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Review

Clinical research in small genomically stratified patient populations

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Abstract The paradigm of early drug development in cancer is shifting from 'histology-oriented' to 'molecularly oriented' clinical trials. This change can be attributed to the vast amount of tumour biology knowledge generated by large international research initiatives such as The Cancer Genome Atlas (TCGA) and the use of next generation sequencing (NGS) techniques developed in recent years. However, targeting infrequent molecular alterations entails a series of special challenges. The optimal molecular profiling method, the lack of standardised biological thresholds, inter- and intra-tumor heterogeneity, availability of enough tumour material, correct clinical trials design, attrition rate, logistics or costs are only some of the issues that need to be taken into consideration in clinical research in small genomically stratified patient populations. This article examines the most relevant challenges inherent to clinical research in these populations. Moreover, perspectives from the Academia point of view are reviewed as well as initiatives to be taken in forthcoming years.

1. Introduction

In recent years, we have witnessed a dramatic change in the paradigm of cancer treatment. In the first few decades of Oncology as a discipline, a treatment decision was made based on the histological diagnosis of a tumour. Nowadays, it is increasingly more common that a drug is given to a patient on the basis of a specific molecular alteration found in his/her tumour [1]. This new concept in cancer treatment has already yielded

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clinical successes such as targeting human epidermal growth factor receptor 2 (HER2) in breast cancer [2–4], epidermal-growth factor receptor (EGFR) in non-small cell lung cancer (NSCLC) [5], proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homologue B (BRAF) in melanoma [6,7] or KIT in gastrointestinal stromal tumour (GIST) [8]. The advantages compared to classic chemotherapy treatment, in which a cytotoxic drug was administered regardless the specific molecular characteristics of a given tumour, seem clear [9]. Following up on this new model, often called precision medicine, drugs are being developed for smaller and smaller molecular subpopulations such as ROS1 and NTRK1 translocations in NSCLC [10,11], BRAF mutations in low grade gliomas [12], MET amplifications in gastric cancer [13] … all of them present in less than 5% of cases approximately.

This radical change is the consequence of a deeper understanding of cancer biology [14]. The development of '-omic' platforms such as next generation sequencing (NGS) techniques has enabled delivering massive amounts of genetic information from a given tumour in a faster, cheaper, more precise and more sensitive way compared to classic sequencing methods [15]. This profound study of cancer biology has led to the knowledge of a series of aberrations which have been termed differently depending on the molecular level they are found: genomic, proteomic, transcriptomic, epigenomic or metabolomic alterations [16]. Some international research initiatives such as The Cancer Genome Atlas (TCGA) [17,18], the International Cancer Genome Consortium (ICGC) [19], Catalogue of Somatic Mutations in Cancer (COSMIC) [20] or Genomics of Drug Sensitivity in Cancer [21] have compiled the information of those '-omics' alterations and have helped to better molecularly characterise tumours [22–24]. These data publicly available have decisively contributed to the shift of paradigm of treating cancer from histologically oriented to molecularly oriented treatment [25]. If that alteration is an oncogenic driver then it becomes a potential target worth exploring [26].

However, this 'personalised' concept of cancer treatment has its limitations. One of them is the fact that there are molecular aberrations that occur only in a small subset of tumours. These can be termed 'small patient populations'. Although the term 'rare disease' varies from country to country (the European Union defines it as a disease or disorder that affects less than 1 in 2000), one can easily see the resemblance of the definitions. Precision medicine aims to take into account individual variability in genes, environment, and lifestyle for disease treatment and prevention, and as such, in oncology, it focuses on the genetics of disease to identify effective therapies.

When a drug is developed to target a specific alteration, the clinical trials designed to assess safety and efficacy face the problem of finding and selecting the small number of patients whose tumours harbour infrequent aberrations. The two key players in the design of clinical trials, Academia and Industry, should join forces and work together in order to efficiently overcome this problem.

While some of the biological challenges of the 'Precision Medicine' approach in oncology have been reviewed elsewhere [27–29], there are many logistical issues that affect the development of clinical trials to prove the overall efficacy of the change in strategy. The aim of this article is to review the challenges faced by clinical trials in small patient populations, as well as strategies to improve the outcome of those patients.

2. Drug development in the era of precision medicine

Development of NGS platforms has produced an array of different devices, some of them enabling a quick and cheap multiplex profiling of the most important genes involved in cancer. Consequently, they are to replace old equipment for the selection of the optimal treatment for a patient given the specific molecular characteristics of his/her tumour. In the development of companion diagnostics and molecular profiling approaches, one strategy that has been used in the past is the establishment of one specific test able to find one specific alteration for which there is a specific matched drug available [30] (strategy known as one test/one drug). Second generation devices enabled a multicategorical approach that can assay multiple genes (multiplexed analysis) that predict sensitivity or resistance to multiple cancer therapies Alternatively, massive parallel sequencing of tumours with current NGS techniques allows simultaneous evaluation of a broad spectrum of alterations [31]. This strategy gives more comprehensive data about the underlying biology of a tumour, in opposition to the one biomarker-one drug approach which only assesses one alteration at a time. This 'omniscient' model not only permits the assignment of a matched targeted therapy to a given alteration but it is also potentially hypothesis-generating by the identification of novel oncogenic drivers [32]. Ultimately, the 'omniscient' knowledge of data usually becomes 'reductionist' by focussing only on a number of aberrations for which targeted agents are available [33]. Still, NGS analysis can produce many variants of unknown significance and incidental findings (such as variants with an uncertain association with hereditary diseases) that unease physicians. Because of this, for the purposes of clinical research, NGS may probably focus on targeted gene panels with a limited number of alterations with immediate clinical implications which produce information that can be easily reported to patients and treating physicians [34].

The advantages of focussing drug development of some specific targeted therapies on genomically stratified patient populations, even if small, are multiple: