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HER2-Low Breast Cancer: Clinicopathologic Landscape, Prognostic Controversies, and Therapeutic Advances

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Abstract: Breast cancer is a complex heterogeneous disease and remains one of the common malignant tumors threatening women's health worldwide. Currently, precision therapy guided by molecular subtyping has significantly improved the prognosis of breast cancer patients. Human epidermal growth factor receptor 2 (HER2), as a critical therapeutic target for breast cancer, has long been classified into HER2-positive and HER2-negative subtypes based on expression levels [1]. With the advancement of clinical research, the classification of HER2 expression has evolved. The DESTINY-Breast04 (DB04) study was the first phase III study to demonstrate that patients with HER2-low expression derive significant survival benefit from HER2-targeted antibody-drug conjugates (ADCs) [2], thereby establishing HER2-low expression breast cancer as a novel therapeutic subtype. Despite this therapeutic breakthrough, whether HER2-low breast cancer represents an independent molecular entity or a distinct clinical subtype remains controversial. Furthermore, its prognostic implications are still debated. This review summarizes the epidemiological characteristics, biological features, heterogeneity, survival outcomes, therapeutic advances, and resistance mechanisms associated with HER2-low breast cancer, aiming to provide evidence to refine clinical recognition and optimize management strategies.

Keywords: HER2-low breast cancer; Molecular subtype; Antibody-drug conjugates (ADCs)

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1. Introduction

According to reports, the global incidence of breast cancer is on the rise, making it the most prevalent malignant tumor affecting women's health worldwide [3]. Human epidermal growth factor receptor 2 (HER2), a transmembrane tyrosine kinase receptor encoded by the ERBB2 gene, is highly associated with the aggressive biological behavior and poor prognosis of breast cancer, serving as one of the key therapeutic targets. The American Society of Clinical Oncology/Pathologists (ASCO/CAP) guidelines classify HER2 expression into

negative and positive categories based on immunohistochemistry (IHC) and in situ hybridization (ISH) results. HER2-negative is defined as IHC 0, 1+, or 2+ with negative ISH, while HER2-positive is defined as IHC 3+ or 2+ with positive ISH. Among all breast cancer patients, nearly 15% exhibit HER2-positive expression. These overexpressed HER2 proteins form dimers and participate in tumor cell survival, proliferation, invasion, and metastasis by activating signaling pathways such as PI3K/Akt [4]. Consequently, HER2-positive breast cancer typically exhibits more aggressive biological characteristics and is associated with higher tumor grade and poorer prognosis, particularly in untreated cases where patients face a higher risk of recurrence. In recent years, HER2-targeted drugs, including monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs), have markedly improved the prognosis of HER2-positive breast cancer patients by inhibiting HER2 signaling pathways to halt tumor cell growth and metastasis. However, these conventional targeted therapies show no benefit in tumors with low HER2 expression, which account for 30–60% of cases[5]. With advancing research, the DESTINY-Breast04 trial demonstrated that ADC therapy significantly improves survival in patients with HER2-low metastatic breast cancer, thereby challenging the traditional binary classification of HER2 status and making HER2-low expression a new focal point of discussion. Nevertheless, due to the lack of reliable pathological interpretation of HER2-low expression and comprehensive multi-omics data analysis, whether HER2-low breast cancer constitutes a distinct molecular subtype remains unresolved.

2. Detection of HER2 expression levels

HER2 testing for breast cancer was initially used solely to predict patient prognosis. In 1998, trastuzumab, the first clinically available HER2-targeting monoclonal antibody drug, was introduced, leading to the demand for standardized companion diagnostics to assess HER2 status. To identify patients who might benefit from novel targeted therapies combined with chemotherapy, ASCO/CAP issued the first HER2 testing guidelines for breast cancer in 2007. HER2 testing in breast cancer primarily evaluates HER2 (ERBB2) mutations, HER2 protein expression, and gene amplification. IHC is used to detect HER2 protein expression levels, while ISH is employed to assess HER2 gene amplification. If HER2 IHC expression is uncertain, a combined IHC and ISH strategy is recommended [6]. The 2024 HER2 Testing Guidelines recommend that all patients with invasive breast cancer should undergo HER2 status testing, with HER2 classified as HER2-positive, HER2-negative, or HER2-low expression based on IHC and in situ hybridization results. The specific interpretation criteria are as follows: IHC 0 indicates no staining or ≤ 10% faint incomplete membrane staining; IHC 1+ indicates > 10% faint incomplete staining; IHC 2+ indicates > 10% weak-to-moderate complete membrane staining or ≤ 10% strong complete staining; and IHC 3+ indicates > 10% strong uniform membrane staining. HER2-positive cases include HER2 IHC 3+ or IHC 2+/ISH amplification, while HER2-negative cases include HER2 IHC 0, IHC 1+, or IHC 2+/ISH non-amplification [7].

Based on the results of the DESTINY Breast-04 clinical trial, “HER2 low expression” is currently defined as HER2 IHC 1+ or IHC 2+/ISH non-amplification. With the expanding indications for HER2-targeted ADCs, the clinical recognition of HER2 low expression (IHC 1+ or IHC 2+/ISH-) has gained increasing importance. Traditional detection systems primarily relying on IHC interpretation face new challenges, particularly in distinguishing HER2 low expression from negative cases. IHC detection methods inherently have limitations such as insufficient dynamic range and high subjectivity in scoring, leading to suboptimal identification of low-level HER2 expression. Currently, several emerging methods aimed at overcoming the limitations of existing

detection technologies and scoring systems are under development. Emerging techniques such as quantitative immunofluorescence (QIF) and artificial intelligence-based image analysis have demonstrated potential in enhancing the objectivity, accuracy, and standardization of HER2 detection. In the future, HER2 detection is expected to evolve toward greater standardization, quantification, and multimodal integration, laying the foundation for more precise identification of patients with varying HER2 expression levels and optimizing the application of next-generation anti-HER2 targeted therapy strategies.

3. Clinical-pathological features of HER2-low tumors

Currently, there is no consensus on the clinical-pathological characteristics of HER2-low breast cancer. A meta-analysis of 23 retrospective studies showed that HER2-low expression was more common than HER2-zero expression, particularly among the hormone receptor-positive (HR-positive) patients, where HER2-low accounted for 67.5% of cases. In contrast, only 48.6% of HR-negative patients exhibited HER2-low expression [8]. Two earlier studies on the molecular profile of HER2-low expression breast cancer reached similar conclusions. Schettini et al. and Agostinetto et al. employed the PAM50 assay to investigate the molecular features of HER2-low expression breast cancer. The results demonstrated that HER2-low expression breast cancer represents a heterogeneous subgroup, primarily composed of luminal A (50.8–56.9%) and luminal B (22.8–28.8%) subtypes, while HER2-enriched (3.5–3.6%) and basal-like (13.3–17.7%) subtypes were relatively rare [9-10]. Zhang et al. utilized MammaPrint and Blueprint detection technologies to investigate the genomic configuration of 281 cases of HER2-low breast cancer. Their study revealed a similar distribution of molecular subtypes, with luminal A accounting for 65.5%, luminal B for 28.8%, HER2-enriched for 1.1%, and basal-like for 4.6%. These molecular profiling results collectively indicate that the majority of HER2-low breast cancers (79-94%) exhibit luminal gene signatures[11]. Previous studies have demonstrated that HER2-low patients often exhibit more favorable clinical and pathological features. Denkert et al. pooled data from 2,310 patients and reported that HER2-low tumors were associated with lower Ki-67, lower histological grade, lower TP53 mutation rates, and reduced pCR after neoadjuvant chemotherapy compared with HER2-zero tumors [12]. A nationwide Korean cohort of 30,491 patients also found that HER2-low tumors were more frequent in HR-positive disease and were associated with lower T stage, lower Ki-67, and fewer lymph node metastases [13]. Zhou et al. similarly reported higher HR positivity and lower proliferation in HER2-low cases [14]. However, some studies showed no statistically significant differences in clinical-pathological features between HER2-low and HER2-zero patients. de Moura et al. conducted a comparative analysis of 49 HER2-Low patients and 264 HER2-Zero patients, finding similar baseline characteristics between the two groups [15]. Current research on the biological characteristics of HER2 low expression has not reached consensus, and the reasons for these discrepancies may be related to differences in HER2 interpretation among various research centers. There is an urgent need for more precise interpretation methods to accurately identify populations with HER2 low expression. Additionally, tumor heterogeneity may also contribute to the inconsistency of results.

HER2 heterogeneity refers to the variability in HER2 expression or amplification levels within the same tumor or across different stages of the same patient, encompassing both intra-tumor and inter-tumor heterogeneity. According to relevant literature, HER2 expression heterogeneity can be observed in up to 34% of breast cancers [16-19], with HER2-low expression breast cancer exhibiting significantly higher frequencies of HER2 heterogeneity compared to HER2-zero or HER2-positive patients [20]. The presence of HER2 intratumoral heterogeneity may lead to

inaccurate HER2 status assessment and inappropriate treatment strategies [21]. Studies have found that HER2 intratumoral heterogeneity may result in ineffective binding or uptake of anti-HER2 drugs by tumor cells [22], thereby reducing patient response to anti-HER2 targeted therapy and adversely affecting prognosis. Multiple studies indicate that tumors with HER2 heterogeneity are often associated with larger tumor size, higher grade, and lymph node positivity, all of which are biological markers predictive of poor prognosis [23-25]. Therefore, accurate evaluation and dynamic monitoring of HER2 status in breast cancer are crucial for guiding anti-HER2 targeted therapy and optimizing treatment efficacy, aiming to maximize the identification of patients suitable for novel antibody-drug conjugate therapy and prevent the loss of potential targeted treatment opportunities.

4. Survival outcomes of HER2-low breast cancer

Current studies on the prognosis of HER2-low breast cancer have yielded conflicting results. In a multicenter cohort study involving 28,280 patients with stage I-III breast cancer, Tan et al. reported that patients with HER2-low expression had significantly better recurrence-free survival (RFS) and overall survival (OS) than those with HER2-zero expression, regardless of hormone receptor status. These findings support further differentiation between HER2-low and HER2-zero breast cancer [26]. Kang et al. retrospectively analyzed 1,572 patients with stage I-III breast cancer who received neoadjuvant chemotherapy, including 818 HER2-zero and 754 HER2-low expression patients. The results showed that the HER2-low group had a higher proportion of hormone receptor-positive patients (81% vs. 56%) and a higher rate of pathological complete response in the HER2-zero group. Survival data analysis revealed that the HER2-low cohort had superior 5-year DFS and OS. However, this difference lost statistical significance after stratification and adjustment for hormone receptor status [27]. Based on over 700,000 cases of HER2-low expression breast cancer from the National Cancer Database (NCDB), Pfeiffer et al. conducted a large-scale retrospective study, which found that the proportion of patients achieving pathological complete response (pCR) was 23.6% in HER2-negative patients, compared to only 16.3% in HER2-low expression patients. Moreover, HER2-low expression was associated with improved overall survival (OS), particularly evident in HR-positive cancers at stages III-IV [28]. However, some studies have reported that the prognosis of HER2-low expression and zero expression patients is comparable, with no statistically significant difference. In a retrospective analysis of 1,111 HER2-negative breast cancer patients, De Nonneville et al. found no significant association between HER2 status and the rate of pathological complete response (pCR) or survival outcomes [29]. Tarantino et al. included 5,235 HER2-negative breast cancer patients at stages I-III and analyzed the survival data of HER2-low expression and HER2-zero expression patients, revealing no significant difference in prognosis between HER2-low expression and HER2-zero expression breast cancer patients [30].

The inconsistency in these research conclusions may be attributed to the interaction of multiple factors, including the intrinsic biological characteristics of tumors, differences in treatment options, and methodological variations. Firstly, HER2-low breast cancer exhibits high heterogeneity, a biological feature that significantly contributes to prognostic disparities. In HR-positive tumors, HER2 low expression is often associated with luminal molecular signatures, and the relatively favorable prognosis observed is largely attributed to the dominant role of the ER signaling pathway and its lower proliferative activity, rather than the level of HER2 expression itself. Conversely, in HR-negative patients, HER2 low expression frequently coexists with basal-like characteristics, but its biological behavior may differ from that of classic triple-negative breast cancer due to a typical driver gene profile or differentiation status, leading to variations in survival outcomes across studies. Secondly, the

choice of treatment options is another factor contributing to these differences. In recent years, the widespread use of ADC drugs has reshaped the prognosis of HER2-low patients. However, prior to the widespread adoption of ADCs, the primary treatment for HER2-low patients relied on conventional chemotherapy or endocrine therapy. Consequently, previous research conclusions primarily reflected the natural history of HER2-low status during the era of chemotherapy or endocrine therapy, while current and future studies essentially provide "predictive responses" to novel targeted therapies. The changing therapeutic landscape has resulted in a lack of comparability between historical data and contemporary observations. Finally, the inherent selection bias in retrospective study designs, subjective differences in HER2 immunohistochemical interpretation across research centers, and inadequate adjustment for strong confounding factors such as HR status and disease stage in statistical models collectively contributed to biased and inconsistent assessments of the true prognostic effect of HER2 low expression. Therefore, future large-scale, multicenter prospective studies are required to validate the prognostic impact of HER2 low expression in breast cancer.

5. Treatment advances

HER2 is a critical target for targeted therapy in breast cancer. Currently approved HER2-targeted therapies primarily include: monoclonal antibodies (e.g., trastuzumab and pertuzumab), tyrosine kinase inhibitors (e.g., lapatinib, nintedanib, pirrotinib, and tucatinib), and ADCs (e.g., emtrizumab and drotuzumab) [31-33]. These anti-HER2 therapeutics play a pivotal role in both early adjuvant therapy and advanced salvage therapy for HER2-overexpressing breast cancer patients. However, HER2-low expression breast cancer patients often fail to benefit from conventional targeted therapies due to insufficient receptor expression [34]. The publication of favorable clinical data for novel ADCs has significantly improved the prognosis of HER2-low expression breast cancer patients [2].

Antibody-drug conjugates (ADCs) consist of three key components: a highly specific and affinity-rich antibody, a highly stable linker, and a potent small-molecule cytotoxic drug. After entering the bloodstream, the antibody component recognizes the target and binds to tumor cells that express the surface antigen. The ADC antigen complex is then internalized into the tumor cells via endocytosis. Lysosomal degradation releases the cytotoxic drug, which either damages DNA or inhibits tumor cell division, thereby killing the tumor cells [35]. Thus, ADCs combine the advantages of highly specific monoclonal antibody targeting with the antitumor activity of small-molecule cytotoxic drugs, reducing the systemic toxicity of cytotoxic drugs and enhancing antitumor efficacy. Additionally, some ADCs exhibit a bystander effect. The bystander effect refers to the situation where the cytotoxic drug is released from the target cell after internalization and degradation, or is effectively killed by tumor cells in the extracellular space, even though these cells may or may not express the target antigen of the ADC [36-37].

Trastuzumab deruxtecan (T-DXd) is the first antibody-drug conjugate (ADC) to demonstrate a survival benefit in patients with HER2-low expression breast cancer. It is formed by conjugating trastuzumab with a DNA topoisomerase I inhibitor via a stable linker, exhibiting a drug-to-antibody ratio (DAR) of approximately 8, which enables delivery of a higher payload to enhance antitumor activity while reducing off-target toxicity [38]. DESTINY-Breast04 was a study investigating the efficacy of T-DXd in the treatment of advanced HER2-low breast cancer. The results demonstrated that in the HR-positive population, the median progression-free survival (mPFS) in the T-DXd group was significantly superior to that in the physician-selected therapy (TPC) group (10.1 vs. 5.4 months, HR = 0.51, $p < 0.001$), and the overall survival (OS) was prolonged by 6.4 months (23.9 vs. 17.5

months, HR = 0.64, $p < 0.003$). In the overall population, the T-DXd group showed consistent benefits in both mPFS (9.9 vs. 5.1 months, HR = 0.50, $p < 0.001$) and OS (23.4 vs. 16.8 months, HR = 0.64, $p = 0.001$) [2].

Disitamab Vedotin (RC48) is a domestically developed HER2-targeted ADC, composed of a fully humanized anti-HER2 antibody, a VC linker, and the cytotoxic agent MMAE (monomethyl aurostatine, a microtubule inhibitor). With a DAR of 4, RC48 exhibits bystander effects that can kill adjacent cancer cells, thereby enhancing antitumor efficacy compared to conventional chemotherapy. Analysis from the C001 CANCER and C003 CANCER studies demonstrated that RC48 showed promising efficacy in treating advanced breast cancer with low HER2 expression, including an 81.8% disease control rate and a median progression-free survival (PFS) of 5.1 months [39-40].

Currently, several HER2-targeted ADC drugs are undergoing clinical trials to evaluate their efficacy and safety in patients with locally advanced or metastatic breast cancer exhibiting low HER2 expression, including FS-150211, MRG00212, and SYD98513. Additionally, clinical trials for other therapies such as bispecific antibodies and breast cancer vaccines are also being conducted [41], which are expected to provide more treatment options for HER2-low expression patients in the future.

6. Mechanisms of resistance to ADC

As antibody–drug conjugates (ADCs) rapidly reshape the therapeutic landscape of HER2-low breast cancer, resistance has increasingly emerged as a major determinant of long-term efficacy and treatment sequencing. Unlike conventional monoclonal antibodies, the activity of ADCs depends not only on antigen expression levels but also on multiple interconnected processes, including antibody binding and internalization efficiency, linker stability, intracellular drug release, payload target engagement, and the tumor microenvironment. Consequently, resistance mechanisms to ADCs are complex and multifactorial [2,30,42].

At the antigen level, downregulation of HER2 expression represents one of the most direct mechanisms of resistance. Several studies have observed that, during ADC therapy, tumor cells may reduce HER2 protein expression through epigenetic regulation or transcriptional reprogramming, thereby decreasing available binding sites and limiting ADC internalization [9,12,42]. Given that HER2-low tumors already exhibit relatively low antigen density, further reduction in expression may lead to diminished therapeutic efficacy. Notably, these changes are not necessarily driven by genomic alterations but may instead reflect adaptive phenotypic plasticity under therapeutic pressure. This underscores the importance of dynamic reassessment of HER2 status during disease progression [9,12].

With respect to payload-related resistance, the cytotoxic activity of ADCs depends on the specific chemotherapeutic agent they deliver. For example, T-DXd utilizes a topoisomerase I inhibitor as its payload. Tumor cells may develop resistance through upregulation of drug efflux transporters, enhancement of DNA damage repair capacity, or alterations in topoisomerase I expression [43-44]. In addition, dysfunction of intracellular lysosomal processing may impair linker cleavage and payload release, thereby reducing cytotoxic activity. Similar to conventional chemotherapy resistance, payload-related resistance is not HER2-specific but rather represents a broader adaptive response to cytotoxic stress. As a result, partial cross-resistance may occur among ADCs carrying similar payloads, posing challenges for sequential treatment strategies [43].

The role of the tumor microenvironment in ADC resistance has also gained increasing attention. Increased stromal density, abnormal vascular architecture, and elevated interstitial pressure may restrict ADC penetration and intratumoral distribution, thereby attenuating the bystander effect [45-46]. Moreover, the composition of immune

cell infiltrates and local inflammatory signaling may influence antibody-dependent cytotoxicity and intratumoral drug metabolism. Some studies suggest that an immunosuppressive microenvironment may reduce ADC efficacy, whereas modulation of the tumor microenvironment may enhance drug distribution and cellular uptake. These observations indicate that ADC resistance arises not from a single mechanism but from the combined effects of antigen modulation, payload-related resistance, and microenvironmental barriers [46–47].

Overall, resistance to ADC therapy in HER2-low breast cancer is dynamic and multifactorial. These mechanisms not only influence the efficacy of individual agents but also directly affect treatment sequencing and combination strategies. Future research should prioritize longitudinal monitoring of HER2 expression, elucidation of payload-specific resistance pathways, and exploration of microenvironment-targeted interventions in combination with ADCs, to enable early identification and proactive management of resistance.

7. Discussion

HER2-low expression constitutes a substantial population in breast cancer, and with the emergence of novel therapeutic approaches such as ADCs, its clinical significance and therapeutic value are gradually being elucidated. Some studies have demonstrated that patients with HER2-low expression can benefit from novel ADC-based therapies. These findings lay the groundwork for establishing HER2-low expression as a novel molecular subtype and underscore the importance of accurate identification of HER2-low expression patients. However, challenges remain in the detection and diagnosis of HER2-low expression, including inter-method variability, consistency issues in pathologist scoring, and standardization of AI applications. Future research should focus on further exploration of the molecular mechanisms underlying HER2-low expression and continuous improvement of HER2 detection technologies to more accurately delineate HER2-low and HER2-negative status, thereby advancing the investigation of HER2-low expression breast cancer.

Secondly, in clinical practice, the rational selection of ADCs and optimization of treatment sequences to achieve optimal outcomes also pose significant challenges. With the increasing accessibility of ADCs, research on their resistance mechanisms and safety management has become crucial. These challenges necessitate further exploration through high-quality real-world evidence, prospective studies, and translational medicine research to address key issues such as predicting treatment responses, managing treatment-related adverse events, and elucidating resistance mechanisms. Consequently, this also demands accelerated development of more precise HER2 detection and genotyping technologies, advancement of clinical trial designs based on molecular subtypes, and exploration of combination strategies between ADCs and other targeted therapies.

8. Conclusion

In conclusion, although HER2-low breast cancer is not currently recognized as an independent biological subtype, with the development of novel anti-HER2 therapeutic agents, HER2-low breast cancer patients have emerged as a therapeutic priority population. Future efforts should focus on further optimizing treatment strategies and exploring the analysis of relevant biomarkers to achieve more precise therapeutic outcomes.

Disclosure statement

The authors declare no conflict of interest.

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