HERA – NEW LESSONS FROM A NEW TRIAL

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The HERA trial is a large international randomised trial testing the efficacy of the new biological drug trastuzumab (Herceptin) in early breast cancer. HERA is being conducted in Australia by the Australian New Zealand Breast Cancer Trials Group in collaboration with the International Breast Cancer Study Group and the Breast International Group. This is the first time Australian centres have participated in a trial of a biological agent in the adjuvant setting and is an important learning opportunity for all those involved.

Background

HER2 (also known as erbB2 or neu) belongs to a family of receptors that are located on the surface of human cells, and when stimulated they transmit growth signals to the nucleus. In many cancers, these growth pathways become uncontrolled, contributing to cancer development or progression. For example, the receptor may mutate in a way that causes it to always be "switched on". In the case of HER2, about 15% of breast cancers have a gene amplification, so that too many receptors are expressed (and activated) on the cell surface. Cancer cell activity thus increases and "HER2 positive" breast cancers have a worse prognosis than "HER2 negative" breast cancers.

However, determining the HER2 status of tumours is not as straightforward as determining the estrogen receptor (ER) status. Immunohistochemical staining is carried out (and scored from 1+ to 3+), but a more accurate and expensive test is fluorescent in situ hybridisation (FISH), which measures the actual number of HER2 genes in the cells. Trastuzumab is a humanised monoclonal antibody that can block these overexpressed receptors.

Trastuzumab in metastatic disease

The first randomised trial involving trastuzumab compared chemotherapy with or without trastuzumab in women with newly diagnosed metastatic breast cancer[1]. Tumour response rates, time to progression and overall survival were better with the addition of trastuzumab. An unexpected finding was an increase in cardiotoxicity, especially when trastuzumab was given with an anthracycline. Additionally, as in earlier studies of trastuzumab given as a single agent, tumours with an immunohistochemical score of 3+ responded better to trastuzumab than those with a score of 2+.

Problems with an adjuvant trial

Given the activity of trastuzumab in advanced disease, an obvious question is whether it is feasible and effective if given as part of the adjuvant treatment of early breast cancer. An immediate problem is the required size of such a trial, since it will apply to only 15% of women with early breast cancer needing adjuvant treatment. It is important that testing for HER2 is standardised as much as possible, given the ease with which inconsistent results can be obtained. Lastly, while toxicity is always important, it is particularly so when new drugs are given to otherwise well women with potentially long lifespans. Thus intensive cardiac monitoring is a crucial part of any adjuvant trial using trastuzumab.

The HERA trial

Given all these considerations, it is clear that large resources are required to conduct an adjuvant trial. The HERA trial therefore brings together several clinical trials groups across the world, and has been designed and initiated in close consultation with the relevant pharmaceutical company, which is providing strong financial support without impinging on the scientific independence of the various trial committees.

Two biological considerations incorporated into the design of HERA differentiate it from the concurrent American trastuzumab trials. Recent information supports the use of trastuzumab in a three-weekly schedule, rather than the weekly schedule that has been used to date. Thus there will be the opportunity to make indirect comparisons between trials about the cost, patient acceptability and toxicity of these schedules. In addition, there are of course not yet any data on the appropriate duration of trastuzumab in the adjuvant setting, and the American trials are not testing this.

Thus HERA is a three-armed randomised trial. After appropriate adjuvant chemotherapy, 3,000 women will be randomised to either no trastuzumab, trastuzumab for one year or trastuzumab for two years. Follow-up will continue for 10 years. All breast tumour samples will require testing in a single reference laboratory. Frequent cardiac monitoring (either echocardiograms or radioisotope scans) will be carried out using the same protocol for all three arms of the trial. This is an important point, since such intense cardiac monitoring is not usually done in women having chemotherapy alone. This trial will therefore provide the opportunity to assess prospectively the level of cardiotoxicity associated with usual adjuvant chemotherapy protocols and thus accurately measure any additional effects seen with trastuzumab.

Because accrual to this trial will be challenging – over 30,000 women will need to be screened – there is a deliberately pragmatic approach to chemotherapy protocols. Recognising that evidence from randomised trials supports a number of standard chemotherapy regimens, the choice of chemotherapy is left largely to individual investigators.

Lessons to be learned

Participation in this large new trial offers the opportunity to learn several lessons that will be increasingly important to clinical trialists over the coming years. As cancer treatments inevitably become more targeted, so will the requirement to coordinate large-scale tissue collection and testing. In the face of such increasing complexity, it will be important to keep as many aspects of the trial as simple as possible. Thus HERA trialists will generally be able to employ the adjuvant chemotherapy protocols they are used to.

The evolving biological agents requiring rigorous testing in randomised trials will also change the way we monitor clinical trials. For example, we will need to be aware of new and occasionally unexpected toxicities. Even the traditional endpoints of clinical trials may need to be modified if some of these agents are found to have disease-stabilising effects rather than inducing tumour regression. We must therefore continue to scrutinise carefully all available phase II and early randomised trials of new agents before incorporating these new drugs into definitive large scale trails, and maintain an open mind about clinical trial design and conduct.

Reference

1 DJ Slamon, B Leyland-Jones, S Shak, et al. "Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2." *N Engl J Med*, 344 (2001): 783-92.