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# **PRE-ASSESSMENT** *Health Consequences of Long-term Use of Herceptin<sup>®</sup>*

*Before CCOHTA decides to undertake a health technology assessment, a pre-assessment of the literature is performed. Pre-assessments are based on a limited literature search; they are not extensive, systematic reviews of the literature. They are provided here as a quick guide to important, current assessment information on this topic. Readers are cautioned that the pre-assessments have not been externally peer reviewed.*

## **Introduction**

Breast cancer, which is the most common cancer among Canadian women, ranks second to lung cancer as a leading cause of cancer-related deaths. In 1998, 18,023 Canadian women were diagnosed with breast cancer and in 1999, 4,762 Canadian women died from it.<sup>1</sup>

In 25% to 30% of breast cancer cases, a mutation in the human epidermal growth factor receptor 2 (HER2) oncogene leads to the over-expression of the HER2 protein.<sup>2</sup> This protein is found on the surface of cancer cells. It stimulates the growth of these cells, leading to an aggressive form of cancer. Herceptin<sup>®</sup> was developed by Genentech<sup>®</sup> as a treatment for those breast cancer patients who over-express HER2. Herceptin (trastuzumab), which is often used with chemotherapy, is a recombinant humanized anti-HER2 monoclonal antibody that binds to the HER2 protein on the surface of breast cancer cells. Once bound to the HER2 protein, it inhibits further growth of these cancer cells.

## **Research Questions**

The aim of this evaluation is to determine the health implications associated with the long-term use of Herceptin. More than 12 months of Herceptin therapy would be an appropriate criterion for long-term use (Dr. Eva Tomiak, Ontario Regional Cancer Centre, Ottawa: personal communication, 2003 Sep 4).

## **Assessment Process**

PubMed was searched using a combination of descriptors and keywords for breast neoplasms, Herceptin and controlled clinical trials, resulting in 108 records. A second search for review articles was limited to the publication years 1998 to 2003. The overlapping results with those from the controlled trial search were excluded. The Cochrane Library 2003, issue 2 was searched and updated when issue 3 arrived. Grey literature was obtained through searching the web sites of health technology assessment and related agencies and their databases. Google<sup>™</sup> and other Internet search engines were used to search for additional web-based information.

## **Summary of Findings**

A literature review revealed numerous clinical trials and reviews published on Herceptin. Several studies (Table 1) reported on the side effects associated with Herceptin use. Most notable were those trials reporting cardiotoxicity among patients who were administered regimens containing Herceptin and an anthracycline. None of these studies, however, evaluated the health consequences associated with the long-term use of Herceptin.

**Table 1:** Side effects experienced by breast cancer patients receiving Herceptin treatment in clinical trials

Study, year, publication	Number of patients, length of treatment	Side effects
Cobleigh et al, 1999, J Clin Oncol <sup>3</sup>	N=222, 36 weeks	Cardiac dysfunction (4.7%)
Slamon et al, 2001, New Engl J Med <sup>4</sup>	N=469, median 40 weeks	Cardiac dysfunction (27% of patients received Herceptin with an anthracycline)
Fountzilas et al, 2001, Ann Oncol <sup>5</sup>	N=34, 12+ weeks	Anemia, fatigue
Baselga, 2001, Eur J Cancer <sup>6</sup>	N=235 not specified	Cardiac dysfunction
Fleming et al, 2002, Clin Cancer Res <sup>7</sup>	N=64, not specified	Fever, chills, fatigue, rash, nausea, vomiting, grades 3 and 4 pulmonary responses
Nabholtz et al, 2002, Clin Breast Cancer Suppl <sup>8</sup>	N=469, ongoing	Congestive heart failure
Osaba et al, 2002, J Clin Oncol <sup>9</sup>	N=400, Up to 18 weeks	Cardiac toxicity
Vogel et al, 2002, J Clin Oncol <sup>10</sup>	N=114, not specified	Chills, pain, anemia, cardiac dysfunction

Several reviews of the clinical effectiveness of Herceptin for breast cancer have been published. One review<sup>11</sup> reported that Herceptin with chemotherapy was more effective than chemotherapy alone for controlling tumour growth among patients with metastatic breast cancer. The authors also reported, however, that the use of Herceptin was associated with an increased risk of congestive heart failure, serious pulmonary events, hematological toxicity, hepatic and renal toxicity, diarrhea and an increased risk of infections.

Another review, completed by ECRI in July 2003, concluded that there was insufficient evidence to determine the safety of Herceptin in the treatment of stage I or II breast cancer or to support its use as adjuvant therapy.

Leyland-Jones and Smith<sup>12</sup> described seven large ongoing trials in North America and Europe that are examining the efficacy of Herceptin as a treatment for breast cancer patients. Four of these trials are examining the health consequences of the treatment, with cardiac safety as the endpoint.

## Conclusion

A literature review revealed numerous clinical trials and reviews published on Herceptin. Several studies reported various side effects associated with short-term Herceptin use, including cardiotoxicity. None of these studies evaluated the health consequences associated with its long-term use.

The National Cancer Institute's database listing Open Clinical Trials of Herceptin and Breast Cancer ([www.nci.nih.gov/clinicaltrials](http://www.nci.nih.gov/clinicaltrials)) revealed six phase III trials that are evaluating the safety and efficacy of long-term Herceptin use. Further assessment of the health consequences from the long-term use of Herceptin will be possible when the results of these trials become available.

## References

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