Research and the Changing Landscape of Oncology: Cancer Therapy

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Introduction

In 2013, Science magazine, a leading American scientific journal, proclaimed cancer immunotherapy as the ‘Breakthrough of the Year’ and went as far as claiming it the ‘turning point in cancer’.

The prominent leading example of immunotherapy, ipilimumab (Yervoy), an anti-CTLA-4 antibody, has been touted as revolutionary in the treatment of metastatic melanoma, resulting in significantly increased overall survival.

Success of ipilimumab in melanoma opened doors to the potential use of immune checkpoint inhibitors in other malignancies, setting the stage for many current immunotherapy research and trials.

Ipilimumab’s approval of use by the US FDA in 2011 arrived a mere decade after the approval of imatinib (Glivec), a kinase inhibitor, in 2001 which transformed the treatment of chronic myeloid leukaemia (CML), producing complete cytogenetic response rate of 76.2% and progression-free survival of 96.7% at 18 months. With the advent of imatinib, a new wave of small-molecule therapeutics, particularly the tyrosine-kinase inhibitors (TKIs), redefined oncologic treatment, with a shift away from broadly-acting cytotoxic agents to more tumour-specific targeted therapies.

These paradigm shifts in the oncologic treatment landscape evolved from rapid advances in global cancer research over recent decades which improved our understanding of cancer biology. These research breakthroughs place us at an exciting, defining moment in the oncology timeline as we enter an era of personalized cancer medicine with immunotherapy and targeted therapy taking centre stage in cancer research and therapeutics today.

This essay discusses past, present and future trends in cancer therapy, highlighting the pivotal role research plays in their development. It delves into the implications of these research and treatment advances in the context of Australia’s cancer care and health system. It also explores the relevance of these therapeutic and research advances to medical students.
Past Highlights

The early-to-mid 20th century saw the explosion of numerous chemotherapeutic discoveries, such as antifolates, thiopurines, vinca alkaloids, which largely relied on large-scale screening of plants, fungi and organisms for compounds with anti-cancer activity.\textsuperscript{11-13} It was the landmark discovery of the effectiveness of nitrogen mustard against Hodgkin’s lymphoma post-World War II which represented the dawn of oncology.\textsuperscript{14} Although many chemotherapeutic agents were available, most were limited by narrow therapeutic index, toxicities and acquired resistance.\textsuperscript{11,12} Little was known about cancer biology then, though subsequent development of chemotherapy and radiotherapy regimens was guided by the hypothesis of tumour cells’ sensitivity to DNA damage.\textsuperscript{15}

Despite subsequent discoveries of the first proto-oncogenes and tumour suppressor genes in 1970s, the first mutated gene in human cancer in 1982, and tumour signalling pathways in 1990s, genetic understandings had minor impact on clinical efforts to control cancer.\textsuperscript{15-17} Drug development continued with compound modifications and large-scale screening, without learning from advances in cancer biology.

Surgery and radiotherapy had always been and are likely to remain the bulk of cancer treatment.\textsuperscript{15} Improvements in technologies in recent decades, such as minimally-invasive surgery, intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) that deliver precise radiation to the target in 3-dimensions and motion respectively, make them more effective therapies, independent to molecular advances.\textsuperscript{15,16,19}
Present Trends

The progress of research in recent decades that brought increasing understanding of the molecular mechanisms of cancer pathogenesis has translated to the discovery, development and application of molecularly-targeted agents (MTAs). MTAs inhibit specific molecular pathways enabling key capabilities or hallmarks in tumour cells (such as growth and maintenance), activate apoptotic signaling and facilitate effector functions of immune cells, effectuating rapid and profound tumour regression. Following successes of imatinib in CML and rituximab in non-Hodgkin lymphoma, emergence of these mechanism-based therapies has changed many metastatic solid tumours from diseases with nearly invariable, early fatality, to chronic diseases with prolonged progression-free survival (PFS) and overall survival. For instance, sunitinib, a multi-targeted TKI demonstrating longer PFS than previously used interferon-α, became the most commonly used first-line agent in metastatic renal cell carcinoma (RCC) which, with the use of other second-line agents including everolimus and axitinib, improved overall survival from several months to years.

Parallel to the development of MTAs is the advancement in genomics and proteomics. We are only beginning to appreciate that chromosomal and genetic defects modify cellular signaling, creating survival advantage for tumour cells. Following the footsteps of the Human Genome Project which identified more than 290 cancer-related genes through collaborative research, the Cancer Genome Atlas (CGA) and the International Cancer Genome Consortium (ICGC) are monumental international efforts to provide a complete catalogue of all cancer genes in major cancer types. Through genetic sequencing and molecular characterization of hundreds of tumours, they aim to provide a comprehensive description of all genomic, transcriptomic and epigenomic changes.

Knowledge of oncogenic mutations and molecular changes holds promise to reveal potential therapeutic targets and develop MTAs to treat specific patients' tumours. Current research identifies oncoproteins in various signaling pathways involved in tumour growth and maintenance present in patient subpopulations, such as EGFR, HER2, BRAF, c-KIT – these act as predictive biomarkers that predict response to specific MTAs. Molecular profiling of patients' tumours performed prior to treatment can determine their mutational status which can be matched to particular therapeutic agents. For example, EGFR inhibitors cetuximab and panitumumab are used for patients with KRAS mutation-negative colorectal carcinomas, extending their PFS when combined with chemotherapy. Gefitinib, another EGFR inhibitor, was used in lung adenocarcinoma expressing EGFR-activating mutation, demonstrating significant PFS in the IPASS study in 2004. Trastuzumab, a HER2-inhibitor, is used as part of the adjuvant therapy for HER2-overexpressing breast cancer. Presence of BRAF V600E mutations in metastatic melanoma predicts favourable use of vemurafenib, an anti-BRAF V600E antibody. With our shift towards precision medicine, molecular heterogeneity of cancers means targeted therapies based on individual molecular aberrations will be increasingly developed and applied in cancer therapy.

The emergence of novel immune-based strategies came with an expansion in understanding of immune controls and responses to tumours, particularly immune escape and checkpoint blockade of inhibitory receptors and ligands, such as CTLA-4, PD1/PDL-1. Dr Jim Allison's
research in immune responses and T cells led to the discovery of ipilimumab and its subsequent use in metastatic melanoma.\textsuperscript{37,38} By stimulating host immune responses, ipilimumab and other immunotherapeutics, including cell vaccines, cytokines and anti-PD1 antibodies, have demonstrated extraordinary clinical efficacy with durable tumour regression, especially in diseases known to respond to immune-based therapies, like melanoma and RCC.\textsuperscript{37,39,40} Immunotherapy is showing promise in treating traditionally non-responding diseases and current trials seek to further evaluate response rates.\textsuperscript{4-6,36,37,41} For example, pembrolizumab and nivolumab, two anti-PD-1 antibodies approved for melanoma, are currently evaluated in solid tumours such as non-small-cell lung cancers, breast and bladder cancers.\textsuperscript{41-43}
Future Directions

Targeted therapy and immunotherapy, with the emerging molecular and genetic characterization of cancers, pose an alluring revolution in cancer treatment. However, much work remains to be done before these novel therapeutics hold dominance in cancer treatment of tomorrow.

Comprehensive catalogues of cancer genes in the CGA and ICGC need to be completed while efficient, extensive methods of molecular characterization and genomic sequencing of tumours have to be developed.\textsuperscript{30,31,35} We need to develop sensitive and specific predictive biomarkers which match genomic abnormalities and predict response to MTAs; they will help stratify patients that may benefit from specific MTAs.\textsuperscript{11,44} Clinical efficacy and safety of MTAs need further evaluation.\textsuperscript{20,45} Drug resistance, especially with MTAs, is a pertinent problem and novel strategies are required to overcome such resistance.\textsuperscript{15} We will need to deepen our understanding of the immune system to uncover components that can be harnessed with immunotherapy.\textsuperscript{46} We can optimize targeted therapies and immunotherapies, expand their applications and evaluate their roles in adjuvant and neo-adjuvant settings.\textsuperscript{12,47-53} This allows us to ultimately establish combined-multi-modal therapies for the individual patient to produce rapid responses with durable remissions.\textsuperscript{12,47-53}

These evaluations will require intensive research and trials to advance the roles these novel therapies play in current and future mainstream cancer therapy. With the redefinition and classification of cancers based on genomics, personalized, precise cancer therapy using multimodal agents based on tumour-specific molecular profiles will likely be the standard oncologic practice of tomorrow.

With emerging innovations in specialized fields, multiple treatment modalities and approaches which may potentially be employed in future cancer therapy are being explored. Investigations are underway in epigenomic engineering where cancer expression can be modulated with precisely reversed epigenetic mutations through genomic editing and reprogramming.\textsuperscript{54,55} Therapeutic radioisotopes with antibodies targeting tumour components are developed in radioimmunotherapy while nanoparticles are explored as delivery vehicles of therapeutics into tumour cells.\textsuperscript{56-61} Novel therapeutic targets such as miRNA, mitochondria and cancer stem cells are investigated. Modulating miRNA expression may inhibit tumour proliferation as miRNA are postulated to be involved in tumourigenic processes and regulating resistance mechanisms.\textsuperscript{62-64} Mitochondrial-targeting agents can possibly suppress tumour metastasis by modulating mitochondrial function and oxidation.\textsuperscript{65-68} Cancer stem cells are increasingly recognized as potential treatment targets with strategies evaluated to inhibit their pathways.\textsuperscript{69}
Relevance of Research Advances and Novel Treatments to Australia Cancer Care

Australia is no stranger to the devastating impact of cancer which was estimated to be its leading cause of burden of disease in 2012 with rising incidence rates. With the global revolution in novel therapeutics and surge in genetic understanding of cancer, Australia has both contributed to and benefited from these recent advances in research and therapy.

Australia’s scientific and medical communities actively contribute to the oncologic scene by continually expanding knowledge of cancer biology and establishing trials for new drugs. Pancreatic cancer is Australia’s major contribution to the ICGC through the Australian Pancreatic Cancer Genome Initiative. By performing whole-genome sequencing and copy number variation analysis of 100 pancreatic ductal adenocarcinomas, research teams uncovered genetic drivers in tumourigenesis and highlighted 4 subtypes with potential clinical utility. This allows investigators to match mutations to specific MTAs and test their efficacy on patient subpopulations. The Australia and New Zealand Breast Cancer Trials Group (ANZBCTG) continuously conducts trials that provided the most reliable evidence supporting use of many treatment strategies in breast cancer, including tamoxifen and combination therapy. In collaboration with other international research groups, such as the Breast Cancer International Research Group, ANZBCTG seeks to further evaluate the use of specific targeted therapies. The Melanoma Institute Australia similarly conducts various clinical trials to evaluate efficacy of novel therapies in melanoma.

While excitement mounts in Australia with the new wave of oncology medicines as prospective therapies, their arrival poses challenges to regulatory and reimbursement processes that may limit access to these medicines.

In Australia, drugs have to be approved for use by the Therapeutic Goods Administration (TGA) and for subsidy on the Pharmaceutical Benefits Scheme (PBS) as recommended by the Pharmaceutical Benefits Advisory Committee. The PBS is currently the only means of providing Australians with broad and equitable access to cancer medicines. Unfortunately, there is often a prolonged PBS approval process for new cancer medicines. Many Australian patients cannot wait for the subsidy approval nor afford the full unsubsidized cost to access new drugs. An illustrative example is in melanoma, with highest world-wide incidence in Australia where the arrival of ipilimumab was highly anticipated. Ipilimumab was registered by the TGA in 2011 for use in metastatic melanoma, but costs AUD$190,341.20 for 4 injections. Subsequent inclusion of ipilimumab on the PBS in 2013 allowed Australians to only pay AUD$150.80.

Subsidizing cancer medicines is costly. Expenditure on cancer medicines by the PBS has substantially grown more than 60% in the five years to 2011, costing $587.5 million in 2012. Many stakeholders question the appropriateness of funding these expensive medicines which may translate to marginal benefits for selected patients, diverting funds from many other competing priorities.
Physical access to novel therapeutics is an additional issue in Australia. A third of Australians with cancer live in rural-regional areas with poor access to cancer treatment and, consequently, face significantly poorer survival outcomes, having up to 300% higher five-year mortality risk for certain cancers.\textsuperscript{87,88} With the revolution of novel therapies, the gap of cancer burden in Australia widens with patients in rural areas bearing a larger disproportionate part of the burden as new therapies are primarily restricted to urban-based tertiary centres.

These challenging issues of timely, affordable and geographical access remain difficult to resolve, expecting to worsen with the burgeoning surge in novel therapeutics. To date, the Australian government remains supportive of continued listing of cancer drugs on the PBS, recognizing their necessity in cancer treatment, while implementing measures to curb expenditure growth.\textsuperscript{89} Establishment of the Rural Cancer Centres Initiative and patient-assisted travel schemes may reduce geographical discrepancy in cancer care outcomes by improving rural-regional access to cutting-edge therapies.\textsuperscript{88}
Relevance of Research Advances and Novel Treatments to Medical Students – Our Future Healthcare Professionals

As cancer survival rates improve, more people are living with cancer today. On average, GPs are said to encounter, annually, 4 new patients diagnosed with a potentially fatal cancer and have, at any one time, 16 patients with cancer. Regardless of the discipline that medical students eventually practice in, they will be expected to manage oncology patients to varying degrees. It is hence important for students to have a firm and comprehensive understanding of cancer management, as outlined in the *Ideal Oncology Curriculum* published by the Cancer Council Australia, including established treatments of surgery, radiotherapy and chemotherapy.

Most common and several rare malignancies have at least a systemic therapy, such as an MTA or immunotherapy, and doctors will encounter patients receiving these novel therapies. As use of newer therapeutic agents become more widespread across disciplines, all healthcare professionals will need to be familiar with them as they become the mainstay of treatment. Medical students today should ideally be aware of them and learn their side-effects as part of medical school oncology education.

Medical students should also be equipped with knowledge in genetics and genome-wide studies and skills in evidence-based medicine. This will allow them to effectively critically appraise and contribute to cancer research.
Conclusion

In over half a century, we have made great strides in cancer therapy with refined treatments and improved five-year survival rates. As we witness the ever-changing landscape of oncologic therapy, from surgery, radiotherapy and chemotherapy, to the advent of MTAs and immunotherapy, it is easy to overlook the work of research that drives and inspires these paradigm shifts to give us the armamentarium in cancer treatment of today. This progress is due to the pooling of expertise of individuals with specialized skills working collaboratively in multidisciplinary teams and convergence of different fields with independent research threads. Each clinician and researcher contributes through small incremental advances to the lattice of knowledge constructed over decades, allowing remarkable breakthroughs to produce novel therapies. We need to maintain concerted international efforts in all aspects of modern oncology – from research, drug development, and clinical application of novel agents – to facilitate the effective translation of cancer biology to therapeutic benefits for cancer patients.

As we stand at the dawn of a new era of cancer research and therapy, we anticipate radical changes to the future landscape. Each wave of discovery will bring new insights, challenges, renewed hope and emerging, promising treatments. Our ceaseless hunt for ever-better treatment will continuously push frontiers of research with ever-expanding understanding of cancer biology and novel therapies.
References


