From targeted to pinpoint: The implementation of pharmacogenomics in clinical oncology

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Abstract

The numerous technological and pharmacological advances of the 20th century triggered hope throughout the oncological community that cancer would be systematically eliminated. However, since the advent of targeted therapies and the hope elicited from such triumphs as imatinib, the pace of progression has slowed to a crawl. Moving forward, cancer researchers and clinicians must continue to identify the major somatic and germline mutations that underscore the pathogenesis of neoplasia and should seek to capitalize on ever–improving DNA sequencing capability with the goal of devising new therapies that achieve higher cure rates, minimize recurrence, and enhance the tolerability of widely used regimens.

How we got here

The 20th century represented one of history's first significant leaps forward in the war on cancer.[1] Sidney Farber's achievement of a partial remission from leukemia through the administration of a novel therapeutic in 1947 signalled to the world that the seemingly unbeatable scourge could, at the very least, be kept at bay.[2] The remainder of the century, regrettably, was marked by mere occasional steps forward, with researchers frequently baffled by infuriating forms of resistance.[3] One notable example of such resistance surrounded trastuzumab (Herceptin), which was originally studied for the management of HER–2 positive breast cancer in 1987. After approval, this drug's benefit was impeded by numerous modes of resistance, including SRC tyrosine kinases, a common mechanism of cancer's resistance to numerous medications.[3] Unquestionably, such feats as the utilization of comprehensive screening programs and aggressive prevention campaigns have improved outcomes for thousands of patients in the modern era.[4,5] In fact, the National Cancer Institute reported that the cancer death rate declined by 23% between 1991 and 2016.[6] However, cancer's pharmacological therapy boasted only minor enhancements. Thus, researchers acknowledged the necessity of a paradigm shift in the field: the blunt tool that targeted all the body's actively dividing cells, conventional chemotherapy, would no longer suffice. The flaws of this practice, ranging from crippling side effects to inadequate remission rates, are well–documented.[7-9] As such, researchers attempted to combat the various neoplastic conditions from a different perspective—by identifying the very pathogenetic mutations that underlie the abnormal growth of cells. With this lofty goal, cancer's first targeted therapy, rituximab (Rituxan) was approved for the treatment of medically intractable B–cell non-Hodgkin lymphoma (NHL) in 1997 (Table 1).[10] Rituximab, which remains a part of the primary regimen for treatment of NHL to this day, contributes to the vastly improved 5–year survival rate for the condition, which now exceeds 90% in low–risk cases.[10] Since this initial discovery, many more targeted therapies have been approved for the management of a wide array of cancers, often targeting aberrant growth factors, angiogenesis, and apoptosis responses within tumour cells. Perhaps most notably, imatinib (Gleevec), blocking the overly active BCR–Abl tyrosine kinase produced by a 9-22 chromosomal translocation, was approved in 2001 for the treatment of chronic myelogenous leukemia (CML).[10] This advancement fostered an increase in 5–year survival for CML from 31% in 1993 to nearly 90% today.[10] While imatinib, rituximab, and other so–called targeted therapies have given oncologists hope to one day offer effective, side effect–minimizing therapies for all cancer types, the pace of progress has once again slowed, with many malignancies still requiring conventional chemotherapy to attempt to slow the rate of growth. As such, many still question how to systematically investigate and implement pharmacogenomics in the new generation of oncology.

One major step forward was thought to be the completion of the human genome project in 2003, which elucidated thousands of novel biomarkers that have since been targeted therapeutically. Furthermore, next–generation sequencing has substantially lowered costs and reduced the required time for screening of mutations within either tumour or host DNA.[11]

Where we are now

A prevalent thrust in oncology today is to utilize comprehensive analyses of the tumour's and the patient's DNA to predict a drug's efficacy and safety.[12] The implementation of pharmacogenomics into the clinic must differentiate between two forms of genetic mutation: somatic and germline.[13]

Somatic (tumour) mutations represent the driving force behind oncogenesis.[14] One example of present relevance is the anaplastic lymphoma kinase (ALK) rearrangement that underlies some forms of non-small cell lung cancer (NSCLC) and can now be precisely targeted with such drugs as crizotinib (Xalkori) and ceritinib (Zykadia).[13] Although these medications did show promise, crizotinib, for example, prolonged survival amongst advanced NSCLC by only 4.7 months as compared to conventional chemotherapy.[15] As such, clinicians and researchers alike must once again face the question of how to enhance this benefit.

One significant component to treatment success is the minimization of treatment–related adverse events. Germline (patient) mutations are major determinants of the pharmacodynamic handling of medications and, as such, play a critical role in identifying patients at high risk of developing serious untoward effects that contribute to treatment discontinuation.[12] To illustrate this, we turn to estrogen–dependent breast cancer, in which treatment with aromatase inhibitors may be limited by severe musculoskeletal pain.[16] Studies have identified single nucleotide polymorphisms (SNPs) in the T–cell leukemia 1A (TCL1A) gene that are significantly associated with this adverse event.[17] Theoretically, such genetic markers, which exist for chemotherapy and targeted therapies alike, could be investigated at the start of cancer treatment to predict those individuals who will discontinue treatment due to intolerability, sparing them unnecessary harm.[12] However, the thorough assessment of such markers through randomized controlled trials (RCTs) would be required before clinical implementation.[13]

The barriers

The most obvious factor to be considered is, as always, cost. While some genetic modifications occur in the vast majority of tumours, others are far less common.[12] A recent cost–effectiveness analysis

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Table 1 | Timeline of Significant Advancement in Cancer Targeted Therapy. Derived from American Society of Clinical Oncology[26]

Year	Significance	Drug	Target	Indication
1997	First FDA-approved targeted cancer drug	Rituximab	CD20	B-cell non-Hodgkin Lymphoma (NHL)
1999	First FDA-approved targeted anti-breast cancer drug	Trastuzumab	HER2	HER2+ breast carcinoma
2001	Fastest approval in FDA history; first drug to target the Philadelphia chromosome	Imatinib	BCR-Abl	Chronic myelogenous leukemia (CML)
2001	First effective c-Kit blocker	Imatinib	c-Kit	Gastrointestinal stromal tumour (GIST)
2003	First FDA-approved targeted anti-lung cancer drugs	Gefitinib, Erlotinib	EGFR	Non-small cell lung cancer (NSCLC)
2004	First FDA-approved anti-angiogenic drug	Bevacizumab	VEGF	Colorectal, lung, ovarian, kidney cancers
2005	Additional colon cancer targeted therapies	Cetuximab, Panitumumab	EGFR	Colorectal cancer
2010	First proven survival benefit for advanced melanoma	Ipilimumab	CTLA4	Metastatic melanoma

on the utilization of ALK testing in advanced NSCLC found that the process was inefficient due to high medication costs and marker infrequency.[18] As many oncologists attest, ALK testing and subsequent targeted treatment portends a significant mortality benefit and, as such, should remain a standard of care.[15,19] However, the cost of such interventions must be considered.

The major barrier in anti–neoplastic drug development is no longer the identification of potential targets, which has been vastly enhanced through advances in molecular technology, but rather differentiating key mutations that underlie the pathogenesis (driver mutations) from non–clinically relevant alterations (passenger mutations). Although stratifying these may be difficult, the silence of the mutation, its location, and its frequency will assist with the demarcation.[12]

Each time a potential biomarker is identified, it must be thoroughly assessed from toxicity, efficacy, and economic perspectives. The only viable means of providing this evidence are large–scale RCTs. This has now emerged as a major bottleneck in the field, since identification of potentially beneficial loci has accelerated with advances in sequencing technology.[11] The concept of thorough analysis of each of these potential sites is daunting. As part of the solution, the American Society of Clinical Oncology implemented the CancerLinQ initiative in 2015 to facilitate collection of global data from patient care in real time, enabling the production of relevant hypotheses to be investigated in an efficient manner.[12,20]

Where we go next

One component of oncology's future will require no significant intervention from researchers—the cost of genomic sequencing and its turnaround time will continue to decrease.[21] Since 2007, when the cost to sequence an entire genome was approximately $10 million, the expense has plummeted to below $1,500 in 2015.[22] Although cost–effectiveness analyses on the feasibility of widespread implementation of genomic sequencing in all aspects of healthcare remain controversial,[23] the application to cancer therapeutics would significantly reduce costs.[24] Ultimately, genomic sequencing will be incorporated into the regular practice of medical oncologists. This process is well underway in British Columbia, under the direction of the B.C. Cancer Agency's Personalized Oncogenomics (POG) program.[25] The hope is that such advances will hasten the development of novel medications.

As noted, the future of oncology will, inevitably, be greatly influenced by RCTs. However, sole reliance on this method of analysis is impractical given cost and time restrictions. Therefore, observational trials, despite their inherent potential for biases and confounders, will play an important role in classifying real–world risks and benefits.[13]

Finally, it must be acknowledged that the future of oncology lies within the sequences of the germline and somatic mutations that are identified. The importance of obtaining specimens from hosts and tumours and of contributing to the developing global database of cancer DNA must be impressed upon all developing clinicians and clinical researchers.[20] Only in this way will we draw closer to the seemingly mythical concept of cancer eradication.

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