Selected Summary

Short-duration adjuvant trastuzumab therapy in human epidermal growth factor receptor 2-positive breast cancers: Has its time come?

Gulia S, Kannan S, Badwe R, Gupta S. (Departments of Medical Oncology, Biostatistics and Surgical Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, India.) Evaluation of 1-year versus shorter durations of adjuvant trastuzumab among patients with early breast cancer: An individual participant data and trial-level meta-analysis. *JAMA Netw Open* 2020;**3:**e2011777.

SUMMARY

In this meta-analysis, the authors used data from six randomized clinical trials (RCTs) in patients with early (non-metastatic) breast cancer that compared short duration (<1 year) with 1 year of trastuzumab as adjuvant treatment. In contrast to the previously published trial-level meta-analysis from the same six studies, this meta-analysis included updated data from the PHARE and PERSEPHONE studies and also extracted individual patient time-to-event data from published Kaplan–Meier survival curves, a unique and more lately reported method to do individual patient data (IPD) meta-analysis. Non-inferiority of shorter duration of trastuzumab in disease-free survival (DFS) compared with 1 year of therapy was assessed in the reconstructed IPD meta-analysis (11 376 patients with 1659 DFS events and 871 deaths) and trial-level meta-analysis (11 603 patients, 1760 DFS events and 930 deaths). The median value (1.3; range 1.15–1.53) of the non-inferiority margins used in the included RCTs was chosen as the non-inferiority margin.

In the IPD meta-analysis, 5-year DFS hazard ratio (HR) for shorter-duration versus 1 year of trastuzumab was 1.14 (95% CI 1.03–1.25 with a p value for non-inferiority=0.004), and HR for overall survival (OS) was 1.17 (95% CI 1.02–1.33). In the trial-level analysis, the HR for DFS was 1.15 (95% CI 1.04–1.26; one-sided p value for non-inferiority=0.002) and for OS, 1.17 (95% CI 1.03–1.33). The risk of congestive heart failure was significantly less with shorter-duration trastuzumab (relative risk 0.53; 95% CI 0.38–0.74). The risk of bias was low, and quality of evidence was graded high for DFS and OS, while moderate for cardiotoxicity. Given these results, the authors concluded that a shorter duration of adjuvant trastuzumab was non-inferior to its 1-year administration and resulted in lower rates of cardiac toxic effects, hence it may be the preferred option for patients with low-risk disease or those with predisposition to cardiac toxic effects.

COMMENT

Breast cancer is the leading cancer among women and the most common cause of cancer-related mortality among women worldwide. Compared to data from western countries, the prevalence of human epidermal growth factor receptor 2 (HER2)-positive breast cancer is relatively high (ranging from 19% to 31%) among developing countries such as India, but with a majority of patients not able to afford therapy due to financial constraints.[1] Therefore, an optimum shorter duration of HER2-directed therapy is of utmost therapeutic relevance to this population. Hence, results of the present meta-analysis would be important to oncologists in providing evidence for best practices.

The authors stated that short-duration adjuvant trastuzumab therapy was non-inferior to its 1-year administration and resulted in lower rates of cardiac adverse effects. However, the non-inferiority limit set at 1.3 is same as in the PRESOPHONE trial, which is the only trial included in this meta-analysis that has proven the non-inferiority of shorter duration of trastuzumab and this corresponds to a 4% absolute difference in 5-year DFS. A 4% survival difference in early breast cancer (which corresponds to a hazard of 30%) can be considered too high and was also one of the major criticisms of the PRESOPHONE trial. The PHARE trial with a more reasonable non-inferiority margin of 1.15 was negative for non-inferiority.

Seven meta-analyses were published in 2019–20 comparing short-duration versus standard trastuzumab therapy, with almost all of them except one having used the same RCTs used in the present meta-analysis and all studies reported nearly equivalent HRs for OS and DFS (Table I).[2–7] While all the others concluded the superiority of the standard 1-year trastuzumab therapy, the present meta-analysis was the first to establish non-inferiority of the short-duration therapy. The present meta-analysis was designed to assess the non-inferiority of shorter duration of trastuzumab, an approach different from those used in the previous meta-analysis that showed the superiority of 1-year trastuzumab therapy, findings of which were also replicated in the present meta-analysis. While the authors of the present meta-analysis justified that by using a non-inferiority analysis design, they preserved the non-inferiority interpretation of its constituent trials, the authors of the previous meta-analysis stated that determining treatment superiority via a meta-analysis of non-inferiority studies is statistically acceptable. Hence, whether the result of this meta-analysis is a statistical jigsaw or a shorter trastuzumab therapy is non-inferior to 1-year therapy with regard to survival is uncertain. Moreover, given the use of a new approach to extract IPD from survival curves that have not been previously used in oncology meta-analysis and the lack of power to contrast between the two shorter-duration regimens (9–12 weeks *v.* 6 months), the results of this meta-analysis should be interpreted with caution and needs to be validated further before recommending a change in clinical practice.

Associated cardiotoxicity with trastuzumab is not negligible although it is usually well tolerated with cardiac events being reversible. Short-term trastuzumab therapy is associated with significantly lower cardiotoxicity compared to standard therapy as found in both the previous and present meta-analyses. However, whether the risk of cardiotoxicity differs among anthracycline-free versus anthracycline-based regimens should be further explored.[8] With the advent of new biomarkers such as high-sensitivity troponin-I and topoisomerase 2β isomerases, we can now risk stratify individuals with greater risk of subclinical cardiotoxicity early into the treatment period. This can help identify target individuals for shorter duration therapies.

Both the present and previous meta-analyses also failed to

TABLE I. Published meta-analysis reports comparing short-term trastuzumab therapy with standard 1-year therapy

Author, year	Number of studies	HR (95% CI) of standard 1-year trastuzumab therapy compared to short-duration therapy	Conclusion
Gulia *et al*. (2020), Present study	6	*Individual patient data* DFS 1.14 (1.03–1.25), one-sided p value for non-inferiority=0.004 and OS 1.17 (1.02–1.33) *Trial-level data* DFS 1.15 (1.04–1.26), one-sided p value for non-inferiority=0.002 and OS 1.17 (1.03–1.33)	Shorter duration of adjuvant trastuzumab was non-inferior to its 1-year administration
Yu *et al*.[2] (2020)	12	DFS 1.32 (1.17–1.49), p<0.0001	Significant linear association between shortened treatment time of trastuzumab and recurrence risk; 3-, 6- and 9-month reductions in treatment time resulted in 16%, 35% and 57% increases in recurrence risk, respectively
Deng *et al*.[3] (2020)	5	DFS 1.10 (0.99–1.23), p=0.09 and OS 1.14 (0.99–1.32), p=0.07	Twelve-month standard duration adjuvant trastuzumab therapy with a tendency towards superior survival
Chen *et al*.[4] (2020)	6 (*n*=11 496)	DFS 1.13 (1.03–1.25), p=0.01 and OS 1.16 (1.01–1.32), p=0.03	One-year adjuvant trastuzumab treatment conferred substantial survival benefits
Goldvaser *et al*.[5] (2019)	6	DFS 1.14 (1.05–1.25), p=0.02 and OS 1.15 (1.02–1.29), p=0.02	One year of targeted HER2 treatment should remain the standard adjuvant treatment in early-stage HER2-positive disease with appropriate cardiac monitoring
Inno *et al*.[6] (2019)	5 (*n*=11 318)	DFS 1.19 (1.08–1.3), p<0.001 and OS 1.22 (1.07–1.39), p=0.003	One-year adjuvant trastuzumab is associated with better DFS and OS compared with shorter durations and should still be considered the standard duration
Niraula and Gyawali[7] (2019)	5 (*n*=12 000)	DFS 1.21 (1.09–1.36), p<0.001 and OS 1.23 (1.07–1.42), p=0.004	One year of trastuzumab for adjuvant treatment of breast cancer improves outcomes compared to shorter treatments in the overall population

HR hazard ratio DFS disease-free survival OS overall survival HER2 human epidermal growth factor receptor 2 CI confidence interval

identify subgroups (hormone positive *v*. hormone negative, early breast cancer *v*. locally advanced breast cancer and metastatic breast cancers) for whom shorter durations might suffice. Numerous studies have also shown that trastuzumab-based neoadjuvant therapy has higher rates of pathological complete response (pCR).[9] Thus, it is also important to identify the optimum duration of trastuzumab among those with and without pCR after neoadjuvant therapy, and evaluate if shorter duration might suffice among those with pCR while longer durations of trastuzumab may benefit those with residual disease. Given the cost of medication being a major barrier for receipt of HER2-directed therapy in low- and middle-income countries, it will be useful if the disease subgroups that benefit from short-duration trastuzumab are identified.

Conflicts of interest. None declared

REFERENCES

1 Gogia A, Deo S, Sharma D, Mathur S. Breast cancer: The Indian scenario. *J Clin Oncol* 2020;**38** (15 Suppl):e12567.

2 Yu KD, Wang X, Chen WK, Fan L, Mo M, Chen H. Tailored duration of adjuvant trastuzumab for human epidermal growth factor receptor 2-positive breast cancer. *NPJ Precis Oncol* 2020;**4:**23.

3 Deng H, Du X, Wang L, Chen M. Six months vs. 12 months of adjuvant trastuzumab among women with her2-positive early-stage breast cancer: A meta-analysis of randomized controlled trials. *Front Oncol* 2020;**10:**288.

4 Chen L, Zhou W, Hu X, Yi M, Ye C, Yao G. Short-duration versus 1-year adjuvant trastuzumab in early HER2 positive breast cancer: A meta-analysis of randomized controlled trials. *Cancer Treat Rev* 2019;**75:**12–19.

5 Goldvaser H, Korzets Y, Shepshelovich D, Yerushalmi R, Sarfaty M, Ribnikar D, *et al*. Deescalating adjuvant trastuzumab in HER2-positive early-stage breast cancer: A systemic review and meta-analysis. *JNCI Cancer Spectr* 2019;**3:**pkz033.

6 Inno A, Barni S, Ghidini A, Zaniboni A, Petrelli F. One year versus a shorter duration of adjuvant trastuzumab for HER2-positive early breast cancer: A systematic review and meta-analysis. *Breast Cancer Res Treat* 2019;**173:**247–54.

7 Niraula S, Gyawali B. Optimal duration of adjuvant trastuzumab in treatment of early breast cancer: A meta-analysis of randomized controlled trials. *Breast Cancer Res Treat* 2019;**173:**103–9.

8 Hurvitz SA. Is the duration of adjuvant trastuzumab debate still clinically relevant? *Lancet* 2019;**393:**2565–7.

9 Wu YT, Xu Z, Arshad B, Wu JS, Zhang K, Wu KN, *et al*. Significantly higher pathologic complete response (pCR) after the concurrent use of trastuzumab and anthracycline-based neoadjuvant chemotherapy for HER2-positive breast cancer: Evidence from a meta-analysis of randomized controlled trials. *J Cancer* 2018;**9:**3168.

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