable further therapeutic personalization and may result in development of novel immune cell therapies applicable across a variety of cancer types. Continued biomedical research and clinical trials are essential to refine these strategies, enhance diagnostic accuracy, and ultimately improve survival rates for all patients with TNBC. The future of TNBC management depends on the integration of cutting-edge science, precision oncology approaches and a commitment to eliminating health inequities.

Disclosure

The authors report no conflicts of interest in this work.

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