E18. Her2 positive breast cancer from optimal diagnosis to optimal treatment

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In the past 20 years, our knowledge of the behaviour and biology of the HER2 receptor in clinical breast cancer has led to a revolution in the way that this aggressive subset of cancers is treated. Furthermore, major pharmaceutical developments and extensive work by academics now allow clinicians to offer patients with this subtype of breast cancer novel and very effective therapies supported by evidence from high quality clinical trials.

Despite this explosion in knowledge there remain a number of key questions, and this lecture will summarise the clinical knowledge, key data from relevant clinical trials and address the outstanding questions.

Diagnosis

The presumption at present is that there is a simple diagnostic of HER2 over-expression that identifies those tumours driven by HER2 biology sufficiently to have a similar biology and sensitivity to therapy. There are clear guidelines on the process for diagnosing HER2 protein overexpression that is of a sufficient level to predict a high chance of sensitivity to anti-HER2 therapies (e.g. ASCO guidelines 2007). These were developed to identify patients who would be candidates for treatment with Herceptin, but in the clinic, knowledge of HER2 overexpression can influence other therapeutic decisions and it is a little unclear whether the same diagnostics (and cut-offs) are valid for all such decisions.

Paraffin-embedded tumour samples should be analysed at a high-quality, experienced laboratory, and the standard algorithms use a mixture of immunohistochemistry (IHC) to measure the level of HER2 protein at the cell surface, and *in situ* hybridisation to look for gene amplification. Most authorities consider the presence of gene amplification the best diagnostic for treatment selection. However, this is not just because there is a good correlation between DNA copy number and protein levels, but also because routine fixation processes mean that protein levels as measured by IHC may not always be an accurate indicator of the level *in vivo* in the patient.

Treatment choices

Advanced

In advanced breast cancer, the use of the monoclonal antibody Herceptin is standard across much of the world, based on acceptable single agent activity and clear increases in response rate, time to progression and overall survival when given in combination with taxanes, as well as impressive levels of clinical activity when given with other chemotherapeutic agents. More recent data suggest that any benefit from giving Herceptin with anti-hormonal agents may be much less, and it is much less clear that this should be the standard of care, though it is an active combination. Non-randomised data suggest that continued Herceptin after progression may be of benefit when combined with a different chemotherapeutic agent, such that this is a common approach in many countries.

Recently, within the USA and Europe, another anti-HER2 therapy has been approved for clinical use. Lapatinib is a small molecule inhibitor of both HER2 and EGFR, but the data available to date suggest that in advanced breast cancer, it is the anti-HER2 action that is responsible for most of its clinical activity. As a single agent it has, like Herceptin, modest activity, but two trials have shown additional benefit when given respectively with either Capecitabine or Taxol in women with advanced, HER2 overexpressing breast cancer. It appears to be well-tolerated, and to have a level of cardiac toxicity that is certainly no worse than Herceptin, and possibly even better, though no direct comparative studies have yet reported. Also, within the past months, data from a prematurely closed, and hence under-powered, study have suggested that continued Herceptin given in combination with Capecitabine may be superior to Capecitabine alone. What these two trials confirm is that continued anti-HER2 targeted therapy, given with Capecitabine, is effective in patients whose tumours have been previously exposed to Herceptin: what they do not confirm is which is the better approach, though the *strength* of the evidence is clearly in favour of Lapatinib.

Neo-adjuvant

Several studies including randomised trials have confirmed that the significant increases in response rate seen from combining taxanes and Herceptin in advanced disease also apply to the neo-adjuvant setting. More importantly, in patients given chemotherapy with Herceptin, it is the pathological complete response rate that is enhanced, and these patients in most non-Herceptin studies go on to have the best outcome. Long-term follow-up from these studies is not yet available, but given

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the data from the adjuvant studies, it is highly likely that this short-term gain will give similar long-term benefits.

Adjuvant

Three large adjuvant trials have all shown clear improvements in disease-free and overall survival for the use of Herceptin with, or after, standard post-operative adjuvant chemotherapy. Two smaller trials have given conflicting results: one, the FinHer trial, gives similar benefits as the large adjuvant trial, but another, the PACS04 study, found much less benefit. A formal meta-analysis of these studies has not yet been done, but the weight of the evidence still points to a clear indication for its use in the adjuvant setting.

Questions

Patient selection

There are some exploratory data from the adjuvant trials that suggest there may be patients with lower levels of HER2 protein who also benefit from the use of adjuvant Herceptin, and there are data that suggest there may be other biomarkers predicting particular sensitivity to the drug. None of these data sets give a robust challenge to the current diagnostic of *ISH+ and/or IHC 3+, but these data cannot be ignored!

Chemotherapy

The main issue is whether there is any role for anthracyclines in non-HER2 overexpressing tumours, and whether there is a clear role for non-anthracycline chemotherapy in HER2 overexpressing tumours. The data for these considerations mostly comes from one prospective study (BCIRG006) in patients selected for HER2 overexpression, and several retrospective analyses of phase III trials of chemotherapy in patients unselected by HER2 status. This gives rise to limitations in the interpretation of the data, and these will be discussed.

Hormone therapy

It is generally recognised that, with a few exceptions, ER positive and HER2 overexpressing tumours appear to benefit less from hormonal therapy than those without HER2 overexpression. Much of these data apply to the use of tamoxifen but recent datasets suggest that it may also apply in many cases to the use of aromatase inhibitors. Thus the role of HER2 status in selection of hormonal therapy is perhaps less certain than it appeared a couple of years back.

Novel treatments

A number of other small molecule HER-family drugs are being developed, and data on these will be discussed as available. There are other approaches under study including vaccines, and other antibodies such as Pertuzumab which have shown activity in combination with Herceptin in patients whose tumours are refractory to Herceptin. Data on these agents will be covered only briefly unless there are compelling new data available.

Conclusion

Accurate diagnosis of those patients whose tumours overexpress HER2 should be a key part of the work-up of all breast cancer patients. This is a clear indication for consideration of anti-HER2 therapy but it is a less clear guide as to the optimal chemotherapy and hormonal therapy to use for that individual.

Conflict of interest statement

The author has received honoraria from Roche (who make Herceptin), GlaxoSmithKline (who make Lapatinib), Pfizer (who make anthracyclines) and Astra-Zeneca, Pfizer and Novartis (who make the hormonal drugs mentioned).

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