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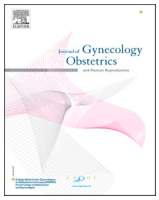

Original Article

The impact of the new histological classification of breast cancer with the introduction of HER 2 low status

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ABSTRACT

Background: Traditionally, breast cancer HER2 status was categorized simply as positive or negative, with a preference for the negative designation due to its more favorable implications. However, recent advancements in classification have introduced a HER2 low status (score 1+ and 2+ without amplification), which is now recognized in a significant proportion of breast cancer cases. This newly identified HER2 low status is currently under investigation for its potential as a positive prognostic marker, particularly in the context of antibody-drug conjugate therapies. This study offers an overview of the novel HER2 classification as applied to our center's patients, providing insights into prognostic factors and outcomes.

Methods: The study analyzed breast cancer patients managed at the university teaching hospital of Tours between 2000 and 2013. Tumors were reclassified according to the new histological classification including the Her2-low status.

Results: Our patient cohort was distributed into three distinct groups: HER2-low (37 %), HER2-negative (57 %) and HER2-positive (11 %). Notably, HER2-positive patients were on average younger (56.5 years) than those in the other groups, who averaged 60 and 61 years, respectively ($p = 0.003$). No significant disparities emerged concerning BMI, recurrence patterns (locoregional or distant), or time to recurrence across these groups. However, differences were observed in terms of tumor phenotype, with luminal A tumors being more prevalent in the HER2 low and negative groups, while the luminal B subtype was predominant in the HER2 positive group. Furthermore, HER2-positive patients exhibited a higher prevalence of negative hormone receptors (43 %), contrasting with 8 % in the HER2-low group and 15 % in the HER2-negative group.

Conclusion: Our study highlights differences in age and hormonal receptor status among HER2 status groups. The introduction of HER2-low classification opens the door to new treatment strategies, especially with antibody-drug combinations that use HER2 receptors to deliver drugs. Although significant differences in survival rates were not found, ongoing research is crucial to understand how this new classification affects patient parameters. Additionally, it is essential to consider individual factors like age and hormone receptor status when deciding on the best treatment approach.

Introduction

Breast cancer is the most common cancer in women with > 58,000 new cases diagnosed annually in France (according to INCa figures). The therapeutic arsenal is particularly broad, as breast cancers exhibit heterogeneity are in their anatomical and pathological characteristics as well as their prognostic factors. Currently, four major molecular types of breast tumors are classified: luminal A, luminal B, Her2-positive tumors, and triple-negative tumors. These classifications help tailor therapeutic approach, which may include surgery, hormone therapy, chemotherapy, and targeted therapy [1–5].

A critical histoprognostic factor is Her2 status characterized by the presence of the Her2 protein, an epidermal growth factor receptor essential role for cell growth, differentiation, and survival. This

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oncogene, located on chromosome 17, codes for a transmembrane tyrosine kinase receptor. Overexpression occurs in 10–15 % of tumors, making them as aggressive, and warranting targeted therapy with anti-Her 2 antibodies (Trastuzumab, Pertuzumab) as adjuvant or neo-adjuvant treatments to improve the prognosis. This status has been dichotomously defined since the late 1990s as either positive (over-expression) or negative (little or no expression). However, the ASCO's 2018 guidelines proposed a new classification: Her 2-positive, low, and negative. The HER2 status is considered positive when a score of 3+ or a 2+ score with positive FISH is found; low status corresponds to scores of 1+ score or 2+ score without amplification, and negative status is designated as 0 [5–9].

Recently introduced cytotoxic agents associated with anti-Her2 antibodies (such as Trastuzumab Emtansine (TDM-1) or Trastuzumab Deruxtecan (T-DX)) have shown considerable efficacy in breast cancers with low Her2 expression [10]. This new nomenclature may expand indications for targeted therapies when coupled with cytotoxic agents for patients with a Her2 low status, representing over half of breast cancer cases, and potentially improving prognoses [10–15].

The primary objective of this study is to evaluate the impact of the new Her2 low status in a cohort of patients treated for breast cancer.

Materials and methods

Study Design: This study constitutes a retrospective epidemiological analysis conducted at a single center, focusing on a cohort of patients who underwent breast cancer treatment from January 1, 2000, to December 31, 2013, at the University Hospital of Tours. The primary aim of our investigation is to assess the implications of the updated HER2 classification.

Inclusion Criteria: All adult patients who received treatment for breast cancer were eligible for inclusion in our study. The diagnosis of cancer was confirmed through pathological examination of surgical specimens.

Exclusion Criteria: Patients who did not undergo any surgical, diagnostic, or therapeutic procedures were excluded from the analysis.

Additionally, patients with pregnancy or a previous history of pelvic cancers were also not included.

Population Description: We assembled a cohort of adult patients treated for breast cancer at the University Hospital of Tours between January 1, 2000, and December 31, 2013. The cohort includes patients with confirmed breast cancer diagnoses, as validated by a pathological analysis of surgical specimens.

Data Collection: For each patient, we collected various data from their medical records including age, gender, type of tumor, hormone receptor status (positive or negative), HER2 status (0, 1+, 2+ amplified, 2+ non-amplified, 3+), Ki67, tumor phenotype (luminal A, luminal B, triple-negative), and recurrence status (locoregional: date at diagnosis, timing of recurrence or distant recurrence: Information regarding metastasis status (date at diagnosis, time to metastasis from the initial tumor, and site of metastasis - bone, visceral, brain) was also documented, along with the date of the last follow-up. Clinical and pathological data for each patient were meticulously retrieved from their medical records, entered into a computerized database, and anonymized to protect patient privacy. Our pathologist (FA) reviewed the tumor samples for HER2 status and tumor phenotypes.

Statistical Analyses: Statistical analyses were carried out using R 3.1.2 software, with the application of relevant packages including Hmisc, Design, and survival. Descriptive statistics summarized basic demographic and clinical characteristics. Continuous variables were presented with 95 % confidence intervals (CI), and categorical data were presented as proportions with percentages (n,%).

No ethics committee approval was deemed necessary for this study.

Results

Between January 1st, 2000, and December 31st, 2013, a total of 1436 patients with breast cancer were treated at the teaching hospital of Tours and enrolled in our study. The distribution of Her2 status within this patient cohort was as follows: Her2 0+ = 734 patients (51 %), Her2 1+ = 311 patients (21 %), Her2 2+ non-amplified = 223 patients (15 %), Her2 2+ amplified = 21 patients (0.06 %), and Her2 3+ = 147 patients (10 %).

This distribution closely aligned with the patterns reported in the existing literature [1,2,6,9]. A summary of the Her2 status distribution in the study population is presented in the table below (Table 1).

The total patient cohort was further categorized into three groups based on the new HER2 classification: HER2-negative (734 patients, 51 %), HER2-low (534 patients, 37 %), and HER2-positive (168 patients, 11 %), as presented in table 2.

The population characteristics are displayed on Table 3

Notably, patients within the Her2 positive group exhibited a younger average age (56.5 years) compared to those in the other groups, whose average ages was 60 and 61 years, respectively ($p = 0.003$).

No significant disparities were observed regarding BMI, recurrence patterns (both locoregional and distant), or time to recurrence among these groups. However, distinctions were noted in tumor phenotypes, with luminal A tumors more prevalent among the Her2 low and negative groups, while luminal B subtype were predominantly found in the Her2 positive group. Additionally, Her2 positive patients showed a higher prevalence of negative hormone receptors (43 %) compared to 8 % in the HER2-low group and 15 % in the HER2-negative group

Despite the HER2 status classifications, no significant differences were found in metastasis or recurrence risks among the different groups. Interestingly, the HER2-low group represented over one-third of the study population, raising pertinent questions about the need for novel treatment strategies for these patients, especially in light of improved outcomes without local or distant recurrence for many.

Discussion

In the present study, we observed notable differences in age and hormonal receptor status according to Her2 status among patients. The emergence of the Her2 low classification presents opportunities for advancements in therapeutic strategies and the utilization of antibody-drug conjugates that leverage Her2 receptors for targeted cytotoxic delivery, offering promising alternatives for patients diagnosed with breast cancer patients.

Cytotoxic agents, as a vital class of anti-cancer drugs, operate by targeting the DNA within cells, effectively inhibiting DNA replication and preventing transcription. Among these agents, topoisomerase inhibitors are particularly important in breast cancer treatment, often used in conjunction with Trastuzumab to enhance therapeutic outcomes. These inhibitors induce single or double-strand breaks in DNA, thereby impeding tumor growth and triggering cell apoptosis ([2,4–6,16–21]).

Recent advances in the form of antibody-drug conjugates, such as Trastuzumab Deruxtecan (T-DXd), have shown significant promise in targeting breast cancers with low HER2 expression. In a phase I trial conducted by Mallet et al. [11], involving patients with HER2-low status, a response rate of 37 % was observed, demonstrating substantial tumor reduction and a median duration of response of 10.4 months,

Table 1
Distribution of Her 2 status in our population.

Her2 0+	734 (51 %)
Her2 1+	311 (21 %)
Her2 2+ non-amplified	223 (15 %)
Her2 2+ amplified	21 (0,06 %)
Her2 3+	147 (10 %)
Total	1436 (100 %)

Table 2
Distribution of Her 2 status according to the new classification.

Her 2: low (1+ et 2+ non amplified)	534 (37 %)
Her 2: negative (0)	734 (51 %)
Her 2: positive (2+ amplified et 3+)	168 (11 %)
Total	1436 (100 %)

Table 3
Population characteristics.

	n	Her2 low	Her2 negative	Her2 positive	p
Age	1436	60 (49–70)	61 (51–70)	56,5 (46–68)	0.003
BMI kg/m2:	1371				0.38
- underweight		5 % (27)	3 % (24)	3 % [5]	
- normal		50 % (256)	46 % (323)	53 % (84)	
- overweight		27 % (140)	31 % (216)	26 % (41)	
- obesity		18 % (94)	19 % (132)	18 % (29)	
Hormone receptors:	1436				<0.001
- Positive		21 % (110)	12 % (91)	14 % (24)	
- Negative		8 % (44)	15 % (109)	43 % (72)	
Her:	1434				<0.001
- 0		99 % (526)	99 % (727)	5 % [8]	
- 0 and 1		0 % (0)	0 % [2]	0 % (0)	
- 1		1 % [8]	0 % [3]	95 % (160)	
Phenotype:	1436				<0.001
- Luminal a		63 % (336)	58 % (429)	5 % [9]	
- Luminal b		29 % (154)	27 % (196)	49 % (83)	
-Triple negative		8 % (42)	15 % (109)	0 % (0)	
Locoregional recurrence	1436	10 % (51)	10 % (77)	11 % [18]	0.83
Metastatic recurrence:	1422	13 % (71)	15 % (109)	21 % (35)	0.05
-Bone	1436	10 % (52)	10 % (76)	11 % [19]	0.83
-Visceral	1436	11 % (58)	12 % (88)	15 % (25)	0.37
-Brain	1435	3 % [15]	4 % (28)	7 % [12]	0.03
Time to recurrence	154	70 (24–121)	55 (26–121)	22 ([14]–69)	0.05

alongside an impressive disease control rate of 87 %. The trial highlighted relatively low toxicity, with manageable side effects primarily including gastrointestinal disturbances and rare instances of interstitial pneumonitis.

Ongoing phase II studies aim to elucidate the efficacy and safety of T-DXd further in patients with HER2-low breast cancer. For instance, the Unicancer DAISY study [7] is actively investigating the antitumor activity of Ds 8201a (an anti-HER2 antibody-drug conjugate) based on HER2 expression levels in metastatic breast cancer patients.

Conversely, inquiry into Pertuzumab in a phase II study targeting 72 metastatic patients with HER2-negative status yielded modest results. The findings demonstrated that only six patients exhibited significant responses [8], underscoring the complexities in managing HER2-low patients and the necessity for tailored treatment strategies.

Significant advancements have emerged from the DESTINY-Breast 04 phase III study, which assessed T-DXd's effectiveness compared to traditional chemotherapy in patients with HER2-low breast cancer. The study showed that T-DXd substantially improved progression-free survival (median 10.1 months) and overall survival (median 23.9 months) when compared to chemotherapy regimens [2,9,10]. Despite the impressive results, adverse effects, notably interstitial pneumonitis, affected a number of patients, highlighting the importance of monitoring during treatment.

The present study is retrospective, which may introduce biases, including selection bias and information bias. Additionally, HER2 status testing may have been subject to variability in interpretation among pathologists, potentially leading to discrepancies in classification and affecting the study's validity. To mitigate this issue, our pathologist (FA) reviewed the tumor samples. While the study collected data on various outcomes, the follow-up duration for some patients may have been insufficient to capture all relevant events, such as recurrences or long-term survival outcomes.

Since the study was conducted at a single institution, local practices and patient demographics may not fully reflect broader populations. However, the analysis included data from 1436 patients, providing a robust sample size that enhances the statistical power of the findings and the reliability of the conclusions drawn. Furthermore, the study's focus on the HER2-low classification is timely and relevant, as this emerging categorization has the potential to significantly alter treatment approaches for a substantial portion of breast cancer patients.

In conclusion, our study identified significant differences in age and hormonal receptor status related to HER2 status among breast cancer patients. The introduction of the HER2-low classification represents a significant shift in treatment strategies, particularly with the advent of antibody-drug conjugates, offering new avenues for targeted therapies. While we did not find statistically significant differences in survival or recurrence rates across HER2 groups, continued research is essential to fully evaluate the clinical implications of this emerging classification. Individual patient factors, including age and hormone receptor status, must also be considered in treatment planning. As we further investigate the nuances of cancer biology and pathology, we aim to enhance targeted therapeutic options, ultimately improving survival and quality of life outcomes for breast cancer patients.

Declaration of interest

The authors declare that they have no conflicts of interest in relation to this study.

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