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Herceptin®: Monoclonal Antibody Therapy for Metastatic Breast Cancer

The Technology

Herceptin® (Trastuzumab) anti-HER2 humanized monoclonal antibody is an intravenous injection developed by Genentech, Inc. for the treatment of metastatic breast cancer.[1] Herceptin® inhibits cell growth by binding the Human Epidermal growth factor Receptor protein 2 (HER2) present in excessive amounts on the surface of some cancer cells.[2] It is the first nontoxic biological therapy to target a specific protein defect that contributes to the aggressive form of breast cancer associated with more rapid progression and shortened patient survival.[2-5]

Regulatory Status

Herceptin® received approval as treatment for metastatic breast cancer on September 28, 1998, by the Food and Drug Administration of the United States National Institutes of Health.[1]

Herceptin® is currently unavailable in Canada. In September 1998, however, Roche Canada signed an agreement with Genentech, Inc. to gain licence to the product and market Herceptin® outside the United States.[6] Roche Canada is presently awaiting approval of the product for the treatment of breast cancer by the Health Protection Branch of Heath Canada.[6]

Patient Group

HER2 protein is over-expressed in approximately 25-30% of human breast cancer cases,[7,8] roughly 5,300 (of 19,300) cases per year in Canada. Patients with HER2 over-expression are associated with poor outcome,[3,4,9] and sensitivity and/or resistance to hormone therapy and chemotherapeutic regimens.[5]

Herceptin® is indicated for treatment of patients whose breast cancer has spread beyond the breast and lymph nodes, whose tumors over-express HER2 protein, and who have received one or more chemotherapy regimens.[1] For patients whose tumors over-express HER2 protein and have not received chemotherapy, Herceptin® is recommended in combination with paclitaxel (Taxol®).[1]

Current Treatments

Conventional treatment options for patients with stage I or II breast cancer, as recommended by professional groups, include breast conserving surgery, removal and pathological examination of the axillary lymph nodes, followed by radiotherapy. Chemotherapy is recommended for all premenopausal women of less than 50 years of age, and for postmenopausal women with estrogen-receptor (ER) negative tumors. Tamoxifen is recommended for postmenopausal women with ER-positive tumors. Two optimal adjuvant chemotherapy regimens recommended for breast cancer are: (i) 6 cycles of cyclophosphamide, methotrexate and 5-fluorouracil; (ii) 4 cycles of adramycin and cyclophosphamide.[10]

The Canadian Coordinating Office for Health Technology Assessment is a non-profit organization funded by the federal, provincial and territorial governments.

Potential Cost

Herceptin® is manufactured and marketed in the United States by Genentech, Inc. in 440 mg multi-dose vials supplied with bacteriostatic water for injection at a cost of $2,262.50 US.[11] The usual adult dosage is unclear; however, patients in a phase II study received an initial loading dose of 250 mg IV, followed by 10 weekly doses of 100 mg each, conducive to an outpatient setting.[12]

Projected Rate of Diffusion

In 1995, Genentech designed an expanded access program, but supplies of the drug were extremely limited. In February 1998, the US National Cancer Institute (NCI) participated in this program to facilitate geographic participation and expand studies of Herceptin® for other indications. An adequate supply of Herceptin® was anticipated by the fall of 1998.[13]

The rate of diffusion of Herceptin® may be partially dependant upon the rate of development and diffusion of diagnostic tests such as the HercepTest® and INFORM HER-2/neu® assays. These tests are used to determine the qualitative presence of HER-2/neu gene amplification, a necessary step to identify patients who may benefit from Herceptin® therapy. The HercepTest®, manufactured by Dako, received approval on September 25, 1998, following Oncor, Inc.'s INFORM HER-2/neu®, which received approval in December of 1997.[2]

NCI and Genentech are currently conducting phase II trials to assess the effectiveness of Herceptin® for the treatment of ovarian and peritoneal cancer. They also plan to explore the use of Herceptin® as treatment for a variety of malignancies including gastric, endometrial, non-small cell lung, pancreatic, prostate, and colorectal cancers.[13]

Concurrent Developments

NCI is currently involved in trials of other

monoclonal antibodies designed to target the HER2 protein. Several phase I studies have been initiated to test a HER2 antibody designated 520C9xH22, produced by Medarex Corporation of Annandale, NJ.[13] Other studies include the evaluation of a different HER2 antibody, 2B1, designed by Chiron Corporation of Emeryville, CA.[13]

The only other monoclonal antibody used to treat cancer, Rituxan® (also sponsored by Genentech), was approved in November of 1997 for the treatment of patients with B-cell non-Hodgkin's lymphoma, a cancer of the immune system.[2]

Adverse Effects

Herceptin® was not recommended for use in combination with anthracycline therapy due to an increased risk of synergistic cardiotoxicity.[2,14,15]

Other side-effects observed with combination Herceptin® and chemotherapy as compared to chemotherapy alone include leukopenia (a reduction in white blood cells), anemia, diarrhea, abdominal pain and infections. Approximately half of patients experienced chills, fever, pain, weakness, nausea, vomiting or headache during the initial loading dose of Herceptin® ; however, these treatable side-effects declined in frequency with subsequent infusions.[14-16]

Assessing the Evidence

Table 1: Results of Clinical Trials with Herceptin®

Clinical Trial	HER2+ Patients	Therapy	Median Time to Disease Progression (P) or Response Duration (RD) (months)	Tumor Response Rate (%)	Survival (1 year) (%)	Myocardial Dysfunction (grade 3/4) (%)
Slamon et al.[14] n_T=469	**n=235** n=146 9 n= 89 A vs **n=234** n=145 9 n= 89 A	**H+CRx** H+AC 9 H+T A	**P=7.2** P=7.6 P=6.7	**45** 50 38	**79** 83 73	- 19 4
		CRx AC 9 T A	**P=4.5** P=5.7 P=2.5	**29** 38 15	**68** 73 61	- 3 1
Cobleigh et al.[15] n_T=222	n=213 vs n=9	H vs none	RD=8.4	15-21	-	2.8

H=Herceptin CRx=chemotherapy (AC and T) AC=Doxorubicin and cyclophosphamide T=Paclitaxel

The clinical benefits of Herceptin® were shown in two clinical trials (Table 1).[14-16] In a randomized, controlled trial, 469 patients with metastatic disease over-expressing HER2 were assigned to receive chemotherapy (CRx) alone (either paclitaxel (T) or doxorubicin plus cyclophosphamide (AC)) or chemotherapy in combination with Herceptin® (CRx+H).[14]

Women who received combination chemotherapy and Herceptin® displayed significantly slower tumor progression, greater tumor reduction by 50% or more in size, and higher one-year survival rates than those who received chemotherapy alone. The median time to disease progression for those receiving combination Herceptin® and chemotherapy was 7.2 months in contrast to 4.5 months for patients receiving chemotherapy alone. The overall tumor response rate in the group receiving Herceptin® was 45% while that of the chemotherapy only group was 29%. The one-year survival rate for the Herceptin® combination treatment was 79% versus 68% for chemotherapy alone. Myocardial dysfunction was more commonly reported in those that received AC+H (19%) than those having received AC (3%), T (1%) or T+H (4%) therapy. (Table 1)[14,16]

In a second clinical trial, involving 222 patients, Herceptin® was found to be an effective monotherapy for a group of patients who had relapsed following previous chemotherapy for metastatic breast cancer. The overall tumor response rate was 15-21% lasting in the range of 6 weeks-18 months (median=8.4 months).[15]

In both clinical trials, patients who responded best to Herceptin® were those who displayed the greatest levels of HER2 protein.[14-16]

Implementation Issues

Familial implications will arise from the use of Herceptin® treatment for metastatic breast cancer due to the genetic nature of the diagnostic test needed to identify patients who would benefit from antibody therapy. The evidence assessed in this brief is based on two clinical trials, a limited number of participants and short-term survival data.[14,15]

Canadian clinical and economic data regarding Herceptin® use in comparison to conventional chemotherapy regimens is necessary before informed predictions can be made on its cost-effectiveness in our health care system. When considering the cost-effectiveness of Herceptin® therapy for metastatic breast cancer, factors such as accuracy of the diagnostic test used to determine HER2/neu over-exspression, and adverse effects on patients receiving Herceptin® must be taken into consideration.

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