
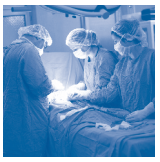


RARE CANCERS: HOW FAR HAVE WE COME AND WHERE SHOULD WE BE HEADING? EXTENDING EVIDENCE-BASED CARE TO PEOPLE WITH RARE CANCERS

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Abstract

Approximately one third of Australians who die of cancer do so from one classified as being 'rare'. While there have been significant recent improvements seen for many patients with common cancer types, this has not been observed for the majority of patients with a rare cancer diagnosis. At the same time, the proportion of patients who are being diagnosed with a cancer that is classified as being rare is increasing, in part due to the realisation that even common cancers may in fact fall into the rare category once they are classified according to specific molecular changes. Strategies undertaken previously for some rare cancer types, for example pediatric and haematologic malignancies or sarcoma, serve as a guide for ways to improve the care of all rare cancer types. In this forum, Australian leaders in managing rare cancers provide an overview of what rare cancers are and some of the strategies for improving management of patients.

Around one fifth of Australians who are diagnosed with cancer and one third of Australians who die of cancer might reasonably have their disease classified as a rare cancer. A practical definition of 'rare' comes from the RARECARE group, being 'an incidence rate of <6 cases per 100,000 population per year'.[1] However, the average outcome for patients with a rare cancer is inferior to those with more common cancers when analysed separately within these data. For the 50% of cancer patients diagnosed with a common cancer type (breast, bowel, lung, melanoma and prostate), five-year relative survival rates improved between 1982-1987 and 2006-2010.[2] In contrast, there has been little change (5% or less) in five-year survival for people with other less common cancer types over the same period, for example, for cervical, laryngeal and pancreatic cancer.[3,4] Despite increases in five-year survival rates for liver, gall bladder and unknown primary cancers and stable rates for brain cancer and mesothelioma, five-year survival rates remained very low for these rare cancer types (~20% or less) between 2006-2010. Better outcomes were seen for testicular (91% to 98%) and thyroid (84% to 96%) cancer. Most other patients diagnosed with one of many types of rare cancers endure a long road to diagnosis, with little specific information or evidence-based care available, even after a diagnosis is finally made.

Nevertheless, three categories of rare malignancy - childhood cancers, haematologic malignancies and sarcoma - have been associated with notable improvements over the last three decades, and these serve as useful guides as to how we may improve the outcome for rare cancers in general.

Childhood cancers

The care of children with cancer is based on decades of highly organised and centralised clinical research that has focused on optimising dose, scheduling and combinations of conventional chemotherapeutics and supportive care.[5] Through academic-led, non-commercial clinical trials, overall five-year survival rates of over 80% from the time of diagnosis have been achieved. This is despite the fact that drug development programs for childhood cancers are scarce due to both the rare nature of all childhood cancers and limited pharmaceutical industry investment in new drugs for them

Haematologic malignancies

Easy and safe access to malignant cells for analysis by flow cytometry has facilitated basic science research in haematologic malignancies, allowing a greater

understanding of their biology and hence how they may be treated. Despite accounting for only 10% of cancer burden and deaths, they have received one third of PBS cancer expenditure,[4] reflecting the successful implementation of effective treatments arising from research, both basic and clinical. Paradoxically, the rarity has facilitated scientific advance, by enabling focus on distinctive morphologic, cytogenetic and molecular characteristics to develop targeted therapies, as described by Chew and Roberts in this forum.[6] As a result, two rare leukaemias (acute promyelocytic leukemia and chronic myeloid leukemia), which have poor prognoses when treated with cytotoxic chemotherapy, are now considered to have very favourable prognoses with targeted therapies.

Sarcoma

Bone and soft tissue sarcomas account for only ~1% of all adult solid malignant tumors, yet represent more than 70 distinct tumor subtypes. Obtaining the correct diagnoses of specific subtypes of sarcoma is becoming increasingly important in delivering tailored and optimal medical care, as outlined by Bae and Desai.[7] The management of one of these, gastrointestinal stromal tumor, has served as a prototypic model for the development of other molecularly-targeted therapies. Unexpectedly, the first clinical trial in this rare disease using imatinib, the tyrosine kinase inhibitor targeting the KIT and PDGF receptors, showed dramatic improvements in disease control and led to its accelerated approval within three years. Opportunities in Australian centres to lead or participate in sarcoma-focused trials have improved due to the establishment of local and international collaborative infrastructure, and may lead to improvements more broadly for sarcoma patients.

Where should we be heading with rare cancers in Australia?

The strategies undertaken previously for the rare cancer types described above would appear to be a rational starting point if we wish to facilitate improvement in the care of all rare cancer types. Increased national coordination is required due to the rare nature of these diseases, as by definition it will be difficult to accumulate sufficient cases for statistically meaningful studies to be done without this. The aim of any such endeavours should be focused in several ways: i) to facilitate more accurate diagnosis, including molecular analysis, allowing focus on distinct rare cancer subsets; ii) participation in small, focused clinical trials and/or streamlining of management protocols with international collaboration; and iii) national and international data capture of patient management and outcomes.

In this issue of *Cancer Forum*, we have brought together expert reviews and opinions from leaders in the management of and research into rare disease. Chan, Goldstein and Zalcberg provide an overview of Neuroendocrine Tumours (NETs),[8] which illustrates how an anatomically disparate group of tumours may be considered as one group defined by their biology (arising from a single cell type of origin). Grimison illustrates how improvements in disease classification have led to more reliable prognostic criteria, multi-disciplinary management, international collaboration and implementation of evidence-based guidelines resulting in dramatic improvements in the outcomes for those diagnosed with testicular cancer.[9] Harrison and Friedlander describe how evidence-based care developed through national and international cooperation can be brought to the clinic for patients with gynaecologic cancers, over half of which may be defined as being rare.[10]

More children and adults under the age of 40 die of brain cancer than of any other cancer type. The great challenge posed by glioblastoma multiforme is slowly being addressed by molecular characterisation, as described by Field and Rosenthal.[11] The clinically diverse group of tumours referred to as 'head and neck cancers', are being found to have distinctive molecular features, as described by Lim, Solomon and Rischin.[12] Despite their rarity, approaches integrating targeting of key molecular drivers into centralised care and protocols are impacting clinical practice. The discovery of rare molecular alterations in lung adenocarcinoma, as described by Hasovits and Pavlakis,[13] raises challenges in their identification and the selection of the most appropriate model for clinical trial design for testing potential new treatments.

The potential of genomics technologies

The extraordinary potential of next generation sequencing (NGS) technology makes it possible for the rare cancer types described above to be divided into molecular 'subsets' for more accurate study. This may, paradoxically, reduce the ~200 rare cancer subtypes identified by RARECARE,[1] to a more manageable number of 'molecular' groupings, providing some context as to prognosis and treatment direction for those patients for whom we currently have little in the way of evidence-based guidance. Many common cancers types may also become 'rare' by molecular association, as has been described above for molecular subsets of melanoma and lung cancer.

NGS technology allows analysis of DNA sequence, RNA expression, as well as regulation by the epigenome, microRNAs and other phenomena and will transform the way we think of rare cancers. NGS platforms are under local development for clinical analysis of tumour tissue and also have the potential to provide analysis of a liquid biopsy from the peripheral blood of circulating tumour DNA,[14] and for less expensive analysis of tumour-derivatives (methylated DNA).[15] One

approach of using an NGS platform to identify potential therapeutic targets in high grade epithelial ovarian cancer is reviewed by Kondrashova and Waring.[16] Utilising these molecular approaches, diagnosis will no longer be pigeon-holed in an organ or histologic subtype, but better 'matched' to molecularly similar tumour types, with direct therapeutic relevance. Just as studying a rare cancer, such as BRCA1/2-associated high-grade serous ovarian cancer (HGSC) can have relevance for related yet BRCA1/2 WT HGSC,[17] matching rare cancers to common cancers may allow their management path to be deduced by association. Context specific tailoring will likely be required, as BRAF mutations require different therapeutic approaches in colorectal cancer compared with melanoma.

However, plausible hypotheses may provide treatment options for patients who have no 'standard of care'. An innovative approach, involving molecular analysis of cancer of unknown primary or CUP, is described by Guccione and Bowtell.[18] Indeed, many rare cancers could be seen as 'cancers of unknown molecular primary' (CUMP) and might be matched accordingly using NGS platforms.

In the near future, it may be more efficient to perform molecular analysis on each rare cancer at the time of first diagnosis, in order for the best molecular match to guide a management plan. Likely prognosis and the most appropriate management and treatment may be better estimated than from our current anatomical and histological characterisation. While at present, molecular analysis of rare cancers is not funded, it is logical to think that within a relatively short number of years, that will become the priority, as it will become less acceptable to treat people based on histology and imaging alone. True evidence-based guidelines for each rare cancer type will take longer, however, as information from molecular profiling, leading to hypothesis-generated choice of treatment, will need to occur within research studies. Even these data will not reach the stringent requirements for regulatory approvals and funding decisions, heralding ongoing challenges for some time to come.

Designing clinical trials for small numbers of patients is challenging. Approaches for studies limited by small patient numbers have been described, using Bayesian methods, optimising external controls, robust biomarker incorporation and adaptive designs e.g. 'basket trials'.[19] International endeavours will be essential and have been building recently, including: the International Rare Cancer Initiative (http://www.irci.info/);[3] international clinical trial groups such as the Gynaecologic Cancer Intergroup, who have recently published consensus statements on the management of 20 rare gynaecologic cancers;[20] and at a more basic research level, the Cancer Genome Atlas rare cancer projects (http://cancergenome.nih.gov/cancersselected/RareTumorCharacterizationProjects).

We are all in this together: consumer and community engagement

In this era of significant genomic changes ahead of us, it is of great importance to involve Australian patients and their families, as all too often they feel they have to fight to find support and management options in our current system. Together, we can be more strategic, designing and harnessing new approaches, including innovative ways of accessing new treatments. The common themes recurring throughout are of the need for centralised coordination of management and research of rare cancer patients and of the potential utility of detailed molecular analysis. One approach to this has been to develop a website that allows individual rare cancer patients, or their approved proxy, to enter clinical data into a database. Details are available at CART-WHEEL.org and this program enables the community to work with researchers as a partnership.[21] Additionally, support for consumers, patients and their families is provided by Rare Cancers Australia, a charity whose purpose is to improve awareness, support and treatment of Australians with rare and less common cancers http://www.rarecancers.org.au/.

We hope that this issue of *Cancer Forum* will inform and inspire readers about rare cancers, and at the same time show that there is significant hope for improved outcomes that may yet reach the same levels we have seen for other cancer types.

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