Short-course adjuvant trastuzumab will increase cure rates in patients with human epidermal growth factor receptor 2-positive breast cancer

Internationally, breast cancer is the commonest cancer in women, comprising 25% of cancers. It is also the most frequent cause of cancer death in women, comprising 14.3% of the total in economically less-developed regions.[1]

Human epidermal growth factor receptor 2 (HER2) is over-expressed or positive in 20 - 25% of patients with early breast cancer. Trastuzumab is an antibody that blocks the HER2 receptor, and adjuvant trastuzumab has been shown to increase overall survival (OS) and disease-free survival (DFS) in HER2-positive patients, but is associated with a risk of adverse cardiac events.[2]

Despite the significant clinical benefit associated with adjuvant trastuzumab, ~90% of patients in South Africa (SA) with HER2-positive breast cancer do not currently have access to adjuvant trastuzumab. The main reason for the lack of access to trastuzumab in SA is the cost.[3] This is the case for patients managed in both the public sector and the less well-resourced of the private medical schemes.

Trastuzumab is conventionally given for a 12-month period. However, a new study confirms that it is probable that a much shorter course, given for 9 weeks, will increase the survival and DFS rates in patients compared with no trastuzumab, as there is no major loss of effectiveness.[4] It is estimated that the 9-week course of trastuzumab has a hazard ratio (HR) of 0.7 compared with no trastuzumab, and results in a 30% increase in patient survival. It is also associated with fewer cardiac complications and will be more affordable.[4]

The studies

A Cochrane systematic review and meta-analysis of adjuvant trastuzumab has shown a clinically significant improvement in survival. For OS, the HR was 0.66 (95% confidence interval (CI) 0.57 - 0.77; $p<0.00001$) and for DFS it was 0.60 (95% CI 0.50 - 0.71; $p<0.00001$).[2] There was also cardiac risk associated with this treatment. For adverse cardiac events, the relative risk (RR) was 5.11 (90% CI 3.00 - 8.72; $p<0.00001$), and for a decline in left ventricular ejection fraction it was 1.83 (90% CI 1.36 - 2.47; $p=0.0008$).[2]

The 12-month adjuvant trastuzumab regimen was chosen empirically, and was supported by the HERceptin Adjuvant (HERA) trial.[5] In 5 102 patients, a regimen of adjuvant chemotherapy with no adjuvant trastuzumab was compared with regimens of either 1 or 2 years of adjuvant trastuzumab. One-year trastuzumab regimens compared with regimens with no trastuzumab resulted in better DFS and OS. The 2-year regimen showed no further benefit. The 10-year survival rates for regimens with no adjuvant trastuzumab and for the 1-year trastuzumab regimens were 63% and 69%, respectively. The rates of cardiac events in regimens with no trastuzumab and for the 1-year trastuzumab regimens were 0.9% and 4.4%, respectively.

In the PHARE trial,[6] 6 months of adjuvant trastuzumab was shown to be marginally less effective than the 12-month regimen in terms of DFS in a non-inferiority study. The 2-year DFS was 93.8% (95% CI 92.6 - 94.9) in the 12-month group and 91.1% (95% CI 89.7 - 92.4) in the 6-month group.

To date, shorter courses of trastuzumab have not been prospectively compared with no trastuzumab in an adequately powered trial. The FinHer study was designed primarily to evaluate different chemotherapy agents; however, it included a subset analysis of 232 patients in whom a 9-week course of trastuzumab was compared with no trastuzumab.[7] This showed that this regimen had efficacy that was numerically similar to the 1 year of trastuzumab, but the study was not powered to demonstrate statistical significance. For distant DFS, the HR was 0.65 (95% CI 0.38 - 1.12; $p=0.12$). In patients with positive nodes there was a statistically significant increase in DFS, with an HR of 0.57 and a p-value of 0.047.

New evidence of the activity and lower toxicity of the short course of trastuzumab has now come from the Italian Short HER study,[4] presented at the prestigious meeting of the American Society of Clinical Oncology recently but not yet fully published. In this study, 1 253 patients from 82 centres were randomised to 12 months' or 9 weeks' adjuvant trastuzumab (long v. short HER). This was a non-inferiority study. Comparing long HER with short HER, the 5-year DFS rates were 87.5% v. 85.4%, respectively, and the 5-year OS rates were almost identical at 95.1% and 95.0%. However, non-inferiority criteria were not reached in the frequentist analysis, with an upper limit of the CI set at 1.289 for DFS. For OS, the HR was 1.06 (90% CI 0.73 - 1.55) and for DFS the HR was 1.15 (90% CI 0.91 - 1.46). However, importantly, the researchers also carried out a Bayesian analysis that showed a 78% probability that the 9-week regimen was not inferior to the 12-month one.

This study also showed that prognostic factors in patients influenced the relative benefit of long HER as opposed to short HER. Patients with stage III disease or with four or more positive nodes, 15% of the group overall, benefited most from long HER. The evidence of non-inferiority was highest in the remaining patients.

In addition, cardiac toxicity was less with the short HER regimen. Long HER compared with short HER showed a statistically significant decrease in left ventricular ejection fraction over time ($p=0.023$), and the rates of cardiac events of grade 2 or more were 14.4% and 5.1%, respectively, with an HR of 0.32 (95% CI 0.21 - 0.50; $p<0001$).

The drug cost of a 9-week trastuzumab regimen is a fifth of a 12-month one. The total doses of trastuzumab administered are 20 mg/kg and 110 mg/kg, respectively.

An estimate of the HR for overall survival for 9 weeks' trastuzumab compared with no trastuzumab is 0.7, which is calculated as follows: for 1 year's trastuzumab compared with no trastuzumab, the HR is 0.66,[2] and for 9 weeks' trastuzumab compared with 1 year's trastuzumab, the HR is 1.06.[4] An estimate of the HR of 9 weeks' trastuzumab compared with no trastuzumab would therefore be ~$0.66 \times 1.06 = 0.70$.

An estimate of the HR for disease-free survival for 9 weeks' trastuzumab compared with no treatment is 0.69. For 1 year's trastuzumab compared with no trastuzumab, the HR is 0.60,[2] and for 9 weeks' trastuzumab compared with 1 year's trastuzumab, the HR is 1.15.[4] An estimate of the HR for DFS of 9 weeks' trastuzumab compared with no trastuzumab would therefore be ~$0.66 \times 1.15 = 0.69$. The HR in the underpowered FinHer study was 0.65.

In a recent publication in the *SAMJ*,[3] the affordability and value of trastuzumab were reviewed. Using value (outcome divided by cost) as a parameter, it was proposed that there were two ways forward to provide this important and effective therapy within the finite resources of our healthcare system. These were: (*i*) the use of shorter courses of trastuzumab, which would be both active and more affordable; and (*ii*) identifying those prognostic groups that would

benefit the most from adjuvant trastuzumab. The short HER studies support these proposals.

Conclusions

Randomised trials of short courses of trastuzumab compared with no trastuzumab cannot now be done, as a 'no adjuvant trastuzumab' arm would be ethically unjustified in a study setting, even though this question is very relevant to low- and middle-income countries. Nevertheless, the studies done provide us with strong and coherent evidence of the clinical value of a short-course trastuzumab regimen.[8] There will be further debate about 12-month trastuzumab v. shorter treatments in all countries, balancing benefits, costs and toxicity. Patients with stage III disease or four or more positive nodes are likely to continue with 1 year's trastuzumab in well-resourced healthcare systems.

In SA, however, a decision needs to be made about how to make best use of this important treatment across all sectors of the healthcare system. Is it defensible to restrict adjuvant trastuzumab to the minority of people who can afford the 1-year course? Or should we accept the current evidence that a 9-week course is almost as effective and certainly less toxic, as well as an effective use of our healthcare resources? Moreover, the best available evidence indicates that 9 weeks of trastuzumab increases patient survival by about 30% compared with patients who receive no trastuzumab. Why should we not make it available to the large proportion of patients who currently have no access to it?

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