The clinical effectiveness of trastuzumab for breast cancer: a systematic review

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Executive summary

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Executive summary

Background

Breast cancer is the leading cause of cancer deaths amongst women in the UK. Figures suggest that about 13% of women initially presenting with breast cancer have advanced disease (stage III/IV) and about 50% presenting with early or localised breast cancer will eventually progress to advanced disease.

The prognosis of metastatic breast cancer (MBC) depends on age, extent of disease, oestrogen receptor status and previous chemotherapy treatment. There is also evidence that the over-expression of the product of the HER2 oncogene is an important prognostic factor, indicating a more aggressive form of the disease with a more rapid progression and shortened survival time. MBC is considered to be incurable and treatment is usually focused on relieving symptoms and improving quality of life (QoL) with as little treatment-related toxicity as possible. Trastuzumab (Herceptin®, Genentech Inc, South San Francisco, CA, USA), a recombinant humanised monoclonal antibody that specifically targets the epidermal growth factor receptor 2 (HER2) protein, is a relatively new anti-cancer agent that may be beneficial in a specific group of patients who are identified as having tumours that strongly overexpress HER2.

Objective

The objective of the review was to evaluate the effectiveness of trastuzumab in the management of breast cancer.

Methods

Only randomised controlled trials (RCTs) were initially considered for inclusion. Included trials had to evaluate trastuzumab alone or in combination with other agents versus systemic therapy without trastuzumab, and had to include individuals with breast cancer.

No RCTs of trastuzumab used as monotherapy for the treatment of breast cancer were found. The National Institute for Clinical Excellence (NICE), therefore, requested that non-comparative Phase II studies of trastuzumab used as monotherapy for the treatment of HER2-overexpressing (at level 3+) breast cancer be evaluated for inclusion in the review, and these data have subsequently been added.

Several databases were searched using strategies designed specifically for each database. Additional references were identified through reviewing manufacturer and sponsor submissions made to NICE, the bibliographies of retrieved articles, conference proceedings and by searching the Internet.

Data were extracted by one reviewer and checked by a second. Quality assessment was conducted independently by two reviewers. Disagreements were resolved by consensus and, when necessary, by recourse to a third reviewer. The primary outcomes of interest were tumour response, QoL, time to disease progression, overall survival and relief of symptoms. Studies were grouped according to the type of intervention (monotherapy or combination therapy).

Results

Combination therapy

There was only one included RCT of trastuzumab plus chemotherapy (cyclophosphamide plus anthracycline or paclitaxel) versus chemotherapy alone. The study population included women with HER2-overexpressing MBC at level 2+ or 3+ who had not received prior treatment for MBC. The overall quality of the included trial was considered to be good. Trastuzumab was administered for the duration of the trial in weekly infusions as long as the treatment was considered to be beneficial.

The addition of trastuzumab to chemotherapy resulted in significantly less disease progression and treatment failure, longer progression-free survival and greater complete and overall tumour response when compared to chemotherapy alone. There was a significantly greater incidence of congestive heart failure reported among

those receiving trastuzumab plus chemotherapy compared to those on chemotherapy alone. The incidence seemed to be highest with trastuzumab plus anthracycline (approximately one-quarter of participants), rather than with trastuzumab plus paclitaxel. (Information relating to the results of a subgroup analysis was marked as confidential and was, therefore, removed from the review.)

Monotherapy

There were no RCTs found that met the initial inclusion criteria, therefore, this section is based on non-comparative Phase II studies. The overall quality of these studies according to the checklist for case series was found to be moderate. Trastuzumab monotherapy was shown to have some antitumour effects in terms of overall tumour response (partial and complete), which ranged from 12 to 24% in the three studies. An independent response committee assessed tumour response outcomes in two studies, whereas tumour response was assessed by the investigators in the third study (H0650g). Similar durations of tumour response were reported by two studies of 9 (study H0650g) and 9.1 months (study H0649g).

Only one study (H0649g) reported the number of complete (five (3%)) or partial (26 (15%)) tumour responses for participants with tumours overexpressing HER2 at level 3+. In study H0650g, the overall tumour response rate for this group of participants was reported for both treatment groups combined as 31% (26/85). These results demonstrated that the majority of tumour responses occurred in participants with tumours over-expressing HER2 at level 3+.

Two studies reported data on survival endpoints (H0649g and H0650g). Study H0649g reported the overall median survival time using Kaplan–Meier methodology as 13 months (range 0.5–30), and that for participants with tumours overexpressing HER2 at level 3+ as 16.4 months. The median follow-up for this study was 12.8 months. In study H0650g, 67% of participants were reported to be alive at a median follow-up of 11 months, with survival duration ranging from 1.2 to 35.3 months. Trastuzumab when used as a single agent appeared to have a relatively low toxicity level.

Conclusions

Trastuzumab when used in combination with chemotherapy seemed to be more effective than chemotherapy alone for the treatment of MBC overexpressing HER2 at level 3+ in individuals who had not received prior treatment for MBC. However, it seemed to be associated with congestive heart failure, particularly in patients that received anthracycline-based chemotherapy.

Trastuzumab monotherapy when used as second-line or subsequent therapy for the treatment of MBC overexpressing HER2 at level 3+ appeared to have some antitumour effects in terms of overall tumour response based on non-comparative studies (which provide relatively weak evidence) of moderate quality.

Implications for further research

Further large well-conducted RCTs are required to provide more evidence of the effectiveness of trastuzumab when used within its licensed indications, in addition to other indications.

Publication

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