Pharmacotherapeutic report, summary

Trastuzumab (Herceptin®) for 'HER2-positive early breast cancer'

Recommendation by the National Health Care Institute [*Zorginstituut Nederland*] dated 10-09-2013, based on a re-evaluation by the WAR (Scientific Advisory Committee) after 4 years of provisional inclusion on the NZa Expensive Medicines Supervisory Rule

In 2006 (t=0), trastuzumab was assessed for inclusion on the Expensive Medicines Supervisory Rule for the indication '***Adjuvant treatment of patients with early breast cancer (invasive, non-metastatic) with HER2 overexpression, after surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)***'. The supervisory rule of the Dutch Healthcare Authority (Nza), which ended as of 1-1-2012, states that re-assessment should take place four years after provisional inclusion (point in time t=4) in order to provide a definite decision on continued inclusion. As of 15 May 2012 the Minister of Health, Welfare and Sport (VWS) decided that the reassessment data should be used for advice on insured benefits. This re-assessment requires supplementary data on the pharmacotherapeutic value of trastuzumab with respect to comparative treatment(s). This could be data from randomised clinical studies (RCTs), follow-ups of earlier RCTs and observational studies (including 'outcomes research') carried out between t=0 and t=4. These data are compared with the results of the initial assessment at t=0.
The therapeutic value at t=0 was determined via comparison with standard chemotherapy.
The Scientific Advisory Committee of *Zorginstituut Nederland* reached the following conclusion.
- the therapeutic value of one year's treatment with trastuzumab in combination with chemotherapy (mainly the AC-T schedule) for the treatment of early HER2-positive breast cancer is greater than that of chemotherapy alone.

Trastuzumab [powder for intravenous infusion]

Registered indication. At t=0 (2005), the indication then being assessed was limited to 'Adjuvant treatment of patients with early breast cancer (invasive, non-metastatic) with HER2 overexpression, after surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable). By 2011, European market authorisation had been extended to include the following further indications:
'Herceptin is indicated for the treatment of patients with HER2-positive, early breast cancer:
- subsequent to surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).
- subsequent to adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- in combination with adjuvant chemotherapy comprised of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant treatment with Herceptin, for locally advanced (including inflammatory) disease or tumours >2 cm in diameter'.
In addition trastuzumab has market authorisation for the treatment of HER2-positive, metastatic breast cancer and the treatment of HER2-positive stomach cancer.

Posology. Three-weekly schedule: Initial loading dose 8 mg/kg followed by 6 mg/kg/three weeks. Weekly schedule: Initial loading dose 4 mg/kg followed by 2 mg/kg/week, beginning one week after the loading dose.

Mechanism of action. Trastuzumab is a recombinant, humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor-2 (HER2). HER2 overexpression is associated with a shorter disease-free survival. Binding of trastuzumab to HER2 inhibits the proliferation of human tumour cells and stimulates antibody-dependent, cell-mediated cytotoxicity.

Specific details. Schedules based on a taxane, anthracycline and cyclophosphamide are currently among the most commonly used therapeutic options. HER2-positive cancer exists when tumours demonstrate overexpression or HER2 gene-amplification, as shown with an accurate and validated assay (IHC 3+ or positive FISH/CISH).

Summary of the therapeutic value

Intended effects. T=0: The addition of trastuzumab to treatment with doxorubicin/cyclophosphamide followed by paclitaxel or with only an anthracycline resulted in a 50% risk reduction of the disease recurring in HER2-positive patients with primary operated breast cancer. In comparison with anthracycline alone, a significant effect was also found in the duration of general survival.
T=4: Overall survival and disease-free survival of patients with HER2-positive early breast cancer, when treated with trastuzumab in combination with the usual anthracycline-containing chemotherapy was significantly and clinically relevantly greater than that with chemotherapy alone.

Unintended effects. The most important adverse effects of trastuzumab are heart failure (particularly in combination with anthracyclines), infusion reactions and (neutropaenic) infections. In practice these adverse effects can be properly managed by means of prevention and monitoring.

Experience. Extensive experience has been gained with trastuzumab.

Applicability. The contraindications (including hypersensitivity, severe dyspnoea during rest) have not altered since t=0. Insufficient details about interactions are available. Trastuzumab should only be used by patients with HER2-positive tumour tissue (IHC 3+ or FISH+ or CISH+).

Ease of use. Trastuzumab is administered by intravenous infusion during one hour over a three-weekly or a weekly schedule during a year. The three-weekly schedule is used most frequently in the Netherlands. Trastuzumab is administered in combination with chemotherapy.

Final conclusion. For the treatment of early HER2-positive breast cancer, one year's treatment with trastuzumab in combination with chemotherapy, in particular the AC-T schedule, has an added therapeutic value in comparison with chemotherapy alone.