HER-2 /LOW POPULATION IN INFLAMMATORY BREAST CANCER RECURRENCE

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Abstract. *HER-2/positive breast cancer cells are more prevalent in inflammatory breast cancer (IBC), roughly 35% vs. 20% in other forms. This study aimed – to investigate the impact of HER2-low (erBb2 2+) on the risk of inflammatory breast cancer (IBC) recurrence. 60 females with HER2-low and HER2-positive IBC underwent surgery between July 2020 and July 2022. HR+/HER+(erBb2 3+) group had an OS of 74.6 % compared with 76.0 % in the group with the HR+/HER2-low (erBb2 2+) subtype, and 70.1% in the HR-/HER+ group. Moreover, recurrence-free survival was 20.2 % for the HR+/HER2-low - group, 22.4% for the HR+/HER+ group, and 10.6 % for the HR-/HER+ group. Her-2/low IBC patients have well-answer to target treatment, without disease progression or with stable disease. Further studies should focus to the mixing of chemotherapy and target treatment with Her-2/low-focused.*

INTRODUCTION

HER-2/positive breast cancer cells are more prevalent in inflammatory breast cancer (IBC), roughly 35% vs. 20% in other forms [1]. Compared to other forms, IBC identified in women at a younger age has more regrettable and aggressive results; it, has 2 times the survival time in the third stage as opposed to the fourth stage [2]. IBC patients have a higher relapse frequency compared with other forms (approximately 20% vs. 4%) [3].

As per the 2018 ASCO guideline update, breast cancers are HER-2/positive, if there is confirmation of HER-2/overexpression by fluorescence in-situ-hybridization (FISH) - (score 3+). 2+ needs characterization status, with an extra survey for specific evaluation. IHC 0 and 1+ is negative. 2+ breast cancer are HER-2/negative, thus no target treatment is recommended; HER2/CEP17 extent < 2.0 and HER-2 copy run from 4.0 to 5.9 on cell, at that point there's HER-2/positive breast cancer [4, 5].

A concept that uses a combination known as 2+ and known as negative FISH was proposed by a researcher named HER-2/low IBC. HER-2/low immunohistochemistry, comprising mainly of hormone receptor HR+ tumors (65-83%), while the rest are HR/negative and show a predominance of TN-BC [6,7].

The target of HER-2/negative IBC culminates in the disappointment of endocrinological treatment, and the target of HR+ is also known to be limited [8], due to the dependence on standard chemotherapy, survival is therefore limited [9].

The paradigm of having or not having HER-2, which categorizes it as negative or positive, has to be adjusted, due to a new, transitional value that we must consider when selecting therapy for these patient populations.

This study aimed - to investigate the impact of HER2-low (erBb2 2+) on the risk of inflammatory breast cancer (IBC) recurrence.

Material and Methods

The study was carried out in accordance with the Helsinki

Declaration, GCP (Good Clinical Practice), and Ukrainian legislation on medications. The participants were 60 females with HER-2/low and HER-2/positive inflammatory breast cancer, operated on and treated in our institute between July 2020 and July 2022. Patients were divided into three groups of 20 patients: 1) HR+/HER-2/low, 2) HR+/HER+, and 3) HR-/HER+. All patients underwent chemotherapy in adjuvant mode, in accordance with

the following scheme: TCH=docetaxel and carboplatin plus Herceptin [10].

Patients were observation for 24 months.

Recurrence-free survival (RFS) was defined as the time from surgery to disease relapse. HER-2 Immunohistochemistry was performed according to the generally accepted methodology. Each of these outcomes necessitates specific patient management [20]. Fluorescence microscopy was used to perform fluorescence staining (FISH) on material from paraffin blocks [11].

Statistical Analysis

We used Mann–Whitney U-test to compare two or more groups. Kaplan-Meier curves were used to estimate survival data, while the p-value associated with the long-rank test was calculated. The Fisher's exact tests were used to evaluate associations between categorical data, while Spearman correlation was used to determine the correlation between hormone status and HER-2 gene expression levels. All analyses were conducted in R (version 4.0.2).

Results

All 20 patients in the HR+/HER-2/low group, 20 in the HR+/HER+ group, and 20 in the HR-/HER+ group had information available and were included in this study. There were 55.8% postmenopausal patients in the HRplus/HERplus group and 62.1% of patients in the HR+/HER+ and HR-/HER+ groups. Furthermore, patients in the HR-/HER+ group performed significant worse than those in the HR+/HER+ group ($p<0.05$). Relapses were revealing that the incidence in HR+ groups reached up to 23.4 %, which was considerably higher than in HR-negative groups.

Survival analysis

HR+/HER+(erBb2 3+) group had an OS of 74.6 % compared with 76.0 % in the group with the HR+/HER2-low (erBb2 2+) subtype, and 70.1% in the HR-/HER+ group. Moreover, recurrence-free survival was 20.2 % for the HR+/HER2-low - group, 22.4% for the HR+/HER+ group, and 10.6 % for the HR-/HER+ group.

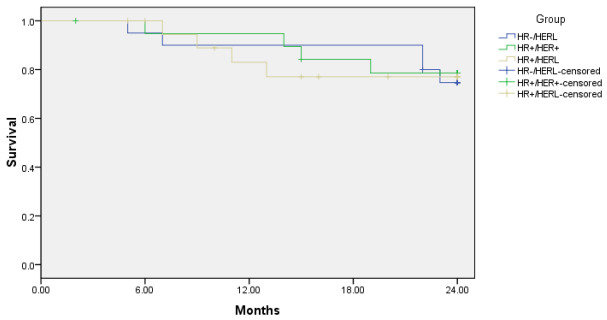

Figure 1. **Weighted Kaplan–Meier curves of overall survival (OS) after treatment of inflammatory breast cancer based on HER2 status**

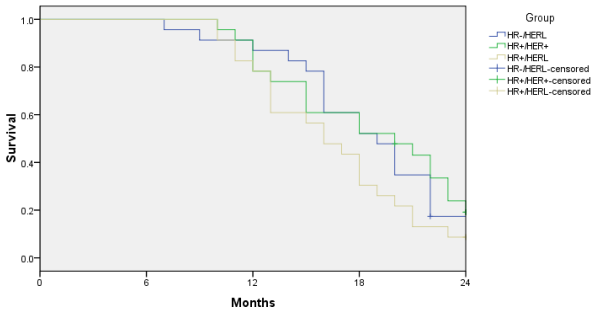

Figure 2. **Kaplan–Meier curves of recurrence-free survival (RFS) after treatment for inflammatory breast cancer based on the molecular subtypes**

Discussion

HER-2 targeted treatment is effective not only in HER-2/positive patients, but also in HER-2/low patients [26], as evidenced by our favorable results. According to Yu K. et al. [27], patients with ER positivity had a higher chance of improved survival than those with ER negativity corresponding to our study. The findings revealed that patients with HR+ IBC had a significantly higher survival rate (median OS 31 months) than those with HR-negative IBC (24 months). Thus, HER-2/low IBC was shown to be a heterogeneous disease with variant molecular subtypes associated with distinct prognostic outcomes as other breast cancers, and systemic therapies such as hormonotherapy and anti-HER-2 targeted therapy were effective in the treatment of IBC.

In this work, we presented analysis of molecular characteristics of primary HER-2/low IBC and a comprehensive analysis of its prognosis. In our cohort, HER-2/low IBC represented 57% of all tumors, with the majority (77%) being HR+, these findings being in line with previous reports [12].

Our findings show that HER-2/low IBC tumors, as opposed to HER-2-zero and Her-2/positive tumors, can be identified as a new subset of inflammatory breast cancer using standardized FISH. HER-2/low tumors have a distinct biology that influences treatment response and prognosis. This is especially important for hormone-receptor-negative tumors that are resistant to treatment. Our findings lay the groundwork for a better understanding of the biology of breast cancer subtypes as well as the development of future diagnostic and therapeutic strategies [13].

Conclusions

Currently are present a two-type approach (HER-2-beneficial vs. harmful) to guide clinicians in treatment decisions. However, a significant proportion of patients (over 50%) classified as HER-2-negative are, in fact, Her-2/low, a population with a high unmet clinical need. Recent anti-HER-2 retailers has demonstrated encouraging for protection in Her-2/low.

Her-2/low IBC patients have well-answer to target treatment, without disease progression or with stable disease. Further studies should focus to the mixing of chemotherapy and target treatment with Her-2/low-focused.

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