



## Making a case for a \$2700-a-month drug

Barbara Sibbald

A new class of biotherapeutic cancer drugs costs \$2700 a month but its proponents make no apologies. Trastuzumab (Herceptin), the first monoclonal antibody approved for use in Canada, adds an average of 5 months to the lives of up to a third of women with metastatic breast cancer. And although the price has raised ethical questions about whether people have a right to a therapy regardless of its cost, those involved say it's not exorbitant given the expense of development and production.

Neil Cohen, a spokesman for the drug's manufacturer, California-based Genentech, Inc., says the high cost is due to the years of research and development — including a phase 3 clinical trial involving 900 patients — manufacturing costs and ongoing research into other possible uses.

Dr. Brian Leyland-Jones, a lead investigator for the trastuzumab clinical trials, says it costs between \$250 and \$500 million to bring a regular pharmaceutical product to market. "The costs are phenomenal," he argues. He is presently involved in another trial in which the drugs needed for 8 patients cost \$250 000.

Research into monoclonal antibodies has been under way for 15 to 20 years. Rituximab (Rituxan), which targets non-Hodgkin's lymphoma, entered the US market 2 years ago but is still awaiting Health Canada approval. A 22-day course of that drug costs US\$9438. Trastuzumab, the second monoclonal antibody and the first gene-directed therapy, received Health Canada approval in August.

In the US, Genentech dodges the tricky ethical issues by providing trastuzumab and its other drugs free to uninsured or underinsured patients. Over the past 12 years, Genentech has given away more than \$200 million worth of its drugs.

However, that's not the case in Canada, where administrators are wondering just how much the public health care system can afford. Ontario has agreed to pay for the new breast cancer drug, and BC is following suit, but other provinces haven't made a decision yet. This uncertainty will no doubt contribute to what ethicist Margaret Somerville calls a "surge" in court challenges over withholding medically necessary treatment.

Somerville, the director of the Centre for Medicine, Ethics and Law at McGill University, agrees that Canada's health care system can't pay for everything. "We can't afford to offer every treatment to everyone . . . but we have always lived with the myth that we can." She says the soaring litigation is a sign that this "myth is being shattered."

But the cost shouldn't override the "huge promise" inherent in trastuzumab and this whole new family of drugs, says Leyland-Jones, professor and chair of McGill's Department of Oncology. "This is just the tip of the iceberg," he says, since other drugs based on monoclonal antibody drugs are now being developed. "They are discriminate, selective drugs aimed at specific genetic targets," he says. "It's entirely different from chemotherapy or radiation."

Side effects are negligible. Leyland-Jones says some patients report chills and fevers the day of their first infusion, but nothing more. "Patients said it's like taking water," he said. The drug is administered weekly.

Leyland-Jones says cancer therapy has been evolving since the end of the last century. The first advances were in surgery, followed by the introduction of radiation. Those developments were followed by the arrival of chemotherapy in the 1940s. This latest step is "fourth-generation therapy — the selective gene-targeted therapies."

Trastuzumab has been in the making since 1986, when American oncologist Dennis Slamon and German molecular biologist Axel Ullrich discovered that as many as 35% of breast tumours contained a mutation in the HER2 (human epidermal growth factor receptor 2) oncogene (also known as *c-erbB2*). This mutation causes breast cells to make abnormally high amounts of the HER2 protein (overexpression), which appears as a receptor on the surface of the cell. These receptors receive chemical signals from the body to grow, stimulating the cells to grow out of control. Ullrich and Slamon also discovered an antibody that clung to the HER2 protein, marking the cancer cells for death. Genentech owns the rights to the antibody.

The drug was extensively tested in a 4-arm study: trastuzumab alone; trastuzumab with the chemotherapy combination doxorubicin and cyclophosphamide; trastuzumab with chemotherapy including paclitaxel (Taxol); and paclitaxel alone. The women taking trastuzumab combined with doxorubicin and cyclophosphamide had an increased (27%) risk of cardiac dysfunction, including impaired left ventricular function and heart failure. However, trastuzumab combined with chemotherapy including paclitaxel was found to improve survival by an average of 5 months over chemotherapy alone in women with metastatic breast cancer and overexpression of the HER2 protein.

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