



AWARDS

CANCER COUNCIL AUSTRALIA'S STUDENT ESSAY COMPETITION

Cancer Council Australia's annual essay competition is open to Australian residents enrolled in a medical course in an Australian university. Students are required to submit an essay on an issue related to cancer control. In 2011, the topic was "Personalised cancer treatment - fad or future?". The essays are judged by members of Cancer Council Australia's Oncology Education Committee.

This article is the winning essay by Jillian Mellor. As the winner, Jillian attended the International Summer School on Oncology for medical students in Vienna from 13-22 July 2011.

PERSONALISED CANCER TREATMENT – FAD OR FUTURE? A MEDICAL STUDENT'S PERSPECTIVE

Jillian Mellor

MBBS 2nd year, University of Sydney
Email: jmel3232@uni.sydney.edu.au

Responsible for one in eight deaths globally,¹ cancer is the most common human genetic disease. Last year, more than 43,000 people died from cancer in Australia,² making it one of the nation's leading causes of mortality and moreover a spur to optimise cancer treatment.

Personalising cancer treatment promises increased treatment efficacy, reduced drug side effects, early intervention based on risk factors and more accurate diagnosis. Personalised therapy, the idea of tailoring clinical therapy towards a patient's biology and pathophysiology is not new.³ Oncology particularly has a long history of personalised care by stratifying patients according to their risk of developing a certain disease.⁴ Personalised treatment can be defined in contrast to what some have called the "blockbuster" therapeutic model – large pharmaceutical companies developing drugs for mass markets, to the detriment of those who are non-responders or who respond with adverse effects.

Despite the promising potential of this new paradigm based on the genetic revolution of the past decade and subsequent fast-paced growth in cancer genomics, the clinical application of this information has been sluggish.⁵ Currently, the clinical utility of personalised cancer treatment, in terms of assisting in management and to improve health outcomes, is limited. The question remains then whether personalised cancer treatment is a practically redundant fad or a viable and sustainable paradigm shift for clinical practice.

To answer this question, this essay will begin with an overview of the revolution in cancer genomics that ostensibly promises this new medical paradigm of

individualised cancer treatment, before moving to examine the clinical application in terms of both the benefits and limitations of such a paradigm for the patient, the healthcare team and society. It will look at the hurdles to current and future use of personalised cancer treatment.

For the purposes of this essay, the phrase "personalised treatment" means therapy based on individual biology and pathophysiology. In a more holistic sense "personalised medicine" encompasses more of the patient-doctor interaction than just biology, including but not limited to the patient's needs and wishes, their disease process and psychosocial environment.

Promise of cancer genomics

Cancer. This simple six-letter word belies its complexity. What we think of as cancer is a heterogeneous group of over 100 distinct diseases,⁶ currently classified according to their organ tissue of origin. Central to our understanding is the genetic basis for cancer, essentially the uncontrolled growth of cell clones caused by abnormalities such as substitutions, deletions, insertions, rearrangements and epigenetic modification in the genome, called somatic mutations. This means that human cancer genomes, or oncogenomes, can be uniquely understood in terms of the mutations that they have accumulated over time. Currently, 384 genes – almost 2% of protein-coding genes – have been found linked to mutations causing cancer.⁷

Hereditary mutations, located within the patient's germline, confer an increased risk of developing cancer. About 20% of the identified cancer genes have germline mutations.⁸ Contrast this with somatic mutations that occur in genomes

of normal cells during cell division. These replication errors accumulate over decades so that thousands, in some cases hundreds of thousands of somatic mutations accumulate to cause cancer.⁹ Approximately 90% of cancers are caused by somatic mutations (with a 10% overlap with germline mutations).⁸

Since the release of the sequenced human genome in 2003 with the completion of the Human Genome Project, the field of human genomics has effectively exploded. The vast terrain that is the human genome, about 25,000 genes, is being mined and catalogued systematically, using high-throughput technologies, for aberrant genes that could potentially be targeted for therapy or used as biomarkers to aid diagnosis.⁵ Cancer genomic research is an international effort including groups such as the International Cancer Genome Consortium, through which Australian researchers are contributing by analysing mutations in ovarian and pancreatic cancer.¹⁰

The following is a brief summary of the promise of personalised cancer treatment.

Diagnosis: Biomarkers of a particular cancer gene, or oncogene, can be identified to specifically diagnose the cancer.

Targeted treatment: Designing 'smart drugs' based on genetic understanding of protein function is the basis of pharmacogenomics. Professor Michael Stratton, Director of the Cancer Genome Project, describes identified mutated cancer genes as 'Achilles' heels', ready to be exploited as targets for drug development.⁴ Additionally, subsets of patients who are likely to respond to a particular drug can be identified for treatment. For example, trastuzumab is a monoclonal antibody developed against the amplified HER2 protein, present in 20% of breast cancers. HER2 status, either gene copy number or the protein expression level, is the best predictive marker available for assessing response to trastuzumab.¹¹

Limit adverse drug effects: All patients metabolise drugs differently; patients who are genetically unable to metabolise drugs can be identified to avoid unnecessary adverse effects.

Limit disease progression: As an early warning for disease recurrence, cancers can be detected by monitoring for leaked DNA fragments of the oncogenome in the circulation. This technology is currently used in leukaemia surveillance.

Risk stratification: Some germline mutations predispose an individual to disease. These mutations can be identified to calculate the risk for the patient. For example, BRCA 1 and BRCA 2 predispose towards breast and ovarian cancer and furthermore predispose towards an increased risk of recurrence following remission.¹²

Benefits and limits for the patient, the doctor and society

Some cancer patients are already benefiting from personalised treatment. The successful targeting of specific mutated oncogenes, such as the BCR-ABL fusion protein, tyrosine kinase of chronic myeloid leukaemia (CML), has transformed cancer care.⁶ In addition, patients

with germline mutations, such as BRCA 1 and BRCA 2, have been successfully screened for these mutations and treated early to prevent the development of disease. This being said, there are limitations for patients; these can be defined as lack of accessibility in a still-developing system and the expense of specially designed drugs.

At this point in time, patient care is limited until doctors become familiar and comfortable utilising genetic information. This global problem, which occasionally hits the headlines as reported by *The Times* (England), Doctors 'lack training in genetics to cope with medical revolution', is a natural consequence of the past decade's genetics explosion.¹³

Finally, the Australian community is hopeful of the benefits of genetics and yet divided as to its utilisation. According to the 2003 Kirby Oration by Professor David Weisbrot, titled *The Human Genome: Lessons for Life, Love and the Law*, the concerns of the community are based to an extent on a 'genetic muddle' that blurs all things genetic, from medical genetic testing to genetic engineering, stem cell research and nuclear fall-out.¹⁴ This limits public acceptance and utilisation of genetic technologies, ethical issues of privacy and discrimination. This is on top of a widening divide in the community between those who use genetic testing and those who don't; older, poorer, especially Indigenous Australians are less likely to use the 'new' genetics.¹⁵

Moving beyond current barriers

If personalised cancer treatment is to move beyond esoteric clinical management, it must overcome many hurdles. These hurdles could be seen as teething problems in the face of a changing medical paradigm, problems that include: a still-developing regulatory framework able to promote innovation; funding of pricy genetic diagnostic tools and treatments; increasing medical genetic literacy; and the ongoing need for acceptance from the Australian community.

Genomics regulatory framework

The idea of a rampant biotechnology industry is scary. Even ardent conservatives such as American political scientist Francis Fukuyama advance the need for strong government regulation of the biotech sector.¹⁴ As the Human Genome Project was nearing completion, the Australian Law Reform Commission (ALRC) published their report, *Essentially Yours*, detailing the protection of privacy, protection against unfair discrimination and maintaining ethical standards in genetics.¹⁵ With worldwide acclaim for its breadth and quality, the Commonwealth accepted the vast majority of these recommendations.¹⁵ Australia therefore has a good regulatory system. And yet the reins cannot be held too tight if the industry is to be attractive to private investment and innovation, essential to its long-term viability. On this front, the ALRC explored the balance between encouraging investment and ensuring that cost-effective clinical genetic services are not compromised.¹⁶

Increasing costs - who will pay?

The future of personalised cancer treatment in Australia depends on cost-effectiveness for the consumer and

AWARDS

the Commonwealth. Market fragmentation caused by the move to personalised cancer treatment is going to shake-up 'big pharma'. Instead of drugs developed for mass use (and mass profit), drugs designed through pharmacogenomics for a niche genetic market will be exceedingly expensive. Who will cover this prohibitive cost – the patient, their health insurer or Medicare? With one in two Australians not covered by private health insurance,¹⁷ the gap between the haves and have-nots is wide.

Education for doctors and medical students

Increased genetic literacy among clinicians will support increased clinical utility. Within the Royal Australian College of Physicians is the opportunity to sub-specialise in genetics, becoming experts in genetic interpretation and counselling. This must be supported by doctors in other specialities being comfortable handling genetic information and referring patients for genetic testing. Moreover, for personalised cancer treatment to be viable into the future, medical schools are going to have to ground their graduates in the clinical aspects of genetics. This issue was raised as a recommendation by the Australian Law Reform Council, that is, that all future doctors should be trained in the use of relevant genetic counselling and genetic services.¹⁵

Public acceptance and genetic literacy

There is an underlying unease in the Australian community about the pace of change. These worries range from loss of control, fears about the beginnings of 'genetic determinism' and qualms about the ability of public authorities to effectively regulate this area in the interest of the public.¹⁵ These are understandable concerns. The social and ethical implications of genetic knowledge and development is profound. In fact 3% of the budget for the Human Genome Project was invested in the social and ethical issues that would arise from genetics. Another concern regarding predictive genetic testing is discrimination. For example, if a person is predisposed with an increased risk of developing disease, there is the concern that employers may discriminate or that insurance companies may refuse health insurance on this basis. On this latter issue, the Investment and Financial Services Association has a policy on genetic testing and life insurance that states that no applicant will be required to undergo a predictive genetic test.¹⁸

Conclusion

Personalised treatment promises much for cancer care, although the current clinical utility is unrealised. These hurdles can be and must be surpassed to take clinical advantage of the ongoing genetic revolution. Clinical sequencing of patient's genomes will be an addition to the clinical examination of the patient, not a replacement for it, providing a necessary aid in diagnostic, therapeutic and prognostic decisions. Personalised cancer treatment is a viable, sustainable and necessary paradigm shift for clinical practice.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008 v1.2. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Cited April 25, 2011. Available from: <http://globocan.iarc.fr>
2. Australian Institute of Health and Welfare. Cancer in Australia 2010: an overview. Canberra: AIHW; 2010. Series no. 60. Cat. no. CAN 56.
3. Chung WK. Implementation of genetics to personalize medicine. *Genet Med.* 2007; 4(3):248-65.
4. Stratton M. Exploring the Genomes of Cancer Cells: Progress and Promise. *Science.* 2011; 331(6024):1553-8. doi: 10.1126/science.1204040.
5. Chin L, Gray JW. Translating insights from the cancer genome into clinical practice. *Nature.* 2008; 452(7187):553-63. Pubmed PMC2730524.
6. Taylor BS, Ladanyi M. Clinical cancer genomics: how soon is now?. *J Pathol.* 2011; 223:319–27. doi: 10.1002/path.2794.
7. Santarius T, Shipley J, Brewer D, Stratton MR, Cooper CS. A census of amplified and overexpressed human cancer genes. *Nat Rev Cancer.* 2010; 10:59-64. doi:10.1038/nrc277.
8. Cancer Gene Census [Internet]. Cambridge, UK: Wellcome Trust Sanger Institute. Cited April 25, 2011. Available from: <http://www.sanger.ac.uk/genetics/CGP/Census>
9. Greenman C, Stephens P, Smith R, Dalgleish GL, Hunter C, Bignell G, et al. Patterns of somatic mutation in human cancer genomes. *Nature.* 2007; 446(7132):153-8. doi:10.1038/nature05610.
10. International Cancer Genome Consortium. Goals, Structure, Policies & Guidelines. Toronto, Canada: Ontario Institute for Cancer Research; 2008. Available from: http://www.icgc.org/files/icgc/ICGC_April_29_2008_en.pdf
11. Esteva FJ, Yu D, Hung M, Hortobagyi GN. Molecular predictors of response to trastuzumab and lapatinib in breast cancer. *Nat Rev Clin Oncol.* 2010; 7(2):98-107. doi:10.1038/nrclinonc.2009.216.
12. Futreal PA, Liu Q, Shattuck-Eidens D, Cochran C, Harshman K, Tavtigian S, et al. BRCA1 mutations in primary breast and ovarian carcinomas. *Science.* 1994; 266:120-2. Pubmed PMID: 7939630.
13. Henderson M. Doctors 'lack training in genetics to cope with medical revolution' [Internet]. The Times. 2010 Feb 24. Available from: <http://www.timesonline.co.uk/tol/news/science/medicine/article7038239.ece>
14. Weisbrot D. The Kirby Oration "The Human Genome: Lessons for Life, Love and the Law". Sydney: ALRC; 2003 Nov 20. Available from: <http://www.alrc.gov.au/news-media/2001-2005/kirby-oration-human-genome-lessons-life-love-and-law>
15. Australian Law Reform Commission. Essentially Yours: The Protection of Human Genetic Information in Australia (ALRC Report 96). Sydney: ALRC; 2003. Available from: <http://www.alrc.gov.au/publications/report-96>
16. Australian Law Reform Commission. Gene Patenting and Human Health (DP 68). Sydney: ALRC; 2004. Available from: <http://www.alrc.gov.au/dp-68>
17. Private Health Insurance Administration Council. Quarterly Statistics December 2010. Canberra: PHIAC; 2010. Cited April 25, 2011. Available from: <http://www.phiac.gov.au/resources/file/quarterlystatistics/110221%20QtrStatsDec10.pdf>
18. Centre for Genetics Education. Life Insurance Products and Genetic Testing in Australia [Fact sheet]. Sydney: NSW Government; 2007. Cited April 25, 2011. Available from: <http://www.genetics.edu.au/pdf/factsheets/fs23a.pdf>