

Rare tumors research in emerging countries

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Abstract

Rare tumors, when considered as a group, represent a significant burden to society as they may account for up to 25% of the mortality by cancer in nations like the United States. In contrast with the current scenario in highly incident cancer types, little progress has been achieved in the treatment of the most rare cancers. The reasons for this apparent stagnation are mostly intrinsic to logistical difficulties in performing large clinical trials in rare diseases and will be addressed further in this article. Because both cancer incidence and clinical research are booming in emerging nations, we also aim to address the current and future role of these countries in research and the drug development process in rare tumor types.

Discussion

Traditional measures of benefit in health-care policies dictate the focus of interest for research and the drug development process. Although rare diseases are not considered a public health priority, the sheer numbers of all known rare tumors represent a significant burden to society; for instance, it is believed that more than 200 cancers with an incidence lower than 40,000 cases are reported each year in the United States, and they may account for up to 25% of the mortality by cancer in that country.^{1,2} Despite efforts mainly driven by research carried out in developed countries, little progress has been seen in the treatment of the majority of rare tumor types. Furthermore, diagnosing rare tumors may be challenging, and the scenario for the stricken individual is further darkened by the lack of appropriate knowledge about the course of disease and its management. Not surprisingly, this outlook is perceived as deeply frustrating by patients suffering from such devastating disorders.²

The reasons for this stagnation are multifactorial and could be discussed extensively. One of the main problems is logistical as the low incidence of the rare tumors makes the patient recruitment process cumbersome.

Therefore, a large number of institutions have to become involved in even relatively small trials, making them complex, slow, and costly; one obvious consequence is a high rate of early trial termination owing to poor recruitment,³ which accounts in part for the paucity of evidence-based data. This poor accrual is caused not only by the small number of cases but also by the unavailability of effective population screening programs and education-based actions (“disease awareness”), which makes early diagnosis elusive. Moreover, recruitment to clinical trials is further undermined by the regrettable tendency to keep these patients in community hospitals instead of referring them for treatment in highly specialized institutions. Fortunately, important initiatives are underway now, such as the existence of international specialized scientific journals and websites, national and international registries, and mounting pressure to concentrate the treatment of uncommon cases in highly specialized clinics.

Our current model of drug development, which is highly business- and profit-oriented, is also a handicap for those rare diseases with regard to improvements in treatment. Historically, there has been limited interest from pharmaceutical companies in investing in innovation in diseases that will not make their compounds a “best seller.” The restricted market makes the intervention uninteresting for patent-holders once the costs deriving from development and regulatory approval processes are not likely to be recovered. Therefore, the development of an “orphan drug” is particularly challenging for a pharmaceutical company, and this also includes the development of accurate diagnostic methods. It is clear that current pharmacoeconomic tools and marketing studies will not back investments in rare diseases, and even promising compounds may end up not being properly studied. However, one has to admit that the current system has undeniably led to remarkable progress in many tumor types^{4,5} and it is unlikely to be changed in the near future. This indicates that alternative, creative strategies should be sought when it comes to tackling the apparent stagnation in the treatment of rare tumor types.

Notwithstanding, a less pessimistic outlook has been proposed by renowned experts who have postulated that “the physiologic basis for tumors being rare is one and the same as the reason that they are ultimately so treatable” or, in other words, many of them could arise from single or less complex genetic aberrations.⁶ This implies that the impact of the introduction of rationally developed compounds might be higher in these cancer types⁷ as compared to more prevalent cancers such as breast, colorectal, prostate, and lung cancer, which are driven by multiple genetic abnormalities that could mitigate the biological effect of anti-can-

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cer agents in a general patient population.

Rare tumors are of public interest but not necessarily a health priority, and thus specific policies should be discussed. The Orphan Drug Act of 1983 from the United States and EC141/2000 and 847/2000 from the European Union (EU) legislation came into force in order to create an incentive for the development of treatments for rare diseases.⁸⁻¹⁰ These initiatives have been recognized as major steps toward promoting equity in the drug development process for diseases with disparate prevalence. Since then, a growing number of orphan drugs have been registered; in the 24 years since this law was passed in the United States, 282 such drugs and biological products, providing treatment for more than 14 million patients in the United States, have come to market under its aegis. In the 8-10 years before 1982, in contrast, only 10 treatments for rare diseases had been approved by the FDA and brought to market.¹¹ However, at least outside the United States, their accessibility remains a concern.¹² For instance, in a survey commissioned by the European Commission and reported in 2004, only 9 of 25 EU member states had access to all 10 orphan drugs approved in previous years and only one member had all of them on the national reimbursement list.¹³ The scenario appears to be even more problematic in developing countries. As per drugs approved in 2006-2007, the EU orphan drugs included Atriance for acute lymphoblastic leukemia; Evoltra for acute lymphoblastic leukemia; Nexavar for renal cell

carcinoma; Revlimid for multiple myeloma; Sprycel for chronic myeloid leukemia; and Sutent for gastrointestinal stromal tumors and renal cell carcinoma.¹² As of May 2010, none of them was widely covered by the National Health System in emerging countries such as Brazil, and this is probably the case in many other developing nations.

Cancer incidence is booming in emerging countries, and the national rates are rapidly reaching those reported in Western Europe and North America.¹⁴ Clinical research has also boomed in developing countries over the last 10-15 years,¹⁵ and there is little evidence that this tendency will be reverted over the next few years or decades. Most of this progress is a result of heavy investment and commitment from pharmaceutical companies. The sustainability of clinical research in developing countries, however, remains highly dependent on pharmaceutical companies, and one challenge for a greater participation in clinical trials targeting rare tumors is the financial incentive from trials doomed to have low recruitment. On the other hand, soaring costs with slow recruitment end up intimidating pharmaceutical companies, in a vicious cycle that is difficult to break.

It is our view that academia could help partially fill this gap. Generally speaking, there is a clear tendency from investigators to invest available public resources in tumors that have a high incidence, which is understandable but redundant, as these are the tumor types that already benefit from a great deal of private investment. Similarly, many unanswered questions are not directly related to drug treatment but involve more fundamental questions such as the role and/or type of surgery, radiation therapy, appropriate tumor classification, or novel schedules for currently available treatments instead of new drugs. These questions are unlikely to be addressed by trials sponsored by pharmaceutical companies and could be preferentially addressed by academic research in developing economies. In addition, emerging countries should take advantage of a high incidence of some types of cancer, some of them now considered rare in developed countries, such as hepatocarcinoma in parts of Asia, cholangiocarcinoma in Asia and parts of South America, esophageal cancer in Brazil, gastric cancer in South America and parts of Asia, triple negative breast cancer in Latin America, and cervical cancer in most of the developing world. Comprehensive epidemiological studies should be carried out in each emerging country, who should take the lead in the clinical research process for those cancers. Finally, basic research focusing on rare tumor types is also likely to pay off in the long term as regards academic merit, owing to lower competition when compared to the tumors with higher incidence and issues related to the tumor biology previously mentioned in this text.⁶

Emerging countries should also consider

investing in organizational infrastructure, such as comprehensive, accurate national databases and rare tumor registries. Encouraging the development of reference centers focused on the treatment of rare tumors will pay off in the long term, and may allow institutions to build expertise and boost the recruitment of these patients to clinical trials, while providing the best possible medical care to patients. The establishment of effective regional, national, and international research collaboration networks (e.g. Grupo Latino Americano de Investigações Clínicas em Oncologia - GLICO, Brazil) could also help to boost accrual to trials in rare tumor types, as effective referral networks could be a more cost-effective strategy than opening trials in multiple sites to recruit only a handful of patients. The lack of specific legislation for research and development in rare diseases in the developing world is also a problem that must be addressed; this includes taxing policies, financial incentives (such as specific grants to support research), marketing, and accessibility to approved drugs. This would also help to open pharmaceutical companies' eyes to investing in rare tumor research in emerging countries either through national or global initiatives.

In conclusion, the research process in rare tumors has witnessed important initiatives but is still relatively inefficient and needs improvement urgently. This is particularly challenging for patients and investigators in emerging countries who could do more to contribute to this process. There are no easy solutions but a number of aspects and potential solutions have been raised by the authors in this article such as: i) government participation in the development of new agents in rare tumors; ii) incentives in terms of extending patent life for developments reaching commercial level (similar to what has been proposed in favor of development of new agents against pediatric cancer); iii) less stringent registration requirements for active compounds, with greater acceptance of non-randomized data as evidence of effectiveness for rare diseases, with some successful examples in the recent past;⁷ iv) less bureaucracy in the clinical trials regulatory process leading to lower drug development costs; v) research more focused on specific, relevant molecular processes in tumors, leading to smaller clinical trials in enriched patient populations and faster drug development.⁷

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