

The Emerging Role of Biomarkers in Cancer

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Biomarkers profoundly impact the issue of access, cost, toxicity and overall value of newly evolving therapeutics for human cancer. Thus, biomarker research and adoption in clinical practice guidelines requires serious attention from the clinical community and funding agencies.

Biomarkers are tumour-associated proteins or genes identified from the primary tumour, circulating cancer cells, blood serum, or metastatic tissue that provide an indication of:

1. Risk and aggressiveness of disease at diagnosis (prognostic value)
2. Responsiveness to various therapies (predictive values)
3. Potential development of new cancer agents—identifying new “targeted” therapy based on molecular structure.

Some biomarkers indicate which patients will benefit from a given treatment, e.g., estrogen receptors predicting responsiveness to hormonal therapy; Her2/Neu gene status to trastuzumab (Herceptin) therapy; c-kit molecule to imatinib (Gleevec), and so forth.

Some will identify patients who do not require a given therapy, e.g., ER negative status indicates no benefit from hormonal therapies in breast cancer; Her2/Neu—if not expressed—indicates no benefit from Herceptin or lapatinib in breast cancer; the presence of K-RAS mutation predicts no benefit from cetuximab (Erbix) and panitumumab (Vectibix) in colorectal cancer, etc.

Biomarkers may also identify those who may require different types of treatment, e.g., a low Recurrence Score in the Oncotype Dx 21 gene test identifies breast cancer patients who may benefit from hormonal therapy alone and do not require the addition of adjuvant chemotherapy; the BRCA-1/2 genes identify women at high risk for breast and ovarian cancer who, in addition to chemopreventive strategy (tamoxifen, raloxifen), may also benefit from bilateral mastectomy and/or oophorectomy.

Biomarkers will lead to significantly improved quality of life by avoiding the toxicity of unnecessary therapy, while also lowering costs and contributing to overall societal benefit compared to therapeutic approaches not guided by biomarkers. While the process of identifying and testing new biomarkers is costly, the long-term ben-

efit of avoiding unnecessary treatments more than justifies the investment.

More information on the principal biomarkers in current practice or under investigation, according to tumour site, with comments highlighting cost-benefits in quality of life and saved dollars can be found on the CACC website with other background relating to this Report Card (www.canceradvocacy.ca).

Challenges of Biomarker Research

Fiscal issues – One of the big problems with biomarker research is the slow rate of progress related to lack of funding. This could be overcome if longer-term fiscal gains were more clearly understood—in proportion to the strength of evidence from ongoing research.

Logistical issues – Some of these challenges will be more difficult to overcome. Specifically, there is increasing difficulty accessing tumour tissues from patients in a given trial to retest a preliminary observation, partially because tumour samples are small and many more tests per sample are now being contemplated.

Example: Herceptin resistance may evolve, identified by the expression of the molecules PTEN and c-myc, which are both potential biomarkers. The two preliminary reports on this subject require confirmation. The only way to do it is by accessing tumour samples of patients who participated in all five randomized Herceptin trials.

However, the pathology specimens in most of these trials are not easily available. They are consumed either by the primary research or by required centralized retesting to confirm the status of Her2/Neu or ER and PgR biomarkers.

These steps are important, but they all require the extra specimens. As a result, very often the only effective way to confirm a preliminary biomarker observation appears to be to launch yet another full-fledged randomized trial, with assessment of biomarkers as the main objective. Yet the idea of launching another Herceptin vs. placebo randomized trial is clearly not feasible. Aside from the logistical and financial barriers, there are ethical and potentially legal issues in withholding a curative therapy from the placebo arm of the trial.

When is a Biomarker Ready for Prime Time?

This brings up the important question: when should researchers and oncologists consider altering guidelines? Which is the greater mistake: to act prematurely on newly identified biomarkers or to fail to save lives and dollars by not acting until overwhelming evidence offers absolute certainty?

For instance, the data are now mature associating chemotherapy resistance with the absence of Her2/Neu expression, particularly if linked with a positive ER expression. However, no major change has yet been made in clinical practice guidelines. A great majority of node positive patients are still receiving dose intensive CEF in Canada—and/or taxol added to AC in the US. Yet chemotherapy intensifications (with anthracyclines or taxanes) have produced minimal benefit for the 70–75 per cent of breast cancer patients with Her2/neu negative tumours and/or with a positive expression of estrogen receptor biomarkers.

The reluctance to act more assertively on biomarker data probably reflects ongoing generalized concern that acting prematurely could disqualify patients from a potentially curative therapy—with obvious serious consequences.

False positive results are not infrequent—the very reason why most oncology representatives and journal editors are cautious in accepting results based on smaller patient samples, even with statistical significance. However, a refined balance exists between these legitimate worries and not acting at all, even once the evidence is available. In both instances patient interests are not well served.

Cancer patients and their physicians increasingly feel a compelling need for full information about the most recent research, even if the data are not completely mature. In the absence of new, prospectively randomized biomarker studies confirming important preliminary results, clinicians and patients may have to resort to tailor-made individual decisions. While the obvious choice is participation in a clinical trial that could produce new evidence or confirm a preliminary observation, many patients will not fit trial criteria and therefore have fewer options. Thus, patients and their physicians try to balance need and hope with uncertainty, and make therapeutic decisions in a grey zone.

Quality Control

Essential aspects of biomarker development include the reliability, quality and reproducibility of techniques identifying individual biomarkers. If these are faulty, negative consequences occur both in giving and not giving a certain treatment. Good candidates would not receive a curative therapy; and patients who would not benefit may receive the drug, perhaps for a long time, deriving little benefit but more toxicity, at times considerable.

Poor quality control has been evidenced in North

America and Europe, e.g., falsely negative estrogen receptor tests disqualifying thousands from curative hormonal therapies; or clinical errors occur due to inaccurate immunohistochemistry tests for Her2/Neu.

Once a biomarker is of proven value, conducting the tests for patients requires uniformity and quality control, particularly if done by multiple laboratories. This is a priority and should be enforced not only by independent research groups but also by provincial and national bodies regulating cancer developments.

Funding

Ultimately, the successful entry of biomarkers into clinical practice guidelines will be determined by the funding available for both the research and the cost of routine use.

In this process, conclusions based on strong evidence should stimulate social interest—and eventually financial support. As molecules such as the recently identified biomarker K-RAS* gene have shown a clear cost-benefit, public funding for their use should be expedited.

On the other hand, if the evidence is weak then funding is clearly less warranted. Patients and clinicians need to see a direct interaction between the strength of research results and their adoption in publicly funded health care.

In summary, ongoing challenges occur at two levels.

- Research of biomarkers is often slow, with industry or granting bodies not always prospectively allocating funds for biomarker research.
- Once a biomarker is proven to contribute—even with a high level of evidence, such as the Oncotype Dx 21 gene assay—Canadian health ministries, cancer agencies and institutions refuse funding, arguing that its routine use may not contribute significantly over established practice.

Conclusion

Considering the magnitude of the side effects and the expense of most cancer therapeutics, restricting therapies to those patients most likely to benefit will substantially improve their cost-benefit and serve the best interests of patients. Biomarkers are essential to making these decisions.

Recommendations

Provincial health ministries should set aside a fixed percentage (two to four per cent) of their drug budget to finance:

- the research of biomarkers,
- routine use of biomarkers already established as useful in individual patient management.

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