Adjuvant Trastuzumab (Herceptin) in Breast Cancer

evaluating its cost-effectiveness in regional breast cancer

SUMMARY

Breast cancer that is human epidermal growth factor receptor 2-positive (HER2+) tends to be more aggressive, more resistant to standard chemotherapy, and carries a poorer prognosis. In women who have HER2+ breast cancer who also have involved lymph nodes or a tumour larger than 1 centimetre , 12 months of Herceptin added to standard chemotherapy reduces risk of death by a third, compared to chemotherapy alone. Herceptin is however expensive (an added cost of NZ$ 74,000 in NZ), and also carries the risk of (usually reversible) cardiac side-effects. We evaluated the cost-effectiveness of 12 months of adjuvant or added Herceptin compared to standard chemotherapy alone. We specifically investigated Herceptin's cost-effectiveness across four different breast cancer subtypes, representing relatively good to relatively poor prognoses.

We evaluated Herceptin in the treatment of HER2+ early regional breast cancer in women

Herceptin is given intravenously every three weeks for a total period of 12 months, and patients also have cardiac monitoring scans every 3 months to monitor for the risk of heart failure. The target population here is women with node-positive ('regional') HER2+ breast cancer who are "fit" for Herceptin on initial cardiac assessment. They are further divided into four different breast cancer subtypes, defined by estrogen receptor (ER) status and progesterone receptor (PR) status. ER+/PR+/HER2+ subtype has the best prognosis, ER-/PR-/HER2+ has the worst prognosis, and the other two subtypes fall in between these two extremes.

We used a macrosimulation model to estimate cost-effectiveness using NZ data

For each subtype, the model estimates how much health benefit is gained (in quality-adjusted life years or QALYs) from Herceptin, and how much it costs or saves the health system. These are combined into an Incremental Cost-Effectiveness Ratio or ICER.

Is it cost-effective?

The cost-effectiveness of 12 months of Herceptin for early regional breast cancer varied markedly by breast cancer subtype *and* by age. For the best prognosis subtype (ER+/PR+/HER2+), the cost-effectiveness ranged from NZ$73, 500 per QALY for 25-44 year-old women, through to NZ$ 338,000 per QALY for women who were 85+ years. For the worst prognosis subtype (ER-/PR-/HER2+), it ranged from NZ$ 34,200 per QALY for 25-44 year-olds through to NZ$ 148, 900 for women who were 85+ years.

If we used a cost-effectiveness threshold of NZ$ 45,000 per QALY (i.e. we assume the government is happy to pay NZ$ 45,000 for 1 QALY), then Herceptin would only be cost-effective for women up to age 45 and 70 in the two poorest-prognosis subtypes, ER-/PR+/HER2+ and ER-/PR-/HER2+ respectively.

Our bottom line

In this evaluation of Herceptin in early regional breast cancer, the poorer the prognosis, the greater the health gains from Herceptin, and the better the cost-effectiveness. Within each subtype, the health gains (and the cost-effectiveness) were better for younger women than for older women. This analysis demonstrates the value of investigating cost-effectiveness by different subtypes within a disease, potentially allowing more targeted allocation of limited health resources.

IN MORE DETAIL

Herceptin to Reduce Breast Cancer Mortality in Early Regional Breast Cancer

In women with HER2+ breast cancer that are node-positive, 12 months of Herceptin (in addition to standard chemotherapy) is recommended to reduce mortality from breast cancer. While the optimal duration of Herceptin is unknown and multiple trials are underway, 12 months of Herceptin remains the standard of care. Herceptin is however expensive (an added cost of NZ$ 74,000 in NZ), and also carries the risk of (usually reversible) congestive heart failure. Differences in the cost-effectiveness of Herceptin by age is well-described, but differences in cost-effectiveness by breast cancer subtype (hormone receptor status) less so. Here we specifically investigated Herceptin's cost-effectiveness across four different breast cancer subtypes, representing relatively good to relatively poor prognoses.

In our model:

- Herceptin is given every 3 weeks intravenously for a period of 12 months as an outpatient
- Herceptin is given concurrently with standard taxane chemotherapy for first 4 months
- Women also undergo cardiac monitoring scans every 3 months until the end of treatment as per current practice in NZ.

We compared Herceptin added to standard chemotherapy, to chemotherapy alone.

QALY or Quality-Adjusted Life Year:

The remaining life expectancy, adjusted for quality of life. Think of one QALY as one year of life in perfect health.

Model

We began with a NZ population of women aged 25 years and above with HER2+ regional breast cancer, deemed fit for Herceptin based on initial cardiac assessment. We used a Markov model to follow this population through to death or 110 years. The model 'allowed' for women to die of breast cancer, die of other causes, and develop moderate or severe congestive heart failure as a side-effect of Herceptin. The model estimated:

- Health gain in quality-adjusted life years or QALYs
- Health system costs in NZ$
- Cost-effectiveness in Incremental Cost-Effectiveness Ratios (compared to no Herceptin)

ICER or Incremental Cost-Effectiveness Ratio:

The difference in costs between one intervention and its comparator, divided by the difference in health gain. An ICER tells you how much more (or less) cost-effective an intervention is compared to something else.

This was done for each of four subtypes:

- ER+/PR+/HER2+ (best prognosis)
- ER+/PR-/HER2+
- ER-/PR+/HER2+
- ER-/PR-/HER2+ (worst prognosis)

Prognosis here refers to *baseline* prognosis (i.e. prognosis before any Herceptin has been taken).

Assumptions in the Model

Our model contains multiple assumptions. Some of these assumptions apply across all BODE^3 evaluations, and are described in a range of protocols at the BODE^3 website here. Some assumptions are specific to this topic: please email tony.blakely@otago.ac.nz for more information.

Some of our key assumptions include the following:

- We used a health system perspective and so did not include costs and consequences beyond the health system (such as productivity costs).
- We allowed for expected or background disease and limited the maximum amount of QALYs that could be gained with increasing age.
- We applied a 3% discount rate to costs and QALYs gained.
- We assumed the benefit of Herceptin lasted for eight years.
- We calculated the dosage of Herceptin based on a 70 kg average female body weight, as used by NZ pharmacists.
- For simplicity, we assumed that all patients who developed congestive heart failure while on Herceptin did so at 6 months, that they discontinued Herceptin at that point and received half the benefit of a full 12-month course, and that their heart failure symptoms were reversible, lasting 6 months.

QALYs, Costs & Cost-Effectiveness

QALYs	The QALYs each patient gained were greater for the poorer-prognosis subtypes than for the better-prognosis subtypes. Within each subtype the QALY gains were also greater for younger women than for older women. For example, 25-44 year-olds in the best prognosis subtype (ER+/PR+/HER2+) gained 0.98 QALYs, compared with 2.09 QALYs for the equivalent age group in the worst-prognosis subtype (ER-/PR-/HER2+).
Costs	The mean incremental health system costs did not vary much by age or by subtype.
Cost-Effectiveness	The cost-effectiveness of 12 months of Herceptin for early regional breast cancer varied markedly by breast cancer subtype *and* by age. For the best prognosis subtype (ER+/PR+/HER2+), the cost-effectiveness ranged from NZ$ 73, 500 per QALY for 25-44 year-old women, through to NZ$ 338,000 per QALY for women who were 85+ years. For the worst prognosis subtype (ER-/PR-/HER2+), it ranged from NZ$ 34,200 per QALY for 25-44 year-olds through to NZ$ 148, 900 for women who were 85+ years. The other subtypes lie predictably between these two extremes. In general, Herceptin only fell below NZ$ 45,000 per QALY for the two worst prognosis subtypes, and only for women up to the age of 45 (ER-/PR+/HER2+) and 70 (ER-/PR-/HER2+) years.

A Note on Cost-Effectiveness Thresholds and Willingness-To-Pay

There is no consensus on a cost-effectiveness threshold in NZ. Our statements on cost-effectiveness stem from World Health Organization guidance, which is based on Gross Domestic Product (GDP) per capita. In NZ, GDP per capita is approximately NZ$ 45,000. If the ICER for an intervention is less than NZ$ 45,000 per QALY, we deem it cost-effective. However, you can use your own threshold or other yardsticks of cost-effectiveness. It should also be noted that policy decisions are made on multiple considerations, and cost-effectiveness is only one of these.

Cost-effectiveness Threshold or Willingness-To-Pay:

Society's willingness to pay for an extra unit of health gain e.g. a QALY. If the ICER for an intervention is less than the threshold, the government can view it as cost-effective and may fund it. If ICER is greater than the threshold, it is not deemed to be cost-effective and the government may not fund it.

Costs, QALYs & Cost-Effectiveness in Different Populations

Age	As described above
Ethnicity	Herceptin was more cost-effective for Māori than for non-Māori across all breast cancer subtypes.
Deprivation	Similar cost-effectiveness for most deprived patients as compared to least deprived.

Equity Analysis

Māori have higher background disease and death rates compared to non-Māori. Māori can be therefore automatically "disadvantaged" in economic evaluations because Māori have a more limited envelope of QALYs that can be gained from health interventions. We therefore conducted an 'equity analysis' to adjust for this, applying non-Māori rates of background disease and death to Māori instead of using Māori rates. Cost-effectiveness for Māori improved even further.

Uncertainty in our Results

There is unavoidable uncertainty present in the values we put into our models, and thus uncertainty in estimates of costs, health gains, and cost-effectiveness. The most uncertainty came from the cost of Herceptin, and cancer excess mortality rate ratios for each of the four subtypes.

Changing Some Assumptions

The results of the evaluation are sensitive to different assumptions. For example, if we started by just looking at pooled results (across all subtypes) for the 50-54 year age group in the main analysis, where the ICER was NZ$ 56,000:

What if we discounted at 0% instead of 3%?	Cost-effectiveness improves from NZ$ 56,000 to NZ $37, 200.
What if we reduced the cost of Herceptin by 30%?	Cost-effectiveness improves from NZ$ 56,000 to NZ$ 41,300.
What if we assumed the benefit of Herceptin lasted 20 years instead of 10 years?	Cost-effectiveness improves NZ$ 56,000 to NZ$ 50, 400.

Our Bottom Line

1. In this evaluation of Herceptin in early regional breast cancer, the poorer the prognosis, the greater the health gains from Herceptin, and the better the cost-effectiveness. Within each subtype, the health gains (and the cost-effectiveness) were better for younger women than for older women. If we used a cost-effectiveness threshold of NZ$ 45,000 per QALY, then Herceptin would only be cost-effective for women up to age 45 and 70 in the two poorest-prognosis subtypes, ER-/PR+/HER2+ and ER-/PR-/HER2+ respectively (the two ER- subtypes).
2. This analysis demonstrates the value of investigating cost-effectiveness by different subtypes within a disease, potentially allowing more targeted allocation of limited health resources.