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Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer: A Critical Review

Khaled Elmahdi-Omran[1,2]*

[1]Department of Oncology, Tobruk Medical Center, Libya

[2]Department of Medicine, University of Tobruk, Libya

Abstract

Human Epidermal Growth Factor Receptor 2 (HER2) positive breast cancer patients carry a high risk of recurrence. Moreover, patients who didn't achieve pathological Complete Response (pCR) after Neoadjuvant Therapy (NAT) have a higher risk of relapse than those who did. KATHERINE trial was addressing that group of patients who were HER2 positive early breast cancer, and had the Residual Invasive Disease (RID) after NAT. In the trial, patients were randomized in two groups and assigned to receive adjuvant therapy, either trastuzumab-emtansine (T-DM1), or trastuzumab, and the primary end point was invasive Disease-Free Survival (DFS). The investigators of the trial concluded there was a 50% reduction in recurrence and death with adjuvant T-DM1 in comparison to adjuvant trastuzumab alone. However, the trial was designed to assess HER2 status on pre-treatment biopsies rather than postoperative samples, and not considering the discordance in HER2 status between the two samples, bearing in mind, HER2-loss after NAT has been frequently reported phenomenon, which could be due to either heterogeneity of the tumor or false positive result of the HER2 expression status testing of the primary tumor sample. Heterogeneity is a sign of aggressiveness of the tumor, and false positive HER2-overexpression would lead to an irrelevant and an ineffectual therapy. Concordantly, a considerable number of studies concluded that, patients with HER2-loss had shorter DFS. Therefore, HER2-loss should have been considered a confounding factor, and patients who manifested loss of HER2 amplification should have been distributed equally between the two arms of the trial to eliminate bias.

Keywords: HER2-loss after neoadjuvant therapy; Discrepancy in HER2 expression; Trastuzumab; T-DM1; HER2+ Early breast cancer

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Correspondence:
Khaled Elmahdi-Omran, Department of Oncology, Tobruk Medical Center, Tobruk, Libya, Tel: +218-927097082; E-mail: kelmahdiomran@gmail.com

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Introduction

Early breast cancer with amplification of HER2, carries a high risk of recurrence [1-3]. Moreover, patients with this category of the disease, who have RID after NAT, possess worse prognosis than those who have pCR [4,5]. Minchwitz et al. investigated in KATHERINE trial, the impact of T-DM1 as adjuvant therapy in comparison with the standard therapy (trastuzumab) on this group of patients considering they carry a high risk of relapse [6]. T-DM1 is an antibody-drug conjugate of trastuzumab and emtansine, a microtubule inhibitor chemotherapy. The investigators of the trial randomly assigned HER2 positive early breast cancer patients who had RID after NAT to receive either adjuvant trastuzumab or T-DM1 in 1:1 ratio, and allocated certain variables during stratification of patients between the two groups. Some variables were obtained at the time of diagnosis rather than post-NAT, such as Estrogen Receptor (ER), Progesterone Receptors (PR), and HER2 status. Discordance of HER2 amplification after either chemotherapy or anti-HER2 therapy is a well-documented phenomenon. Based on compelling previous studies such as the one performed by Mittendorf et al. [7] in 2009 for instance, there would be a substantial number of patients who were involved in the KATHERINE trial were expected to have had lost HER2 overexpression after NAT. In this regard, the current review is questioning whether ignoring this group of patients during stratification and matching between the two arms of the trial could have led to selection bias, particularly if losing HER2 amplification after NAT would have been a confounding variable, and had an impact on DFS.

Summary

A phase III, open-label trial was directed by Minchwitz and colleagues involved a group of early breast cancer patients, whose tumors showed over-expression of HER2 at diagnosis, and received NAT included taxane (with and without anthracycline) plus anti-HER2 therapy, trastuzumab, and

still had RID either in the breast or the axilla at the surgery. Those patients were randomized to receive 14 cycles of adjuvant trastuzumab or T-DM1. DFS was set to be the primary end point of the trial. During 12 weeks post-surgery, patients were randomly assigned in a 1:1 ratio between the two arms of the trial. During the stratification of the patients, the following variables were considered between the two groups, clinical stage at presentation if it was operable or not, hormone-receptor status, whether the patient received neoadjuvant single or dual anti-HER2 blockade therapy, and nodal status post-neoadjuvant therapy. Patients were clinically assessed during the 14 cycles of therapy and thereafter in a planned schedule of follow up until year 10. The investigators of the KATHERINE trial concluded that, there was a 50% risk reduction of recurrence of invasive breast cancer or death when adjuvant T-DM1 was compared with trastuzumab alone for HER2 positive early breast cancer patients who completed their NAT, and still had RID [6]. Consequently, T-DM1 was globally approved for HER2 positive early breast cancer patients who have RID after completion of NAT; and an indication of T-DM1 in breast cancer was upgraded from advanced to early disease, for the first time [8,9].

Evaluation

Initially, the aim of improving DFS of a group of patients who carry such a high risk of recurrence was an appreciable effort made by Minchwitz et al. Especially, the design of the KATHERINE trial was ingenious in the way of investigating a new line of therapy *vs.* a standard inadequate therapy after a NAT which identified that high-risk group of patients.

Nonetheless, few questions were raised about the randomization process of the trial. Was the phenomenon of HER2-loss after NAT therapy expected to occur, leading to discordance between the HER2 status pre-treatment and postoperatively? Did HER2-loss after NAT therapy influence prognosis?

First, the change in expression of HER2 after NAT therapy was reported repeatedly. A retrospective study made by Niikura et al. in 2016 showed that, there was a loss of HER2 expression in 21.4% of 2,811 patients received NAT therapy. The same outcome was observed by Mittendorf et al. [7] in 32% of their sample. Several other studies and reports meant to investigate the discordance rate in the expression of HER2 before and after therapy, either on breast cancer or gastric and gastro-esophageal cancers elucidated that, chemotherapy or chemotherapy with anti-HER2 therapy can alter HER2 expression status [10-29]. According to the author of the KATHERINE trial, HER2-loss rate was assessed in more than two-thirds of the patients and the activity of T-DM1 on this subgroup of patients was planned to be analyzed. Therefore, out of the 1,486 patients involved in the KATHERINE trial, there was a considerable number of them had their RID left with low or even zero expression of HER2.

Secondly, the prognostic value of HER2-loss after NAT was investigated by several studies. For instance, Mittendorf et al. [7] demonstrated that, Recurrence-Free Survival (RFS) was significantly worse for patients who had their RID lost HER2-overexpression post-treatment after a median follow up of more than three years. A comparable conclusion was depicted in a cohort study made by Guarneri et al., who observed that patients who showed HER2-loss in their RID after NAT had tended to have a high risk of recurrence. Another study by Wang et al. [23] provided evidence that RFS was shorter for the matching group of patients. Similar results were achieved by other researchers who consolidated the concept of losing HER2-expression after NAT had a prognostic impact [7,12,15,17,23,26]. Moreover, what was proven in early breast cancer regarding HER2-loss, and its prognostic outcome was studied and reported in metastatic breast cancer, gastric cancer, and gastro-esophageal cancer, and similar results were attained [12,19,21,29]. It is worth mentioning that, Yoshida et al. [24] pointed out in 2012 and 2017 that, HER2-loss did not affect the patients' prognosis, although Yoshida et al. [24] were among the very rare researchers who concluded to the insignificance of HER2-loss [16,24].

Furthermore, comparing biomarkers status (ER, PR, and HER2) of postoperative RID with their matching recurrent disease of same patients, might have given more information about the efficacy of the adjuvant therapy in both arms of the trial, particularly for those who lost HER2 overexpression.

Indeed, HER2-loss after NAT could be attributed to either both human error and laboratory false positive or genuine change at the cellular and molecular level of the tumor [29]. Commencing with the cellular and molecular alteration, or evolution; breast cancer is recognized as a group of diseases showing diverse molecular, cellular, and clinical behavior presenting varied risk factors, responses to therapy, and diverse relapse possibilities as well as different mortality rates. This inconsistent configuration is documented as heterogeneity. In breast cancer, heterogeneity could be presented as intertumoral or intratumoral. Intertumoral heterogeneity reflects the differences among tumor tissues of breast cancer, such as luminal-A, luminal-B, HER2-enriched, and basal-like. However, intratumoral heterogeneity implies variances within a tumor itself, either at different sections of it, or even molecular changes over time, for instance, after exposure to an antineoplastic therapy [3,30]. Malignant clones that evade primary therapy remain proliferating; thus, later, a resistant group of cells eventually dominate, and confer poor prognosis and contract overall survival [31]. Undeniably, patients with intratumoral heterogeneity of HER2 amplification have decreased DFS and retain a high risk of progression of the disease [32]. If it is considered that HER2-loss is indeed a genuine evolutional alteration and is due to heterogeneity, consequently patients lose the HER2 overexpression after NAT would have worse DFS than others who retain the expression of HER2, and that what was concluded by the majority of the above mentioned studies and reports in early and advanced breast cancer as well as gastric and gastro-esophageal cancers about the prognostic value of HER2-loss after antineoplastic therapy. In the same context, the prognostic value of HER2-loss after NAT was noticed in the hormonal receptors too, suggesting that, the loss of hormonal receptors after NAT is not an innocuous sign. A study by Mosele et al. [33] indicated that 61% of their studied metastatic triple-negative breast cancer patients with *PIK3CA* mutation were positively expressing hormonal receptors in their primary tumors. *PIK3CA* mutation is a defined cause of resistance after exposure to endocrine therapy [34]. Reasonably, losing target receptors such as HER2 or endocrine receptor can be attributed to an acquired mutation that would confer resistance to the current therapy as an approach of intratumoral heterogeneity.

On the other hand, as aforementioned, the other explanation of discordance of HER2 amplifications between the primary biopsy and the postoperative sample is human error and laboratory false-positive results. Patients who were falsely diagnosed to have overexpression of HER2 while they didn't would receive irrelevant and ineffectual

therapy such as trastuzumab. Certainly, when they have negative endocrine receptors too (actual Triple Negative breast cancer patients), they should be accounted for a high-risk group.

Statistically, accurate assessment of interventional variables such as proposed new therapy, is supposed to be on characteristically similar groups of the study to eliminate confounding. Any variable that influences the outcome of a trial apart from interventional one would hinder the result of the study. Therefore, the prerequisite balanced distribution of confounding factors between the two arms of the study is essential and would maintain the equal opportunity of both groups [35]. An unmatched study group and control group ought to introduce a significant source of error [36].

Conclusively, According to the overwhelming studies and researches on HER2-loss phenomenon, and how some of them demonstrated that, 33% of the patients had HER2 loss after NAT; there could have been almost 500 patients out of 1,486 who participated in KATHERINE trial lost HER2 overexpression after NAT (postoperative samples). Whether that discordance of HER2 expression between the primary biopsy and the postoperative sample accredited to heterogeneity or false positive primary results, those who lost the HER2 overexpression would have represented a high-risk group of patients who are not expected to show response to therapy from the beginning of the trial. Undoubtedly, HER2-loss after NAT was indeed a confounding variable, and patients acquired this phenomenon after NAT should have been distributed equally between the two arms of KATHERINE trial, T-DM1 (intervention group) and trastuzumab (control group). Consequently, 50% risk reduction in recurrence or death was not necessarily accredited to T-DM1, particularly after the revelation of the outcome results from the phase III KRISTINE study which showed that T-DM1+pertuzumab (T-DM1+P) failed in neoadjuvant setting when it was compared with trastuzumab and pertuzumab+paclitaxel and carboplatin (TCHP) due to locoregional progression with T-DM1+P (TCHP 0% *vs.* T-DM1+P 6.7%). Also, less pCR was achieved with T-DM1+P in comparison with TCHP. It is noteworthy that, patients received adjuvant T-DM1+P or trastuzumab+P accordingly, and three years follow up showed no difference in DFS between the two arms of the study [37].

Conclusion

Discrepancies between HER2 amplification in primary tissue of diagnosis and postoperative samples should have been considered as a confounding variable in KATHERINE trial, and patients who lost HER2 expression in their postoperative sample were representing a high-risk group, who were supposed to be distributed equally between the two arms of the trial to minimize the error and bias. Therefore, a 50% risk reduction in recurrence and death attributed to T-DM1 in KATHERINE trial should be re-evaluated. Hopefully; HER2-loss after NAT would be considered and utilized appropriately in future trials.

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