

Trastuzumab Emtansine for Residual Invasive Human Epidermal Growth Receptor-2-Positive Breast Cancer

Substantial progress has been made in the management of human epidermal growth receptor-2 (HER2)-positive nonmetastatic breast cancer over the past two decades. Initial studies on pathological complete response (pCR) as a surrogate marker for survival gave a better understanding of biology of the disease.^[1] To understand the impact of intensification of the treatment in patients who do not achieve pCR, KATHERINE study^[2] was undertaken.

This study was a phase 3 randomized open-label trial, which enrolled patients with cT1-4, N0-3 disease (excluding T1aN0 and T1bN0), who received neoadjuvant therapy with anti-HER2 agents and did not achieve a complete pathological response. These patients were randomized postoperatively to the continuation of trastuzumab to complete 1 year as the standard arm versus trastuzumab emtansine 1 (TDM1) for the same duration. Patients received neoadjuvant taxanes with or without anthracycline-based regimens along with trastuzumab. The primary endpoint of the study was invasive disease-free survival (iDFS) which was defined as the time from the date of randomization till survival-free from local and/or distant recurrences and/or death. iDFS is not generally used as a primary endpoint; however, with multiple available agents in HER2-positive breast cancer, the benefits of such trials would take much longer to be apparent if only death as primary endpoint is taken.

The trial included 1486 patients who were randomized to TDM1 versus trastuzumab in equal proportions (743 in each group). The median duration of follow-up was 41.4 months (range 0.1–62.7). The median follow-up is considered reasonably sufficient for HER-2 enriched population of breast cancer, wherein most of the events are expected to occur within 2–3 years.

The percentage of patients free from the invasive disease at 3 years was 88.3% in the TDM1 group and 77.0% in the trastuzumab group (hazard ratios 0.50, 95% confidence interval 0.39–0.54, $P < 0.001$). Distant recurrence as the first-invasive disease event occurred in 10.5% of patients in the TDM1 group and 15.9% of those in the trastuzumab group. The authors thus concluded that changing the adjuvant therapy to TDM1 reduces the risk of recurrence of invasive breast cancer or death by 50% compared to trastuzumab alone.

The baseline characteristics of patients were well balanced in both the arms. More than 70% of the patients were hormone-receptor positive. Almost two-third of the patients received an anthracycline-based chemotherapy regimen, and <20% of the patients received pertuzumab and trastuzumab combination. This makes the interpretation

difficult since the addition of pertuzumab to trastuzumab is known to significantly improve the pathological response. Patients who received dual blockade had improved outcomes with experimental arm, events were 9% versus 16% in TDM1 and trastuzumab arm, respectively, however, the number was less in this subset ($n = 290$), and it is difficult to draw the conclusions from this subgroup analysis.

The trial did not address the role of adding pertuzumab postoperatively in patients who have received dual blockade as neoadjuvant. From the APHINITY study, we came to know that the addition of pertuzumab improves the disease-free survival by 3–4 percentage points over trastuzumab.^[3] Still, the comparison of disease free survival (DFS) between KATHERINE and APHINITY cannot be done as KATHERINE included only those patients who did not achieve a complete pathological response and were, therefore, at higher risk, whereas APHINITY included all patients with >1 cm tumor.

When it comes to safety, the TDM1 arm had a higher incidence of Grade 3 and 4 adverse events compared to trastuzumab arm. All the 14 cycles were completed in 71.4% of the patients who received TDM1 versus 81% in the trastuzumab arm. Hence, incomplete anti-HER2 therapy in 10% of the patient is also a matter of concern. Although the PERSEPHONE study has shown that 6 months is noninferior to 12 months, most clinicians may not consider prime time yet to shift to the shorter duration of trastuzumab, as all other trials looking at a shorter duration have failed to show noninferiority.^[4,5] The cardiac events have been much lower than what is reported in the trials using trastuzumab. Previous published data suggest that the average incidence of cardiac events is in the range of 3%–4%.^[6] However, in this study, it is noticeable that the cardiac events have been quite low even in the trastuzumab arm.

This study can bring up a difficult situation for some patients with regard to decision-making. If the patients who have received TDM1 as adjuvant, progress within 12 months of completion or earlier, can we extrapolate the EMILIA data to this group and still use TDM1? If not, we may have to rely on the inferior lapatinib-capecitabine arm, or neratinib with capecitabine as per the latest NALA trial, with its added toxicities.^[7] Still, it is felt that more effective therapy is better used in curative settings rather than preserving it for metastatic disease. Even trastuzumab was first approved in metastatic disease, and the introduction in the adjuvant therapy was not withheld by a similar logic.

Another interesting fact that has come up is the similar number of central nervous system (CNS) metastasis in both arms. We all understand from previous data that TDM1 has better CNS penetration,^[8,9] and we did expect a lower rate of CNS metastasis in the TDM-1 arm.

With only 35% of the survival events, it may be reasonable to believe that it will translate into a significant overall survival benefit since the curves seem to separate at the tail end and may continue to do so with future analysis.

In a resource-constrained setting, the cost-effectiveness of this approach is still doubtful. The usage of trastuzumab in the Indian setting is still not even anywhere close to 100%. With the advent of biosimilars, the usage has increased, but it definitely has not reached the desirable proportions. Moreover, with the lack of standardization in reporting pCR after surgery in many centers, the rational use of TDM1 may be questionable. There is a high possibility that if clinicians start using this approach in every patient, there will be a much higher number of cases who would stop anti-HER 2 therapy halfway into their adjuvant course, which may affect their outcomes. Our patient population comprises large primary tumors and heavy nodal burden. Hence, most of our patients have a higher recurrence rate even after adjuvant treatment. In those settings, we shall not have many treatment options left, as we would have already used TDM1. Moreover, using such expensive therapy for a disease-free survival benefit may also not be cost-effective.

Hence, to conclude, this is a very well-designed, path-breaking trial that has met its primary endpoint, but translating the data to a majority of our set of patients may still not be feasible due to cost and increased toxicities. Still, it appears to be a rational approach with an 11% absolute DFS benefit. It is possible that biosimilar TDM-1 increases the usage in this setting once it is available in India.

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