Problems in rare tumor study: a call for papers

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Abstract

Rare tumor research presents many challenges. Large, randomized clinical trials are often impractical in this field and access to biospecimens may be problematic. These difficulties can best be addressed through multidisciplinary, national and international collaborative efforts among researchers, clinicians, governmental bodies, and patients. Numerous governmental and private organizations now exist to facilitate cooperation between researchers and institutions. Patient advocacy organizations now play an increasingly important role in partnering with traditional research groups to promote rare tumor research. *Rare Tumors* is now beginning an editorial series focusing on the problems of rare tumor research. We wish to invite all researchers and clinicians who are involved in rare tumor research and treatment to contribute their observations on the problems of working in this field, either as a letter to the editor, an editorial on a select issue, or as a review paper.

With this issue, *Rare Tumors* begins a series of editorials and reviews focusing on the "problem" of rare tumor study and clinical care. Rare tumor research presents many inherent challenges. Simply finding a consensus on the definition of what constitutes a "rare tumor" is in itself a difficult prospect. In the United States, "rare" diseases are defined by the National Institutes of Health Office for Rare Diseases as those having a prevalence of 200,000 individuals or less. Subtypes of common cancers, such as adenoid cystic carcinoma of the breast, can also be considered rare if they meet this definition.[1] In Europe, rare diseases are defined as those affecting 1 in 2,000 citizens of the European Union.[2] Although individual rare diseases may be infrequently encountered, rare diseases in aggregate affect tens of millions of individuals in the US, Europe and worldwide.[3] As our understanding of the genetic basis for rare illnesses and tumors grows, it is likely that our conception of what is a rare disease will undergo further transformation and expansion as neoplasms are subdivided into ever finer categories. A recent example of this trend is the recognition of the significance of the presence of *IDH1* and *IDH2* mutations in human gliomas. In that case, the identification of mutations in two $NADP^+$-dependent isocitrate dehydrogenase genes has had important prognostic significance in differentiating subtypes of glioma, itself a rare entity, which may appear morphologically identical, but are genetically distinct.[4] Further advancements in molecular pathology, genomics, proteomics and other disciplines may accelerate this trend towards individual characterization of common neoplasms into uncommon subtypes.

Considerable challenges remain in rare tumor research. Their infrequency makes effective study more difficult, both in the realms of basic and clinical research. Single institutions and cooperative groups may find it difficult to recruit sufficient patients to perform adequately powered clinical trials that can concluded in a meaningful amount of time. Even when such barriers can be overcome, those studying rare tumors are at a disadvantage when competing for grant funding against more common tumors that would accrue to trials much quicker and in greater numbers. In the hierarchy of evidence based medicine, rare tumor study by necessity occurs primarily below the level of randomized, double blinded clinical trials. The lack of financial incentives for the development of clinical trials and drug therapies for small groups of patients with rare disease has long been recognized. The Orphan Drug Act in the United States and similar legislation in Europe has helped address this dilemma in part. In the US, the National Institutes of Health and the Office of Rare Diseases fund the Rare Diseases Clinical Research Network (*http://rarediseasesnetwork.epi.usf.edu/*) a consortium of investigators whose goal is to identify biomarkers associated with rare disease expression and promote new preventative, diagnostic and therapeutic interventions. In Europe, the European Clinical Research Infrastructures Network (*http://www.ecrin.org/*) provides a similar supportive role. Groups such as the Children's Oncology Group (*http://www.childrensoncologygroup.org/*) and the International Society of Paediatric Oncology (*http://www.siop.nl/*) provide excellent models of the quality of research that can be accomplished through national and international collaboration in rare malignancy study. However, similar cooperative mechanisms have not yet evolved in the treatment of adult rare malignancies. Large cohort and case control studies are possible through national registries and other existing databases such as the U.S. National Cancer Institute's Surveillance Epidemiology and End Results program (*http://www.seer.cancer.gov/*).[5] Such projects can provide far greater statistical power to define the incidence and natural history of rare tumors than institutional or cooperative group studies, but they are limited in the insights they can provide into the genetic classification and management of such tumors. Ad hoc networks such as the Rare Cancer Network (*http://www.rarecancer.net*) have effectively utilized internet based communication to bring together a geographically diverse group of investigators with similar interests in rare tumor study.

In recent years, the role of patient advocacy groups has grown in supporting rare tumor research and in affecting public policy. National umbrella rare disease organizations such as the U.S. National Organization for Rare Disorders (*http://www.rarediseases.org/*) and EURODIS/Rare Diseases Europe (*http://www.eurordis.org/*) provide their volunteer member organizations with access to patient educational and advocacy resources, political lobbying and funding opportunities that would be otherwise difficult to obtain for small groups focused on a single disease entity. Patient advocacy organizations for rare diseases have increasingly begun to take on a proactive role in uniting the efforts of patients, researchers and governmental funding bodies. An example of this trend in the field of rare neoplasms is the Chordoma Foundation (*http://www.chordomafoundation.org/*), a non-profit foundation that provides funding and strategic direction for chordoma research, as well as biospecimen bank, patient registry and databank resources, to a multi-institutional, international collaboration of researchers, while also providing direct patient education and support. The Chordoma Foundation has outlined a five-step strategic plan for their vision of the future of chordoma research. This plan starts with resource development to provide the infrastructure for chordoma research in its first phase, progresses to the molecular classification of chordoma biology in its second, and then moves on to identification of target molecules and pathways for chordoma therapy in its third phase. The fourth phase consists of testing potential treatments in the laboratory and the clinic, before beginning the final phase of clinical trials and biomarker

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identification.[6] Such a program provides an excellent model in rare tumor research for others to emulate, which by necessity will require multi-disciplinary collaboration on a national and international basis.

Despite these challenges, rare tumor research can have important ramifications for general oncological practice. Gastrointestinal stromal tumors (GIST) are a rare tumor of the gastrointestinal tract with a US annual incidence of only 5,000 to 6,000 cases. Characterization of the role of the proto-oncogene *KIT* in promoting the growth of GIST, followed by the demonstration of the efficacy of imatinib in treating GIST, facilitated the introduction of small tyrosine kinase inhibitors into the general treatment of solid tumors. The utility of tyrosine kinase inhibitors is now being defined in a wide variety of both rare and common neoplasms.[7,8]

We wish to invite all researchers and clinicians who are involved in rare tumor research and treatment to contribute their observations on the problems of working in this field, either as a letter to the editor, an editorial on a select issue, or as a review paper. Information on the submission process can be found on the *Rare Tumors* website (*http://www.pagepress.org/rt*). Those authors wishing to submit an editorial or review should first contact our editorial staff at office@pagepress.org to discuss the suitability of their topic.

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