

RESEARCH SAVES LIVES

Can we get better value for our investment?

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Uneven access to cancer care has been a major theme of our Report Cards. This year, in another part of this Report, we revisit issues related to the interprovincial variations in access to effective and costly new cancer agents. Many of the agents were proven effective based on results of clinical trials that included Canadian cancer patients. Indeed, under the auspices of the NCIC clinical trials group, Canadian clinical researchers have played a major role in this development, designing and leading international clinical trials that have changed the way medicine is practiced worldwide. However, now that the same agents have been commercialized, Canadian patients are being denied access to many of them. This is largely due to fiscal issues, with very different rules among the provinces and different policies of individual institutions within a given province.

Intimately related to the issue of access is the way clinical research is organized and who will decide the priorities for research. This review scrutinizes how priorities are set for clinical cancer research.

This emerges as an important question, now that the Federal Government has created the Canadian Partnership Against Cancer (CPAC), previously known as the Canadian Strategy for Cancer Control (CSCC).

The genesis of modern era trials, with the formation of larger multicentre groups, has united scientists nationally and internationally, greatly enhancing our ability to generate the evidence necessary for progress of cancer medicine.

The sample size of these new trials enables more statistical precision to be achieved in subset analyses. Most trials have now achieved longer durations of follow up than was possible in the past. Careful peer review has enhanced their reliability. Thus, clinical cancer research is immeasurably better than the research that directed treatment policies in the past.

However, even at this stage of improvement, it is not clear how much of the research is planned in relation to community needs. Research may focus on issues at times unrelated to information required for population-based cancer control. While the pharmaceutical industry funds more and larger multi-centre trials of high

quality, these studies are frequently aimed at testing questions related to products.

The idea that research priorities would include external input encompassing strategic issues and societal considerations has always engendered a degree of opposition from the research community. The principle that research should be conducted largely based on priorities set by the researchers has been staunchly upheld as essential to preserving scientific freedom. Indeed this notion has strong merits.

Yet even in research on such vital issues as the human genome project, some priority setting is inevitable, if only because all research funds have some financial limitation. In like manner, the time has come for societal needs to be defined and folded into priorities for clinical research.

This report focuses on how this might occur, by aiming research to enable more speedy and flexible reactions to initial observations of drug efficacy. The desired result would be a more efficient confirmation of potentially important data, which could then be incorporated into guidelines. One aspect of this type of research seeks not to define the activity of new drugs or curative attempts, but is directed at more accurately selecting patients most likely to benefit from a given treatment, or to improving the logistics of applying the new drugs.

The emerging question is whether enough attention is paid to secondary endpoints, potentially of more societal worth, such as cost of programs introduced and more rigorous identification of cohorts eligible for a given new therapy.

Take the specific example of a recent innovation in breast cancer therapy: trastuzumab (Herceptin). When the drug was combined with chemotherapy it improved the duration of survival in advanced disease¹. Five large multicentre groups then studied the same question: is there a clinically meaningful benefit in giving Herceptin in the adjuvant setting to treat breast cancer?

All five trial results produced the same conclusion: yes²⁻⁵ (See Figure 1). Herceptin prevents approximately 50 per cent of breast cancer recurrences in the subset of patients whose tumors show expression of Her2/Neu

Patients are better served if the treatment selected for them has a high potential for success, sparing them from start-stop attempts that waste precious time.

gene. This degree of effectiveness is considered outstanding in comparison to the recent or past trial results testing newer chemo-hormonal agents or radiation, where comparable figures show only half this benefit, i.e., avoidance of 20-30 per cent of recurrences, at best. In addition, it predicts substantial improvement in overall survival will occur.

As a result, over a short span of several weeks after the results of the first three of these trials became known in the fall of 2005, Herceptin in conjunction with previously established treatments was accepted as standard adjuvant therapy in North America, and more recently in most of the western world. Current guidelines indicate it should be given to the majority of the 20 per cent of newly diagnosed breast cancer patients who present with Her2/Neu positive tumours.

However, the drug is costly. In routine clinical use Herceptin requires approximately \$45-50,000 annually per case. An additional \$20-30,000 can be assumed for indirect costs related to pharmacists, nurses, chemotherapy infusion rooms, etc. The overall cost for this program is estimated at \$165 million annually in Canada, and several billions worldwide.⁶ Also, Herceptin has to be given regularly over the span of a full year and as with all effective cancer treatments, has important side effects such as cardiotoxicity, to an extent not yet fully established in long-term survivors.

There is an urgent need to determine how to select more precisely the patients most likely to benefit from Herceptin; to learn whether it can be given to only those who benefit maximally and not to those who benefit marginally, thereby sparing patients from unnecessary cardiotoxicity as well as the potential time lost to unsuccessful treatment. How can we improve the cost-benefit ratio of this promising treatment? Can we do better?

Part of the answer would be to determine more precisely the subset of cases in which this treatment is optimal. If we could treat 60 cases instead of 100 and still avoid the same number of recurrences, that would be very valuable. At present, Her2/Neu testing on patients' tumour samples is the only way to determine eligibility. Can we test more precisely?

To answer this question, two aspects require scrutiny. First is the issue of testing for secondary markers and a more accurate and cost effective determination of the Her2/Neu gene, that may substantially enhance patient selection and the impact of Herceptin therapy. While the preliminary evidence indicates there is potential for greatly enhancing efficiency and cost saving through testing for these secondary markers, little is being done on a large scale to take full advantage of this important opportunity.

The second aspect is whether we have the mechanisms, laboratories and staff in place to study and utilize these additional tests.

Two examples of secondary markers are the PTEN molecule and the presence of c-Myc. Related to the second aspect is an example of a more cost-effective screening procedure: using CISH instead of FISH to determine the presence of Her2/neu.

The PTEN test Ordinarily, 40 per cent of patients with advanced disease, who test positive for Her2/neu in their tumour, will respond to Herceptin. If the tumour tests negative for Her2/Neu, the response rate is negligible. Nagata et al. tested whether expression of the tumour suppressor gene PTEN might predict which Her2/Neu positive patients with advanced breast cancer would respond to Herceptin. Based on the results of this study, the investigators concluded that 60 per cent of Her2/Neu positive patients with advanced (stage IV) breast cancer responded to Herceptin when PTEN was also preserved, while fewer than 10 per cent responded when PTEN was "lost"⁷. Despite the fact that these results were based on only 60 cases from advanced stage, they are compelling enough to indicate the next logical step would be to measure the loss of PTEN on samples from all patients in the adjuvant trials.

If cases with PTEN loss – about a third of all Her2/Neu positive advanced breast cancer patients – do not respond in the advanced setting, would they benefit in the adjuvant setting? Herceptin may not have to be considered for those. This potentially important premise, in order to be verified, requires rapid retesting

of the tumour samples from patients who have already participated in the adjuvant Herceptin trials.

Despite this possibility, none of the principle five cooperative groups involved with Herceptin trials have reported on retesting for PTEN loss. Yet breast cancer samples from the time of the original diagnosis or mastectomy are kept, by rule, by all cooperative groups for exactly this purpose: to re-examine samples with new tests as they become available.

c-Myc testing In the NSABPB-31 trial, the c-Myc gene was studied along with Her2/Neu in over 600 cases and, as was the case with PTEN, Herceptin was more effective if both the c-Myc and Her2/Neu were identified. These patients benefited more than twice as often as those whose tumours were positive for Her2/Neu but negative for c-Myc. The odds for recurrence reduction were 67 per cent vs. 33 per cent respectively.⁸

The implication of these observations is that if c-Myc is not present, in similarity to the PTEN loss, the impact of Herceptin is substantially lower. This could render those breast cancer cases with otherwise borderline eligibility for the drug (small tumour size, negative axillary nodes, good grade, etc.) more definitively ineligible. However, as with the PTEN example, confirmatory results have not followed from the remaining randomized trials – the European HERA trial of the BIG group, and the North American Breast Cancer Research Group (the BCIRG trial), making it impossible to confirm these results and incorporate the additional markers into clinical guidelines.

CISH retesting Another example where research could substantially enhance efficiency relates to the method of testing for Her2/Neu in the tumour samples at the time of diagnosis, the obligatory first step for determining eligibility for adjuvant Herceptin.

The standard FISH (fluorescence in situ hybridization) and IHC (Immuno-histochemistry) tests are the established techniques for routine determination of Her/Neu status.

Chromogenic in situ hybridization – CISH – is a new test, technically feasible and in many regards superior to FISH. CISH measures the same aspect of the Her2/Neu gene but does not require fluorescence microscopy – costly equipment restricted to large centres. It can be performed more readily, is less complex, cheaper, and provides permanent stains which can be reviewed at a later date, while the FISH signal fades within weeks⁹.

In order to confirm the ultimate comparability of CISH with FISH, present day standards of research would require that all the samples in the Herceptin trials be retested for CISH, to compare the treatment outcomes with the two tests.

CISH retesting could be completed in a matter of

months. If it is confirmed to be similar to FISH – a notion the Europeans have already accepted even without the above confirmatory retesting (e.g. Finland has already switched to CISH) – then the Her2/Neu testing in North America can be greatly simplified, with more efficiency and cost saving. However, despite attempts to popularize CISH in North America^{9,10} none of the five cooperative groups responsible for Herceptin trials appears to be considering retesting with CISH.

CONCLUDING REMARKS

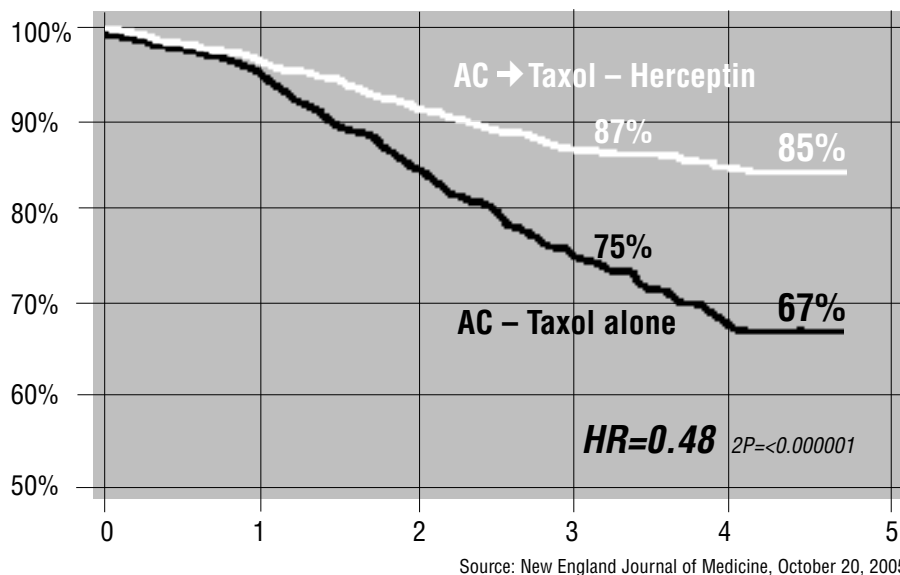
Our review indicates the potential importance of retesting tumour samples for promising tumour markers and studying less expensive ways of conducting tests. To do this would involve retesting tumour samples in the adjuvant Herceptin trials. Although tedious, these steps could have been easily done but so far have not.⁹ While research on new agents or genetic techniques is progressing rapidly, the above examples illustrate the lack of progress in research focused on efficiency in patient care and related savings. The organized cancer system frequently fails to take rapid advantage of research findings already generated, missing opportunities of potential importance to patients and payers. The lack of readiness to address societal needs for efficient, cost-effective cancer care is hampering access to other life-saving and life-prolonging cancer drugs for multitudes of cancer patients.

**It is a complex issue
to convince researchers
coordinating the
clinical trials about
the importance of this
type of research**

It is time for all proponents of cancer control, in common with others in the health system, to recognize the urgent need to target treatments more precisely according to risk/benefit. Just as cancer prevention is moving to target the “at risk” population, the organizations that support treatment must increasingly identify the biomarker indicators that more precisely predict benefit. It may not be very exciting but it is necessary.

Who decides? No one individual or body has the appropriate jurisdiction over leaders of multi-group trials to decree that these retesting studies be conducted.

IMPACT OF ADJUVANT HERCEPTIN ON EARLY BREAST CANCER



Thus, to stimulate, support and coordinate such activities other approaches will be necessary.

Canada could take advantage of this research gap and demonstrate constructive ways for dealing with the spiraling cost of cancer drugs, instead of being included among the pariah nations who deny their citizenry access to powerful new treatments. Such ingenuity would probably be heartily welcomed by researchers, provided the necessary resources were made available.

Recommendations

- 1 A mechanism should be introduced to ensure a larger number of post-market studies of the type outlined above.
- 2 Canadian provincial governments faced with escalating drug costs might set aside two to four per cent of their drug budgets to finance the necessary research for testing of new biomarkers, in order to refine eligibility for costly new drugs more accurately.
- 3 Such innovative moves could be shepherded by the newly-created CPAC to avoid duplication.

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