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How to Identify Active Novel Agents in Rare Cancers and then Make Them Available: A Need for a Paradigm Shift

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In this issue of *European Urology*, Tannir and colleagues [1] reported the results of a prospective phase 2 study of sunitinib in patients with non–clear cell renal cell carcinoma (RCC), an extremely heterogeneous group of biologically different, and rare, tumor types. This study confirmed what has already been suggested by few prospective studies [2,3], which is that sunitinib works also in these rare cancers, but that its activity and efficacy are less evident than in the classical clear cell histotype.

A differential histotype-driven activity of sunitinib (apparently superior in the chromophobe histotype) was also postulated by the authors but could not be proved due the limited number of patients with chromophobe cancer included in the study and the design of the study itself.

Notably, this study indirectly raises two other questions that are more general but nevertheless key: (1) Do we need innovative study designs to test novel agents in rare cancer types? (2) In case of success, how do we make active novel agents, which are also very costly, available to patients with rare cancers (for which use these drugs are usually not registered) in a global situation characterized by a dramatic shortage of economic resources?

I will start by addressing the issue of clinical trial design in rare cancers. The main goal of clinical trials is to try to reduce as much as possible the uncertainty surrounding the activity of new treatments, to move them to everyday clinical practice, and consequently to accept paying their costs for the community. Traditional clinical trials use statistical methodologies that need considerable numbers of patients, which are difficult to collect in rare cancers, to minimize the so-called random error and the frequent low magnitude of the expected effect.

The small differences in favor of new treatments observed in many clinical trials may be due, among other reasons, to the frequent lack of patient selection. Research on biomarkers should thus be an inherent part of research on new drugs, especially in rare cancers. Finding a biomarker could also indirectly help reduce the number of patients needed in a trial. If, for example, we treat patients with a given mutation with an agent targeting the specific product of that mutation rather than treating a general unselected population, the achievable gain is expected to be huge, and if the expected difference is so high, the sample size can be lower.

Besides trying to rely on biomarkers, which may or may not be available, rare cancers would greatly benefit from novel trial designs, such as the so-called adaptive trials, or the use of Bayesian statistics. Adaptive trials [4,5] permit changing aspects of the study or its statistical procedures while the study is ongoing. The overall development of a new drug for a rare cancer may be made easier and faster thanks to adaptive mechanisms such as the intensive use of stopping rules (for safety or for futility), the transformation of a phase 2 into a phase 3 study (in case the early stage of the study was positive), or the use of *drop-the-loser* or *play-the-winner* designs.

Bayesian statistics is an approach to exploit all available evidence. In clinical trials, traditional (or frequentist) statistical methods may use information from previous studies only to make an estimate of the expected outcome. However, the amount of previously available data does not change the number of patients required. In contrast, the Bayesian approach uses Bayes' theorem to formally combine prior information with current information on a

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quantity of interest. The Bayesian idea [6,7] is to consider the prior information and the trial results as part of a continual data stream in which inferences are being updated each time new data become available. In addition, the theory of Bayesian experimental design fits the theory for making optimal decisions under uncertainty, something that perfectly fits the rare tumor scenario.

Before a Bayesian trial begins and data are obtained, probabilities are given to all the possible values (or ranges of values) of an unknown quantity of interest. These probabilities, taken together, constitute the prior distribution for that quantity. After data from the trial become available, the prior distribution is updated according to Bayes' theorem. This updated distribution is called the posterior distribution, from which one obtains the probabilities for values of the unknown quantity after data are observed. This approach is a scientifically valid way of combining previous information (the prior probabilities) with current data. The approach can be used in an iterative fashion as knowledge accumulates: today's posterior probabilities become tomorrow's prior probabilities.

A Bayesian trial provides the clinician with a probability distribution that can be directly used in the clinical decision-making process, for example, in a formal decision analysis. There is an ongoing initiative, Rare Cancers Europe (http://www.rarecancerseurope.org), launched by the European Society of Medical Oncology, which is trying to achieve a consensus in the community of experts on these innovative trial designs in the setting of the development of novel agents in rare cancers [8]. Notably, the US Food and Drug Administration started to suggest the use of Bayesian statistics in medical device clinical trials back in 2006 [9].

Another key point is the off-label use of novel agents in rare cancers, a use that is more widespread than in common cancers. An interesting idea comes from the United Kingdom, where the lack of reimbursement for several novel agents, including some for treatment of kidney cancer, already gave rise to much controversy [10]. Despite these previous controversies, a cancer drug fund (CDF) recently has been established. The CDF is a government initiative to provide access to drugs to treat cancer while they are still going through the National Institute for Clinical Excellence (NICE) process and sometimes also after NICE has turned them down (eg, everolimus for RCC is not NICE approved but is available through the CDF). Decisions about which drugs to fund are made at a local level of 10 strategic health authorities (SHAs) throughout England (but not Scotland or Wales).

The criteria for access to the fund should be based primarily on evidence of clinical effectiveness and anticipated delivery of measurable outcomes, such as improved overall survival, progression-free survival, or improved quality of life. SHAs should also consider cost effectiveness if there are robust data to support decision making. Where treatments are similarly clinically effective or where ranking scores of clinical effectiveness do not differentiate between different therapies, panels should consider cost effectiveness to maximize the number of patients treated from the available funding [11].

As a whole, the issue of how to deal with rare cancer types in an era of molecularly targeted agents and in a situation of global economical crisis is a key priority for both the world of academics and that of politics. Presently, no clear-cut answers are available, but a paradigm shift is urgently needed.

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