Selected Summary

Adjuvant trastuzumab emtansine in human epidermal growth factor receptor 2-positive breast cancer: Take-home points from the KATHERINE trial

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SUMMARY

Patients with human epidermal growth factor receptor 2 (HER 2)-positive early breast cancer have an aggressive clinical course than those with hormone-positive cancer. Patients harbouring HER 2 neu gene amplification tend to have increased risk of recurrence or death with residual invasive carcinoma after neoadjuvant chemotherapy and/or targeted therapy. Trastuzumab emtansine (T-DM1) is an antibody drug conjugate of trastuzumab and emtansine, a microtubule inhibitor. The drug, apart from inhibiting the HER 2 pathway, also releases emtansine to HER 2 overexpressing cell, overcoming trastuzumab resistance and tumour killing. The KATHERINE trial was a multicentric, open-label, randomized study. A total of 1486 patients with HER 2-positive early breast cancer, who had residual invasive disease post-neoadjuvant therapy, were included in the study. Post-surgery, eligible patients were randomly assigned to either the T-DM1 group (14 cycles every q3weeks) or the trastuzumab group. The primary outcome of the study was invasive disease-free survival (IDFS) and the secondary outcome was safety. Planned interim analysis showed fewer invasive disease or death in the T-DM1 group than in the trastuzumab group (12.2% *v.* 22.2%). Three-year IDFS was statistically significantly higher in the T-DM1 group than in the trastuzumab group (hazard ratio 0.50; 95% CI 0.39–0.64, $p \leq 0.001$). The safety profile with T-DM1 was consistent with previous reports; however, there was an increased incidence of thrombocytopenia, liver dysfunction and neuropathy with T-DM1 than with trastuzumab. The trial concluded that among patients with HER 2-positive early breast cancer who had residual invasive disease after completion of neoadjuvant therapy, the risk of recurrence of invasive breast cancer or death was 50% lower with adjuvant T-DM1 than with trastuzumab alone.

COMMENT

Breast cancer is the most common cancer worldwide and the leading cause of cancer-related mortality in women. With the invention of targeted therapy, the treatment paradigm of breast cancer has shifted from a nihilistic to an optimistic approach. HER 2 gene amplification is seen in 15%–20% of primary invasive breast cancer and is associated with poor survival.[1] Targeted agents such as trastuzumab, pertuzumab, T-DM1 and lapatinib block the activation of the HER 2 pathway, increasing pathological complete remission (pCR) rates when administered in the neoadjuvant setting. Despite the significant benefit, 50% of patients progress within 1 year of trastuzumab-based therapy due to acquired resistance.[2] T-DM1 overcomes trastuzumab resistance by virtue of its different mechanism of inhibition of HER 2 overexpression and also causing cell death by emtansine.[3] The correlation residual invasive carcinoma post-neoadjuvant therapy was best established in triple-negative breast cancer followed by HER-2-positive tumours. To overcome the adverse effect of residual disease, the KATHERINE trial intended to intensify/modify adjuvant therapy. This study has shown that there was 50% reduction in invasive disease recurrence when treated with T-DM1 in the adjuvant setting.

This well-designed study had pCR as a new surrogate marker to predict outcomes in breast cancer, which has advantages over using the new treatment to the entire HER-2-positive breast cancer scenario. Inclusion of all HER-2-positive early breast cancer means long duration of follow-up and thus delaying approval of a potentially beneficial drug.[4] Second, choosing a high-risk subset not achieving pCR is a logical and

financially efficient way to prove the beneficial effect of T-DM1. The trial also emphasizes the importance of neoadjuvant-targeted therapy in HER-2-positive early breast cancer.

The benefit of T-DM1 comes along with increased toxicity and cost of therapy. The T-DM1 group had significantly more side-effects than the trastuzumab group. Even the cost of T-DM1 was higher. Although T-DM1 demonstrated clinical benefits, the absolute benefit in terms of cost-effectiveness was not ascertained. About 20% of patients in the trastuzumab group did not complete 14 cycles. Twenty-three patients randomized to the trastuzumab group did not receive planned therapy, while only 4 patients did not receive therapy in the T-DM1 group. This may have a bearing on observed outcomes. Whether the addition of T-DM1 changes the disease biology or natural course may be answered once survival data are available. The choice of a HER-2-targeted agent for relapse in T-DM1 and trastuzumab-exposed patients should be addressed in future trials.

Indian scenario

Many patients in the Indian subcontinent present in an advanced stage with large tumour bulk. Therefore, the probability of residual disease in Indian patients is high. The KATHERINE trial results could be the answer for many patients in India. However, the use of HER-2-targeted therapy is limited due to financial constraints for many patients.[5] The expected cost of treating breast cancer with adjuvant T-DM1 could be ₹3 600 000–₹5 000 000. The majority of patients in India are not covered by insurance nor can they afford the drug, ultimately abandoning the expensive option irrespective of the benefit. Initially, the cost may be prohibitive for upfront use of T-DM1 in India. Hence, it is important to ascertain the cost–benefit analysis of this treatment to counsel our patients. Second, centralized HER 2 testing was limited only to the pre-treatment biopsy samples in this study. Guarneri *et al.* reported loss of HER 2 expression in 15% of patients receiving neoadjuvant chemotherapy with anti-HER 2 agents.[6] The possibility of loss of HER-2 expression after neoadjuvant treatment and its influence on further decision-making and outcomes is important, especially in resource-limited settings. The side-effect profile of the Indian population should also be reviewed. Initiating trials involving adjuvant T-DM1 therapy in India and enrolling our patients is one way to address the above two concerns.

In a nutshell, the KATHERINE trial addresses the unmet need of a poor risk subset of HER-2-positive early breast cancers. It showed clinically meaningful decrease in IDFS with adjuvant T-DM1. The study has brought a new drug in the forefront using a relatively new predictive biomarker, i.e. pCR, in the management of HER-2-positive early breast cancer, setting a new standard of care in this population.

Conflicts of interest. None declared

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