The promise and challenges of rare cancer research

See Series pages e52, e62, and e70

See Online for podcast interview with Richard Carvajal

It is commonly stated that 20–25% of all oncology patients have a diagnosis of rare cancer. The US National Cancer Institute defines rare cancers as those with an incidence of less than 15 cases per 100 000 per year. On the basis of this definition, Greenlee and colleagues analysed data for more than 9 million adults in whom cancer was diagnosed between 1995 and 2004, and reported that 60 of 71 cancer types, primarily defined by anatomical location, were classed as rare. Those cancers accounted for 25% of all adult cancer diagnoses.[1] In a subsequent study, the Surveillance of Rare Cancers in Europe (RARECARE) consortium analysed European population-based cancer registry data for patients with cancer diagnosed between 1988 and 2002.[2] In that study, rare cancers were defined as those with an incidence of less than six per 100 000 per year, and a newly generated list[3] of cancer types was used; 22% of all new cancer diagnoses were classed as rare cancers.

With evolving understanding of cancer biology and the associated changes in the taxonomy of malignant disease, these numbers now underestimate the incidence of rare cancers. Large-scale efforts, including the International Cancer Genome Consortium, the Cancer Genome Atlas, and the Cancer Genome Project, have systematically catalogued genomic alterations in different cancer types and have provided the impetus for changing the classification of cancers from histologically based to molecularly based. As part of a Series of three papers on rare tumours in *The Lancet Oncology*, Niki Boyd and colleagues describe the effects of this change.[3] As a result of the reclassification of common cancers based on molecular and genomic markers, rare cancers are becoming increasingly common.

For example, melanoma, which has an overall estimated incidence of 73 870 (23 cases per 100 000) in the USA in 2015, is not a rare cancer as defined by the US National Cancer Institute.[1] However, on the basis of work by The Cancer Genome Atlas and others,[4] cutaneous melanoma can now be divided into distinct molecular subtypes, including those harbouring *BRAF* mutations, *NRAS* mutations, *NF1* mutations, or no mutations in these genes. The annual incidences of these molecularly defined melanoma subtypes are 12·0 per 100 000, 6·5 per 100 000, 3·2 per 100 000, and 1·4 per 100 000, respectively. Under this new taxonomy, melanoma is no longer classed as one common cancer: rather, it is a collection of rare cancers, each with a unique biology with distinct implications for therapy—an increasingly common pattern in oncology.

Outcomes in patients with rare cancers are worse than those in patients with more common tumour types. For individuals whose cancers were diagnosed between 1995 and 1999, 5-year relative survival was 47% for those with rare cancers and 65% for those with common cancers.[2] Some of the key issues contributing to poor outcomes in rare cancers include difficulties or delays in diagnoses, limited access to centres with clinical expertise, less effective standard treatments, and inadequate funding for preclinical and clinical research programmes. In the second paper in this Series, Jean-Yves Blay and colleagues[5] outline the importance of collaboration between investigators, research consortia, industry, regulatory bodies, and patient advocacy groups to overcome these challenges and enable the advancement of drug development and improve outcomes for patients with rare cancers.

The rapid accrual of patients in the AstraZeneca-sponsored phase 3 trial of standard chemotherapy with or without selumetinib for advanced uveal melanoma (SUMIT) shows the potential of effective collaboration between industry, academia, and patient advocacy groups.[6] In the National Cancer Institute Cancer Therapy Evaluation Program's randomised phase 2 trial[7] of selumetinib alone versus chemotherapy, 101 patients with advanced uveal melanoma were randomly assigned at 15 centres within 3 years. By contrast, in SUMIT, 152 patients were screened and 129 randomly assigned from 29 centres within 9 months. This increase in accrual in a shorter amount of time was achieved by doing the trial in 11 countries, identifying and targeting key referral centres, and partnering with doctors committed to advancing the treatment of uveal melanoma and patient advocacy groups such as CureOM (an ocular melanoma advocacy initiative of the Melanoma Research Foundation).

Despite this success, international trials in rare tumours are still associated with challenges that are

less commonly faced during trials based in only one country, including development of consensus on research priorities for uncommon diseases for which management practices frequently vary substantially in different regions, management of regulatory complexities associated with international trials, distribution of investigational agents to study centres, and securing adequate funding. Organisations such as the International Rare Cancers Initiative[5] have made substantial progress in overcoming these challenges and reducing barriers impeding international collaboration, and will be crucial to sustained success in rare cancer research.

As the techniques available for routine molecular and genomic classification of cancer become increasingly sophisticated, the definition of cancer based on a single molecular aberration will probably further evolve to one based upon gene expression, proteomics, and other systems-based approaches. More refined classification systems will result in even smaller subsets of disease. Although this evolution will provide opportunities to develop mechanism-based therapies that are applicable across several tumour histologies, overcoming the challenges associated with the development of novel treatments for rare cancers will become increasingly essential. In the final paper of the Series, Lucinda Billingham and colleagues[8] discuss approaches to address challenges associated with clinical trial design for rare tumours, including modification of biostatistical design parameters, adaptive and Bayesian trial methods, and alternative strategies such as basket, umbrella, and n-of-1 study designs. As rare cancers become increasingly common, such alternative strategies are becoming more prevalent.

Although guidance for trial conduct in rare disease populations has been issued by the European Medicines Agency[9] and draft guidance has been released by the US Food and Drug Administration,[10] whether positive clinical results emerging from these novel trial designs will translate to new drug approvals is uncertain. The regulatory authorities acknowledge that some standard aspects of drug development might not be feasible for rare diseases. However, approval of all drugs, irrespective of the rarity of the indication, necessitates substantial evidence of efficacy and safety. Because data generated in trials in rare cancer are generally less robust than those generated in studies of prevalent indications, consideration of all available data when establishing the efficacy of an intervention is of greater importance in trials of rare cancers than in those of common cancers.

Thus, rather than classifying interventions as efficacious or non-efficacious in a binary fashion on the basis of one pre-specified endpoint or definition of success, several relevant outcomes could be investigated collectively when examining how the study results should be applied to clinical practice. A definitive statement outlining the level of evidence needed for regulatory approval would enable the design of future rare tumour trials, but a static threshold of efficacy is not possible in view of the continuously evolving landscape of cancer biology and therapeutic options. Rather, continuous reassessment and discussions with regulatory authorities remain crucial to the successful translation of drug development from bench to bedside.

Overall, the convergence of advancing understanding of cancer biology, the ability to routinely do increasingly sophisticated tumour profiling, and rapidly rising numbers of targeted and immunological drugs is bringing closer the promise of precision oncology and truly individualised care. The successes that have been achieved and will be achieved in rare cancer research will enhance the successful development of therapies for patients with all malignancies, both rare and common.

*Kimberly M Komatsubara, *Richard D Carvajal*
Department of Medicine, Columbia University Medical Center, 177 Ft Washington Avenue, Milstein 6-435, New York, NY 10032, USA
carvajalr@columbia.edu

RDC reports grants and consulting fees from AstraZeneca and consulting fees from Merck, Iconic Therapeutics, Genentech, Janssen, and Aura Biosciences, all outside the submitted work. KMM declares no competing interests.

1 Greenlee RT, Goodman MT, Lynch CF, Platz CE, Havener LA, Howe HL. The occurrence of rare cancers in US adults, 1995–2004. *Pub Health Report* 2010; **125:** 28–43.
2 Gatta G, van der Zwan JM, Casali PG, et al. Rare cancers are not so rare: the rare cancer burden in Europe. *Eur J Cancer* 2011; **47:** 2493–511.
3 Boyd N, Dancey JE, Gilks CB, Huntsman DG. Rare cancers: a sea of opportunity. *Lancet Oncol* 2016; **17:** e52–61.
4 Cancer Genome Atlas Network. Genomic classification of cutaneous melanoma. *Cell* 2015; **161:** 1681–96.
5 Blay J-Y, Coindre J-M, Ducimetiere F, Ray-Coquard I. The value of research collaborations and consortia in rare cancers. *Lancet Oncol* 2016; **17:** e62–69.
6 Carvajal RD, Piperno-Neumann S, Kapitejin E, et al. SUMIT: phase III, randomized, placebo-controlled, double-blind trial of selumetinib in combination with dacarbazine in patients with metastatic uveal melanoma. Society for Melanoma Research 2015 Congress; San Francisco, CA, USA; Nov 11–18. SMR.

7 Carvajal RD, Sosman JA, Quevedo JF, et al. Effect of selumetinib *vs* chemotherapy on progression-free survival in uveal melanoma: a randomized clinical trial. *JAMA* 2014; **311:** 2397–405.
8 Billingham L, Malottki K, Steven N. Research methods to change clinical practice for patients with rare cancers. *Lancet Oncol* 2016; **17:** e70–80.
9 European Medicines Agency, Committee for Medicinal Products for Human Use. Guideline on clinical trials in small populations. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf (accessed Dec 11, 2015).
10 US Department of Health and Human Services, Food and Drug Administration. Rare diseases: common issues in drug development guidance for industry (draft guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM458485.pdf (accessed Dec 11, 2015).

Redefining "rare" in paediatric cancers

See **Series** pages e52, e62, and e70

Rare cancers are a diagnostic and therapeutic challenge, particularly in the paediatric population: the total number of paediatric cancer cases accounts for only 1% of all cancers diagnosed in all age groups (figure). Despite its relative rarity and its high chance of cure, paediatric cancer remains the leading cause of death by disease among children in developed countries. In this issue of *The Lancet Oncology*, a Series of three papers[1–3] focuses on how studies can be ameliorated to improve clinical outcomes in adults with rare cancers. The authors of the three reviews all draw attention to the absence of a consensus definition of rare cancer. The European Society of Medical Oncology defines rare cancers as those with an incidence of less than six per 100 000 per year, whereas the US National Cancer Institute defines rare cancers as having an incidence of 15 per 100 000 per year.[4] Rare cancers are estimated to account for 27% of all cancers, or fewer than 40 000 new cases per year in the USA, and cause a quarter of cancer deaths in adults.[1,2]

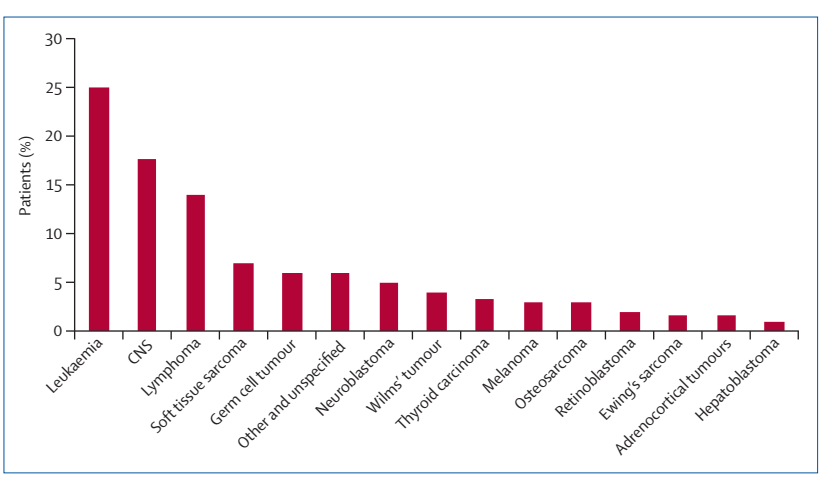

Figure: **Distribution of malignant disease, including rare cancers, in patients younger than 20 years**
Data are from the *International Classification of Diseases for Oncology* by the Surveillance, Epidemiology, and End Results Program and are based on the 2000 US standard population. According to the Children's Oncology Group's definition, rare paediatric cancers include thyroid carcinoma (37%), melanoma (30%), other carcinomas (25%), colorectal carcinoma (5%), nasopharyngeal carcinoma (3%), and adrenocortical carcinoma (1%).

If the adult definition were used, all childhood cancers would be classed as rare. But within the paediatric community, no uniformly accepted definition exists for rare cancers. The European Cooperative Study Group on Pediatric Rare Tumors (EXPeRT) defines rare childhood cancers as those with an incidence of less than two per million that are not being investigated in clinical trials, whereas the Children's Oncology Group has adopted a qualitative definition based on a low prevalence in patients younger than 5 years (except for adrenocortical carcinoma), a higher incidence in adults (including older adolescents and young adults) than in children, and an epithelial (rather than mesenchymal) tumour origin.[5] The Children's Oncology Group definition excludes some rare cancers reported almost exclusively in children, such as pancreatoblastoma and pleuropulmonary blastoma.[5] Irrespective of the definition, rare cancers are estimated to account for roughly 5–10% of all childhood cancers.[5]

In the era of precision medicine, Niki Boyd and colleagues[1] suggest that the definition of rare cancers should also include specific molecular subtypes of common cancers that have prognostic or therapeutic relevance, and provided non-small-cell lung carcinomas as a prime example for adult cancer.

It has long been recognised that each major phenotypic and genotypic type of childhood acute lymphoblastic leukaemia has many subtypes with heterogeneous biological features and treatment responses.[6] For example, in Philadelphia chromosome-like acute lymphoblastic leukaemia, which accounts for roughly 10% of childhood cases, there are subtypes that would respond to *ABL* tyrosine-kinase inhibitors; in others, the JAK–STAT pathway is implicated—a finding that offers novel opportunities for targeted therapeutics.[6] In hypodiploid acute lymphoblastic leukaemia, which accounts for only 2% of childhood acute lymphoblastic