Duration of trastuzumab use in patients with early breast cancer

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 trastuzumb among patients with early breast cancer: An individual participant data and trial-level meta-analysis. *JAMA Network Open* 2020;**3:**e2011777.

SUMMARY

This meta-analysis aimed to compare clinical trials with shorter durations of trastuzumab with 1 year of trastuzumab use for patients with early breast cancer. Six eligible randomized controlled trials (RCTs) were selected, of which three compared 6 months of trastuzumab treatment with 1 year, and the remaining three trials compared 9–12 weeks with 1 year of trastuzumab use. The meta-analysis was presented in two ways. First, individual participant data (IPD) for disease-free survival (DFS) and overall survival (OS) were extracted both manually and through a specialized software, and then survival curves were reconstructed for DFS and OS using a special command. This was possible for five of the six studies in the meta-analysis and included 11 376 patients. Second, a trial-level analysis was done, extracting hazard ratios (HRs) and their 95% confidence intervals from each study using standard statistical methods; all six RCTs comprising 11 603 patients were included.

A median value of the DFS HR of 1.3 for non-inferiority across all studies was chosen. Therefore, to establish non-inferiority for the shorter duration versus 1 year of trastuzumab use, the upper limit of the confidence interval for the estimated HRs of the studies had to be less than 1.3. Cardiac toxicity in terms of the proportion of patients developing congestive heart failure (CHF) was also calculated between the shorter and 1 year trastuzumab use groups.

The meta-analysis was able to show non-inferiority for DFS at both the IPD and trial-level, with the upper limit of the confidence interval being 1.25 and 1.26, respectively, well within the limit of 1.3. The IPD analysis showed a DFS HR of 1.14 (1.03–1.25) and trial-level analysis showed a DFS HR of 1.15 (1.04–1.26). This translated into a 5-year DFS of 85.42% for the shorter duration and 87.12% for 1 year for the IPD analysis. However, for OS the upper limit just crossed 1.3 in both the IPD and trial-level analyses. The relative risk of CHF was almost halved with the shorter duration trastuzumab, 0.53 (0.38–0.74). The authors concluded that a shorter duration of trastuzumab use may be preferred for patients with low-risk disease and for those with cardiac risks.

COMMENT

The optimal duration of adjuvant trastuzumab use has been greatly discussed in recent years. Ever since the FinHer study[1] provocatively suggested that 9 weeks of adjuvant trastuzumab use provided equal benefit for distant DFS as a 1-year treatment, shorter durations of adjuvant trastuzumab use have been explored with much interest. The decision to administer trastuzumab for 1 year in the adjuvant setting is arbitrary and based on no pre-existing evidence. What we know is that in the metastatic setting, continuing trastuzumab for a long period is important for good outcomes. Six studies have looked at shorter duration trastuzumab use in the adjuvant setting, ranging from 9 weeks to 6 months.[2–7] One of these studies had cardiac safety as a primary end-point, and was not powered for DFS.[2] Only one of the short duration studies, Persephone, also the largest one, was able to definitely show non-inferiority.[7] The other large study, Phare, was inconclusive for non-inferiority.[6] The HRs for both Persephone and Phare were similar with point estimates of 1.07 and 1.08 for DFS, respectively.

There are no conventional or established non-inferiority trial designs, and non-inferiority margins are often arbitrarily defined based on a single outcome—in the case of these trials it was DFS. This has led to a large number of patients being randomized over many years at great cost. A recent article on near equivalence outlines strategies whereby available evidence can make alternative therapies such as short duration trastuzumab acceptable, and more cost-effective.[8] One such strategy is the re-evaluation of failed non-inferiority trials. It is important to consider both positive outcomes such as DFS and OS as well as negative consequences such as cost and toxicity. Using near equivalence, if a shorter duration of trastuzumab use is less toxic and less costly than 1 year of trastuzumab, it may be a preferred choice, in spite of uncertainty regarding its effect on DFS and OS, especially in countries such as India.

The first five studies reported with shorter duration of trastuzumab use failed to conclusively show non-inferiority. Therefore, when the sixth and last study Persephone showed a clear non-inferior result, it was important to answer the duration question with a meta-analysis of all previous studies. Of the four meta-analyses for DFS and OS published so far, that done by Gulia *et al*. is the most recent one. The earlier meta-analyses reported by Inno, Gyawali and Chen *et al.*, respectively,[9–11] did a trial-level meta-analysis. All three meta-analyses included five or six RCTs. After a search for relevant studies on various databases and conferences, they extracted HRs for DFS and OS, and various subgroups such as ER-positive and -negative patients, node-positive and -negative patients, etc. Estimates of HRs were pooled and weighted, and a pooled HR was calculated using standard statistical models. The PRISMA guidelines were followed.[12] However, none of the meta-analyses was able to prove non-inferiority of the shorter duration to 1 year of trastuzumab use.

The meta-analysis reported by Gulia *et al.* is different and actually quite clever. Apart from the trial level meta-analysis, independent data for time-to-event analysis for each patient has been extracted from the given survival curves by a referenced method and DFS and OS curves have been reconstructed.[13] This is a herculean task and the effort taken by the investigators must be lauded. Meta-analyses that use IPD are often reliable, robust and believable. Unlike the previous three meta-analyses, the authors were able to show non-inferiority for DFS for the short duration trastuzumab use, compared to the standard treatment of 1 year, but not so for OS. The survival curves for both DFS and OS which were reconstructed were so close that they were nearly superimposable. From the subgroup analysis, it was clear that high-risk patients with ER-negative disease, positive nodes and concomitant therapy benefited more from 1 year of trastuzumab use, but not greatly. This has been seen in the other meta-analyses as well. Also, the risk for cardiac toxicity was significantly reduced in the shorter duration arm.

A debatable issue regarding this meta-analysis is the use of the median HR value of 1.3 for DFS taken from all the studies as the reference for non-inferiority. This value probably may not take into account the heterogeneity of studies included in the meta-analysis. We know that heterogeneity exists in the number of patients, tumour characteristics, definitions of Her-2 positivity

as well as changes in practice over years of accrual among the included studies. All the shorter duration studies, barring one,[6] did not perform a cost-effective analysis for shorter duration trastuzumab use versus 1 year. In view of the escalating healthcare costs, this would have been a meaningful end-point. Furthermore, is the duration of trastuzumab use really relevant in the clinic today? The focus for smaller, node-negative tumours has changed to de-escalation of chemotherapy.[14] Whether we can shorten the duration of trastuzumab use in this setting is not known. For high-risk and larger tumours, neoadjuvant therapy is increasingly being used. If there is residual disease after neoadjuvant therapy, then the better option is TDM1 rather than trastuzumab for 1 year.[15]

Nevertheless, this meta-analysis is important. It gives clinicians more confidence to offer a shorter duration of treatment to the lower risk Her-2-positive patients and those with an underlying cardiac risk. It is a well-conducted meta-analysis and the only one to look at IPD analysis till date. It is also relevant to countries such as India. For those who cannot afford 1 year of treatment (even biosimilars), there is reassurance both for the treating physician and the patient, that shorter duration trastuzumab use will not cause great harm.

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SHONA NAG
Department of Oncology
Sahyadri Hospitals
Pune
Maharashtra
India

[**To cite:** Nag S. Duration of trastuzumab use in patients with early breast cancer. [Selected Summary]. *Natl Med J India* 2021;**34:**285–6.]