

A Critique of the Breast Cancer Clinical Research Process

SAVE TIME, MONEY AND LIVES BY REDUCING
REPETITIVE TESTING OF NEW AGENTS AGAINST PLACEBO

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This article summarizes a study presented to international cancer specialists at the 29th Annual San Antonio Breast Cancer Symposium in December 2007. The study calls for a major overhaul of the clinical trial process testing breast cancer treatments. The present system is becoming obsolete¹ due mainly to the rapid emergence of many new, potentially curative cancer drugs outstripping the capacity of the present system to test them in a timely fashion.

The recommendations aim to markedly reduce the time for a drug to find its way “from the bench to the clinic,” which is currently as much as a decade or more.

The proposals require a fundamental change in cancer drug testing, specifically how randomized trials are conducted in the adjuvant setting. While based on an evidence-based review and common sense, they might be considered drastic to some members of the present cancer establishment. Although the current system has produced a marked reduction of breast cancer mortality over the last 30 years, it could be more efficient and less expensive.

In order to understand the proposed reforms, two factors require review:

1. Clinical trials of new cancer therapeutics, an important step governing the eventual approval of new drugs into clinical use, with process delays affecting human lives.
2. The biology of metastases of human cancer, specifically the difference between “macrometastases” of advanced Stage IV disease versus the “micrometastases” of subclinical early stage disease, the adjuvant setting.

Human Clinical Cancer Trials

At present, it takes a minimum of 10 to 15 years for a new agent to reach the clinic from the laboratory bench, in many cases 15 to 20 years to become fully characterized, because a sequence of at least four, and usually five types of trials are required for each new drug.

Randomized placebo-control trials – those which take time and are most costly – are done first in the advanced stage IV, and then in the same design, for the adjuvant setting.

If results are flexibly applied from stage IV into adjuvant setting, for those new agents when effect is seen beyond reasonable doubt, the complex second set of randomized trials in the adjuvant setting could be skipped. Also, with other suggested reforms calling for enhanced efficiency the time period of testing could be reduced from the present 10 – 15 to less than five years.

Biology of Human Cancer Metastases

Typically, as the tumour becomes more advanced, more resistance to therapeutic agents is seen. Therefore, killing tumour cells with drugs and prolonging patient survival is more difficult in advanced disease. As a corollary, tumour sensitivity to a new cancer agent in advanced disease should predict even greater sensitivity in early disease. This observation may permit skipping the repeat testing of a new agent against placebo in the adjuvant setting.

Are Results of Stage IV Trials Applicable to the Adjuvant Setting?

In order to establish if this complex sequence could be simplified, we reviewed all principal randomized breast cancer trials testing hormones, chemotherapy and biologicals, first in the advanced stage then, in an identical design, in the early adjuvant setting.

In every trial in our analysis, starting from Tamoxifen, (the first hormone studied in human breast cancer ^{2,3,11}), to the new generation of hormones (the aromatase inhibitors), and from early types of chemotherapy regimens^{3,4} to the most recent combinations including the biological Herceptin,⁵⁻⁹ the results were consistent. While responses were seen in Stage IV, there were no cures; but when agents were moved to the adjuvant setting, each one produced a much more powerful clinical benefit. The result was not only a signifi-

cant reduction of recurrences (metastases), but also durable cures, equated with a significant reduction of breast cancer mortality.

Furthermore, the analysis showed that a profound population-based breast cancer mortality reduction was identified in parallel with the introduction of these agents into the adjuvant setting. This was true both in rural and urban areas. However, in the provinces where adjuvant therapy was delayed, or not given uniformly across the whole population, the mortality reduction did not materialize, or was seen at a slower pace. Specifically, in some provinces in Canada breast mortality reduction trends became apparent as early as the 1980s, while in other provinces, as in the majority of western countries, the mortality reductions were recorded as much as a decade later. The irregular timing of decreases in mortality probably represents the uneven transfer of early results from clinical trials into routine practice.

Consequences of Delaying Curative Treatments

If routine use of effective systemic therapy is curative, then we must ask the obvious question, does delay in use of curative agents delay the reduction of mortality? This issue provides the core of our arguments against delays in activating effective cancer treatments. Consider the consequences of delaying use of Tamoxifen and Herceptin.

TAMOXIFEN

Tamoxifen, the most commonly used hormonal therapy against breast cancer, is now credited with saving the lives of hundreds of thousands of women since it moved into routine adjuvant treatment in the mid-1980s.^{2,3} Yet its effectiveness in producing significant responses in Stage IV advanced disease¹¹ had been recognized five to 10 years earlier. How many more lives could have been saved had Tamoxifen been used in the adjuvant setting immediately after its effectiveness became evident from the Stage IV trials? The estimates indicate that, worldwide, up to 20,000 additional lives could have been saved annually or 100,000 lives for every five additional years that it took to conduct all the trials of Tamoxifen in the adjuvant setting.

HERCEPTIN

In 1999, randomized trials showed that Herceptin would double the response rate and significantly prolong life⁵ in advanced Stage IV disease (i.e., when added to conventional chemotherapy in patients whose tumors over-expressed the HER2/neu gene).

Herceptin was then tested in early disease between 2001 and 2005 in four large simultaneous adjuvant randomized trials in North America and Europe.⁶⁻⁹ Each trial produced a benefit that could have been expected from the original 1999 advanced disease study, namely

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a 50 per cent reduction of recurrences as a surrogate for preventing breast cancer death. As a result of such a high degree of proof of efficacy and after intense political lobbying, and despite its cost and complexity of delivery, the drug was approved in North America within six months as part of standard adjuvant therapy for patients with tumours positive for HER2/neu. It took another two years for similar approval in the rest of the western world.

Rather than waiting until 2005/2006, had the drug been introduced into routine use in the adjuvant setting in 2000–2001 when it was shown to be highly effective in advanced Stage IV disease, an estimated 5,000 women's lives could have been saved in Canada and ten times as many in the US. As it is, these breast cancer recurrences were not avoided and we are only now determining the optimum duration of treatment with this very expensive agent.

Delay of Curative Treatments

– The Present Situation

As documented elsewhere in this Report Card, we are faced with a dilemma. More than 40 new agents/indications are waiting in line for further action either in clinical trials or approval for general community use. Drugs such as bevacizumab (Avastin) shown, as early as 1999, to significantly prolong life in Stage IV colorectal cancer¹² are still not used in the adjuvant setting. The same drug was shown to produce a similar benefit in breast cancer in 2005¹³ yet only a handful of patients are receiving it in Stage IV, and not a single patient in the adjuvant setting. The first trial testing Avastin as adjuvant treatment of breast cancer started only months ago. Its results will not be available for another five years.

The most recent example is lapatinib (Tykerb), a drug

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that inactivates the HER2/neu molecule like Herceptin but by a different mechanism.¹⁴ A large North American trial showed two years ago that lapatinib, added to chemotherapy in patients with advanced Stage IV breast cancer who had relapsed on Herceptin, produces a response rate of more than 40 per cent and a median survival twice as long as patients not receiving lapatinib.¹⁴ One might ask “How close are we to offering this highly effective non-toxic drug to Canadian patients with aggressive, advanced Stage IV disease?” The first adjuvant European trial testing adjuvant lapatinib is only just starting, with at least three to five more years before results will be documented. Yet as indicated by the evidence already available, lapatinib in conjunction with Herceptin will almost certainly increase survival in women with early breast cancer.

Conclusion

- The narrowly defined balance between underinvestigation and overinvestigation of new agents has swung too far in the direction of overinvestigation. Both are examples of poor science. This report suggests balance can be restored, with specific proposals for breast cancer.¹⁵
- If we persevere with the status quo, testing new agents as we have always done, new and potentially useful therapies will be increasingly caught in the log jam, and lives will be lost unnecessarily.
- On the other hand, speeding up the process by which new drugs reach a defined population who could benefit from earlier treatment would save thousands of lives, at much lower cost to society.

See the CACC Website for detailed proposals
www.canceradvocacy.ca

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15. Details of the proposals presented by Dr. Ragaz in San Antonio, December 2007, can be found with Background Documents to this Report Card on the CACC website www.canceradvocacy.ca.