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Review Article

Same Story with Different Endings in HER2-Positive Breast Cancer: Why the Benefit of Pertuzumab is Robust in the Metastatic Scenario and Modest in the Adjuvant Setting?

Rafael Caparica[1]*, Adriana Matutino Kahn[2], Daniel Eiger[1] and Martine Piccart[1]

[1]Institut Jules Bordet, Université Libre de Bruxelles (U.L.B.), Belgium.

[2]Department of Internal Medicine, University of Connecticut, USA

ISSN: 2578-0379

***Corresponding author:** Rafael Caparica, Institut Jules Bordet, Université Libre de Bruxelles (U.L.B.), Belgium.

Submission: December 20, 2019
Published: January 08, 2020

Volume 3 - Issue 2

How to cite this article: Rafael C, Adriana Matutino K, Daniel E, Martine P. Same Story with Different Endings in HER2-Positive Breast Cancer: Why the Benefit of Pertuzumab is Robust in the Metastatic Scenario and Modest in the Adjuvant Setting?. Surg Med Open Acc J.3(2). SMOAJ.000560.2020. DOI: 10.31031/SMOAJ.2020.03.000560.

Abstract

While the incorporation of pertuzumab to a chemotherapy and trastuzumab backbone (dual HER2 blockade) yielded a robust improvement in the outcomes of HER2-positive metastatic patients in the CLEOPATRA study, in the adjuvant setting the same magnitude of benefit was not reproduced with the addition of pertuzumab in the overall population of the APHINITY study, being the reasons for this discrepancy unknown so far. In the present manuscript, we discuss biological and clinical differences between metastatic and early-stage HER2-positive breast cancer that may potentially explain the different magnitudes of benefit observed with pertuzumab in the different disease settings.

Keywords: Breast cancer; HER2; Pertuzumab

Introduction

The addition of pertuzumab to chemotherapy and trastuzumab yielded an impressive improvement in the outcomes of metastatic HER2-positive breast cancer patients [1]. Intriguingly, the same magnitude of benefit could not be reproduced with pertuzumab in the adjuvant setting, being the reasons for this discrepancy unknown [2,3]. In this manuscript, we discuss clinical and biological differences between metastatic and early-stage HER2-positive breast cancer, and conclude by proposing potential explanations for the distinct magnitudes of benefit of pertuzumab in different disease settings.

Magnitude of Risk Reduction

When evaluating a new treatment in the context of a clinical trial, events occurring in experimental and control arms are compared [4]. Early-stage HER2-positive breast cancer patients treated with adjuvant chemotherapy and trastuzumab had a 87.8% recurrence-free survival rate at 6 years as per the recently updated results of the APHINITY trial [3]. In the metastatic setting, however, the perspective is different: only 20% of patients receiving chemotherapy and trastuzumab remain alive and progression-free at 3 years [1]. Therefore, events are more frequent in the metastatic setting than in early-disease. In other words, there is more room for improvement in metastatic disease, whereas in the adjuvant setting chemotherapy and trastuzumab already yield high Disease-Free Survival (DFS) rates.

Illustrating this hypothesis, the addition of pertuzumab to trastuzumab and chemotherapy in the metastatic setting yields a 32% relative reduction in the risk of progression, which translates into an 8.2% absolute increase in Progression-Free Survival (PFS) at 3 years, whereas in the adjuvant setting pertuzumab yields a 24% relative reduction in the risk of recurrence at 6 years, translating into a modest 2.8% absolute improvement in invasive DFS (iDFS) [1-3] . When considering only node-positive patients (who present a higher risk of recurrence), the benefit of adjuvant pertuzumab becomes more pronounced (28% relative reduction in recurrence risk yielding a 4.5% absolute 6-year iDFS improvement) [2,3].

In line with this rationale, the KATHERINE study showed improved 3-year iDFS rates with trastuzumab emtansine (T-DM1) compared to trastuzumab in HER2-positive breast cancer patients who did not achieve pathologic complete response (pCR) after neoadjuvant treatment (88.3% *vs*. 77.0%; p<0.001) [5]. Importantly, the KATHERINE study enrolled high-risk patients, who are expected to experience more recurrences than the population of the APHINITY study [2,3,5]. The different profile of patients enrolled in each study and the fact that T-DM1 may be more active in resistant disease may justify the robust benefit of post-neoadjuvant T-DM1 in the KATHERINE trial and the modest benefit of adjuvant pertuzumab in the overall population of the APHINITY trial [2,3,5].

Gene Expression

Breast cancer can be divided into four subtypes based on its gene expression profiles, one of which is the HER2-enriched, characterized by a high expression of genes involved in cell proliferation and in HER2 pathway [6]. Concordance between HER2 status assessed by Immunohistochemistry (IHC) or Fluorescent *in Situ* Hybridization (FISH) and gene expression classification is not perfect: around 65% of HER2-positive tumors per IHC/FISH are HER2-enriched, whereas 25% are of the luminal subtypes, and 10% are basal-like or normal-like. Therefore, HER2-positive disease is clearly a heterogeneous group of tumors [6,7].

HER2-enriched subtype appears to confer increased sensitivity to anti-HER2 treatment, both in early-disease and in metastatic settings [8,9]. Interestingly, primary tumors that are not HER2-enriched can develop HER2-enriched metastases, suggesting that HER2 expression may change as disease progresses [10,11]. Hypothetically, if HER2 expression becomes more frequent as metastases are developed, a more pronounced activity of pertuzumab would be expected in the metastatic setting.

The Immune System

After binding to HER2, trastuzumab and pertuzumab can induce antibody-mediated cytotoxicity and ultimately promote an anti-tumor immune response [12]. When an antibody binds to its target, its Fragment crystallisable (Fc) region is recognized by Fc receptors from lymphocytes and antigen-presenting cells, leading to immune activation [13]. Modified anti-HER2 antibodies with impaired Fc domains cannot induce an effective anti-tumor response despite binding adequately to HER2 [14]. In contrast, the activity of anti-HER2 antibodies is enhanced by Fc domains that are more avid for Fc receptors [14]. Single-nucleotide polymorphisms induce structural changes in Fc receptors, which can become more or less avid for the Fc of anti-HER2 antibodies. Therefore, Fc receptor polymorphisms may enhance or compromise the activity of anti-HER2 antibodies.

Studies evaluating Fc receptor polymorphisms as predictive biomarkers for the efficacy of adjuvant trastuzumab presented contradictory results so far [15,16]. In the metastatic setting, however, Fc receptor polymorphisms were correlated with increased response to trastuzumab, and also with improved PFS rates in patients treated with the anti-HER2 antibody margetuximab, suggesting that immune activation may occur in different ways in metastatic and primary HER2-positive breast cancer [17,18]. Given the contradictory results observed in the metastatic and adjuvant settings, Fc polymorphisms are not established as predictive biomarkers in clinical practice.

Tumor Mutation Burden (TMB) represents the amount of mutations per DNA megabase in a specific tumor [19]. High TMB leads to the synthesis of abnormal proteins that can become "neoantigens" recognized by antigen-presenting cells [19]. In breast cancer, TMB is higher in the metastatic setting as compared to early-disease, with HER2-positive and triple-negative subtypes presenting the highest TMB values [20]. Thus, metastatic HER2-positive patients have tumors with high TMB, and are probably more prone to benefit from treatments that induce anti-tumor immune responses, such as pertuzumab.

Baseline tumor infiltrating lymphocytes (TILs) levels are correlated with prognosis in HER2-positive breast cancer patients [21,22]. However, the role of TILs as predictors of anti-HER2 treatment benefit has yet to be defined: an exploratory study assessed TILs levels in primary tumors and residual disease from 175 HER2-positive patients who received neoadjuvant chemotherapy and trastuzumab: a decrease in TILs levels occurred in 78% of the patients after neoadjuvant treatment, and was associated with higher pCR rates (p<0.001). Intriguingly, high TILs levels (>25%) in residual disease predicted worse survival (p=0.009) [23]. The reasons why high TILs levels in residual disease may be a bad prognostic factor in HER2-positive disease are unclear, although it could be related to an increase in immunosuppressive cells and a decrease in cytotoxic T cells induced by neoadjuvant treatment [24].

Tumor Heterogeneity

Tumor cells that harbor a HER2 amplification have an evolutionary advantage in comparison to HER2-negative cells, since HER2-signalling constantly stimulates proliferation and survival [25]. Interestingly, half of circulating tumor cells detected in HER2-positive early-stage breast cancer patients do not express HER2 [26]. Since the blockade of HER2 is the mainstay treatment of HER2-positive breast cancer, the presence of tumor cells that are not dependent on HER2-signalling may lead to treatment resistance [26].

Assuming that most HER2-positive tumors present HER2-positive and HER2-negative cells; and disease burden is higher in metastatic patients; as HER2-positive cells have an evolutionary advantage in comparison to HER2-negative cells, a dominance of HER2-positive cells in the advanced disease may occur, particularly in the absence of the selective pressure of systemic therapies. A high proportion of HER2-positive cells may render the tumor more sensitive to HER2 blockade, potentially explaining the more robust benefit of pertuzumab in metastatic disease, especially if we consider the high proportion of de-novo metastatic patients (53.4%) enrolled in the CLEOPATRA study [1]. Table 1 summarizes potential reasons for the distinct impact of pertuzumab in the adjuvant and metastatic settings.

Table 1: Potential explanations for the different impact of pertuzumab in the adjuvant and metastatic settings.

Mechanism	Rationale
Magnitudes of Risk Reduction	Overall in the adjuvant setting, DFS rates are already high with chemotherapy and trastuzumab, thus there is more margin for improvements in metastatic disease and in high risk early-stage disease [1-3].
Gene Expression	Metastases from tumours that were not HER2-enriched can present the HER2-enriched profile, which may be associated with a more pronounced benefit of anti-HER2 treatments [10,11].
Immune Activation	Metastatic disease may be more immunogenic than early-disease due to disparities in Fc receptor polymorphisms [17,18].
Tumour Mutational Burden (TMB)	Metastatic HER2-positive tumours have a high TMB, which may render them more sensitive to treatments that induce an anti-tumour immune response, such as pertuzumab [23,24].
Tumour Heterogeneity	In treatment-naïve metastatic patients, the dominance of HER2-positive cells over HER2-negative cells may be more pronounced [25,26].

Conclusion

No irrefutable data can explain the discrepant survival impact yielded by pertuzumab in metastatic and early breast cancer patients, and it is unlikely that one single factor will account for this contrast. Probably tumoral heterogeneity, gene expression patterns at distinct disease stages and differences in TMB account for the heterogeneous benefit of pertuzumab in HER2-positive disease at different stages of evolution. Also, since the induction of an immune response is a mechanism of action of anti-HER2 treatments, the host's immune system and the tumoral microenvironment play also important roles. From a historical perspective, this is not the first time that a significant benefit in the metastatic setting cannot be reproduced in the adjuvant scenario [27]. These findings highlight the importance of evidence-based medicine: A strong biologic rationale and efficacy in the metastatic setting are not a guarantee that the results will be reproducible in early disease. Hence, it is important to have evidence from well-designed randomized trials to support treatment recommendations in each scenario. As the research to depict the molecular characteristics of HER2-positive breast cancer evolves, predictive biomarkers may arise to identify patients who benefit from pertuzumab.

Additional Information

Ethical approval and consent to participate

The present work did not perform any experiments with animals or humans; therefore no ethical approval or informed consent forms were necessary.

Consent to publish

The present work does not contain any patient data in any form; therefore no consent was necessary.

Conflict of Interest

RC has received speaking honoraria from Boehringer-Ingelheim and Janssen; and travel grants from Astra-Zeneca and Pfizer. AMK declares no conflicts of interest. DE has received an ESMO Clinical Research Fellowship funded by Novartis. MP is a board member of Radius; has received consultant honoraria from AstraZeneca, Lilly, MSD, Novartis, Odonate, Pfizer, Roche-Genentech, Camel-IDS, Crescendo Biologics, Periphagen, Huya, Debiopharm, PharmaMar, G1 Therapeutics, Menarini, Seattle Genetics, Immunomedics and Oncolytics; RC, DE and MP have received research grants for their Institute from Roche/GNE, Radius, Astra-Zeneca, Lilly, MSD, Novartis, Synthon, Servier, and Pfizer.

Funding

The present manuscript did not require any funding.

Author's Contribution

All authors participated in all stages of the present work. The final version of this manuscript was reviewed and approved by all authors before submission.

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