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Optimising translational oncology in clinical practice: Strategies to accelerate progress in drug development

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Optimising translational oncology in clinical practice

A B S T R A C T

Despite intense efforts, the socioeconomic burden of cancer remains unacceptably high and treatment advances for many common cancers have been limited, suggesting a need for a new approach to drug development. One issue central to this lack of progress is the heterogeneity and genetic complexity of many tumours. This results in considerable variability in therapeutic response and requires knowledge of the molecular profile of the tumour to guide appropriate treatment selection for individual patients. While recent advances in the molecular characterisation of different cancer types have the potential to transform cancer treatment through precision medicine, such an approach presents a major economic challenge for drug development, since novel targeted agents may only be suitable for a small cohort of patients. Identifying the patients who would benefit from individual therapies and recruiting sufficient numbers of patients with particular cancer subtypes into clinical trials is challenging, and will require

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collaborative efforts from research groups and industry in order to accelerate progress. A number of molecular screening platforms have already been initiated across Europe, and it is hoped that these networks, along with future collaborations, will benefit not only patients but also society through cost reductions as a result of more efficient use of resources. This review discusses how current developments in translational oncology may be applied in clinical practice in the future, assesses current programmes for the molecular characterisation of cancer and describes possible collaborative approaches designed to maximise the benefits of translational science for patients with cancer. © 2014 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0).

Introduction

There is an urgent need for a new approach to drug development for many common cancers, for which treatment progress has been limited and the socioeconomic burden remains unacceptably high. One issue that is central to the lack of progress in cancer treatment is the heterogeneity and genetic complexity of many tumours [1,2]. This leads to considerable variability in patients’ response to therapy and requires knowledge of the molecular profile of an individual’s tumour to guide appropriate treatment selection. Nevertheless, significant advances have been made in the molecular characterisation of different cancer types in recent years, which have the potential to transform treatment through precision medicine [3–5]. It should be noted, however, that such an approach presents a major economic challenge for drug development, since novel targeted agents may only be suitable for a small cohort of patients [2]. Identifying sufficient numbers of patients with rare genetic aberrations for enrolment into clinical trials is a further obstacle. To overcome these challenges and maximise progress in the development of more effective cancer treatments, collaborative efforts between academia and industry are needed.

This review discusses how current developments in translational oncology may be applied in clinical practice in the coming years, reviews current programmes for the molecular characterisation of cancer and describes possible collaborative approaches designed to maximise the benefits of translational science for patients with cancer.

Current challenges in translational oncology

Advances in genomic sequencing in recent years have facilitated the identification of numerous new gene mutations or amplifications that may be appropriate for genomic-driven drug development [6]. For example, in breast cancer, genomic alterations have been found to be focused primarily in PI3K/AKT/mammalian target of rapamycin (mTOR), human epidermal growth factor receptor 2 (HER2), p53 and retinoblastoma tumour suppressor pathways, suggesting the possibility of clustering several genomic alterations into functional pathways [7]. However, these findings and the results of other studies in different cancer types undertaken over the last decade have revealed a highly complex and heterogeneous genomic landscape [1,2,8–10].

Tumour heterogeneity is apparent in almost all tumour phenotypes [11] and exists both between the tumours of patients with the same histopathological cancer type [12] and within individual tumours [13]. Somatic mutations occur throughout the genome over time as a result of exposure to different external or internal forces or carcinogens, with imprints of DNA damage to repair processes affecting the development of cancer (Fig. 1) [14]. Mutation signatures can differ depending on the length of exposure, leading to alterations in drug response, and the number of mutations can also vary considerably between patients and tumour types. Whole genome sequencing may provide insight into the molecular mechanisms underlying these mutations [15,16], and the advent of next-generation sequencing (NGS) has meant that such analysis is now becoming available in academic hospitals. However, interpretation of NGS findings is complex since the technique cannot define the prevalence of particular mutations nor make any inference of their predictive values. Identification of appropriate biomarkers suitable for clinical use and their prognostic and predictive values is also an issue, along with controlling for sample heterogeneity and population-specific differences [6]. Initial studies also failed to take into account differences in mutation frequency (between patients and tumour types), gene expression level and replication time, resulting in spurious findings [17]. Consequently, at present, the technology is generally only validated for research.

Heterogeneity in cancer tumours creates a considerable challenge for the development of targeted therapy. In particular, driver mutations responsible for growth and survival could well vary between patients as a result of inter-tumour heterogeneity, while intra-tumour heterogeneity may lead to the rapid development of resistance to therapy due to genomic variability between cancer cell clones [2,18]. The modest efficacy many targeted agents exhibit as a result of resistance development leads to poorer outcomes, which limits the possibility of reimbursement, reducing the medical usefulness of some agents. Undertaking registration studies for novel agents targeted at rare mutations is also problematic, since it requires large-scale molecular screening in order to gain sufficient numbers of clinical trial subjects. When such agents are applied in the clinic, they will similarly require testing for use in the few patients with the rare mutation. The development of novel targeted therapies should also take into account the pattern of other mutations present, since cross-talk between mutated genes can have a profound effect on the fate of the cell, determining whether cell death or clonal expansion results [14]. Consequently, for some mutations (e.g. PI3K), it may be more useful to consider activation of the pathway rather than the mutation itself; however, the possibility of evaluating ‘pathway activation’ may be several years away.

A number of strategies which aim to counteract tumour heterogeneity are under consideration. For example, combining targeted therapy and immunotherapy in patients with low levels of genetic instability may overcome drug resistance and improve the long-term efficacy of treatment; studies are under way to identify immune system markers in order to investigate this hypothesis further [19]. The molecular mechanisms that drive diversity and heterogeneity in cancer may also be targeted, with particular focus on RNA as its sequence, degradation and structure can be altered by RNA editing, which may change the tumour transcriptome [20]. Approaches aimed at RNA may, therefore, be a potential means of targeting the process that leads to genomic alterations rather than the mutation itself. Additionally, tumour evolution over time may be monitored through the use of liquid biopsies, involving, for example, measurement of levels of circulating tumour DNA (ctDNA) or circulating tumour cells (CTCs) [21–27],
The results of initial studies suggest that ctDNA (Fig. 2) may give a better reflection of tumour burden and estimation of outcome than CTC count, and is also more sensitive [21,22,24]. Technology with which to quantify ctDNA is rapidly evolving, though the application of this measurement in clinical practice to monitor disease progression and response to treatment requires trials to validate its clinical benefit.

Current programmes for the molecular characterisation of cancer

Over the last decade, the molecular characterisation of different cancers has revealed an increasing number of subtypes comprising fewer and fewer patients, which creates a major obstacle to drug development. Clinical trials involving patients with rare mutations...
are almost impossible to conduct at a national level due to the number of individuals that must be screened; this highlights an urgent need for large collaborative networks. A number of initiatives have been developed to meet this requirement, the most well established being in the gastrointestinal, lung and breast cancer fields.

**Gastrointestinal cancer**

SPECTAcolor (Screening Patients for Efficient Clinical Trials Access) is a biomarker analysis platform developed by the European Organisation for the Research and Treatment of Cancer (EORTC) for the genetic profiling of patients with advanced colorectal cancer (CRC) [28]. The platform aims to improve access to and reduce the cost of molecularly-driven clinical trials by centralising screening to improve quality control. A number of centres across Europe are involved in the initiative, with the aim of collecting data from 1000 patients per year. Patients enrolled in SPECTAcolor receive molecular screening early in the course of their disease (just after the development of metastases), and assessments are repeated at 6-monthly intervals in order to assess eligibility for different trials over time. The initial screening included exome sequencing of over 250 genes, though testing is likely to be expanded as investment in the programme increases and science evolves. While trials are independent of the EORTC, participating companies have been asked to adhere to certain standards; the use of a common infrastructure and umbrella protocols may reduce start-up time and facilitate the efficient running of trials. Such standardisation could also avoid the need for the pre-screening of trial centres, making the process more time and cost efficient. Seed money to start up and run SPECTAcolor for 5 years was donated by Alliance Boots and future costs of running the platform will be shared by pharmaceutical companies. The SPECTAcolor model is now being expanded to other tumour types, including melanoma and brain and lung cancers (SPECTAmel, SPECTAbrain and SPECTAlung, respectively; the last one in collaboration with the European Thoracic Oncology Platform [ETOP – see below]).

**Lung cancer**

ETOP aims to promote exchange of knowledge and research in the field of thoracic malignancies as well as to sponsor or perform clinical studies. Lungscape, a programme initiated by ETOP, was developed to study the molecular landscape of non-small cell lung cancer (NSCLC), to allow comprehensive clinico-pathological correlations and to establish robust and standardised procedures for molecular testing in clinical trials [29]. Lungscape will follow a stepwise evolution, with step 1 involving retrospective analysis of more than 2400 resected NSCLC cases with at least 3 years' clinically annotated follow-up. Samples from patients with stage IA–IIIB NSCLC have been collected, enabling the biomarkers to be evaluated at different stages of disease. The first biomarker investigated by Lungscape was anaplastic lymphoma kinase (ALK), and subsequent testing will examine PIK3CA, MET, RANK/L1 and PD1/PDL1, and will screen for about 200 cancer gene mutations by multiplex technology. The tissue biobank and database allow a number of outcomes (e.g. overall survival [OS], progression-free survival [PFS], relapse-free survival and time to relapse) and clinical parameters (e.g. performance status, gender and age) to be investigated according to disease stage; the impact of different biomarkers on risk of relapse can also be evaluated. Seventeen centres are currently involved in step 1. Each case submitted to the database is reviewed to ensure that staging and tissue quality are appropriate. Laboratory testing using 'round robins' and quality assurance procedures is performed locally when possible in order to empower European centres with useful biomarker testing.

Step 2 of Lungscape aims to progress this retrospective analysis into a prospective study in patients with advanced disease, with the primary endpoints being OS and/or PFS improvement and treatment decided by molecular characterisation. In order to move this concept forward collaboration between ETOP and the EORTC has been established (SPECTAlung). Industry is being approached to join this initiative, which will be expanded to other thoracic malignancies. In addition to the very large mutation platform, SPECTAlung, developed in collaboration with the Sanger Institute, a master protocol is being developed to allow rapid access to clinical trials for patients with molecularly defined lung cancer.

**Breast cancer**

The AURORA (Aiming to UndeRstand the moleculear aberRations in metAstatic breast cancer) molecular screening platform is run by the Breast International Group (BIG) and aims to make significant improvements in our understanding of the clonal evolution of breast cancer [30]. The platform will enrol at least 1300 patients with newly diagnosed metastatic breast cancer for whom tissue is available from both the primary tumour and metastatic lesion. Targeted gene sequencing of around 400 known cancer driver genes will be performed on all samples by a central laboratory. Patients with actionable and non-actionable mutations will then be enrolled in a comprehensive follow-up programme and will receive either new targeted agents in clinical trials or standard therapies, with data being collected every 3–6 months to determine response and survival endpoints. Trials for patients enrolled in AURORA will be flexible, with some run by BIG and others by independent companies.

Three phase II trials are already planned as part of the AURORA programme, with patients being allocated to the appropriate study according to the molecular status of their tumour. These studies will involve patients with aberrations whose expected incidences are 9% (Target 1), 1.5% (Target 2) and 25% (Target 3) (Fig. 3). A number of sister programmes to AURORA are also planned, which may focus on the tumour microenvironment, drug resistance mechanisms and use of ctDNA to monitor tumour evolution, though funding for such studies is not yet secured.

While it is recognised that not all institutions will join AURORA, it is hoped that most will enrol patients with aberrations with incidences of <5% (e.g. HER2 mutations), since it is almost impossible to run randomised trials in such cases without international collaboration. Around 30 centres are committed to joining the programme at present. Each centre is pre-screened to ensure the presence of a good pathology department and experience in phase I/II trials. The molecular screening platform is funded by the Breast Cancer Research Foundation and a number of European charities. It is currently being tested in a feasibility study (n = 30) to ensure that the biotrack works from a logistical viewpoint. Additional funding will be sought from various sources in order to expand the programme further.

A multicentre, molecular screening study undertaken in 18 centres across France involving 423 patients (SAFIR01/UNICANCER) has recently provided evidence of the feasibility of personalised medicine for metastatic breast cancer. In this initiative, targetable genomic aberrations were identified in 46% of patients (most commonly PIK3CA, CCND1 and fibroblast growth factor receptor 1 [FGFR1]), providing the possibility of personalised therapy in 13% of individuals [31].

**Challenges in implementing molecular screening platforms**

Funding remains the principal barrier to the implementation of molecular screening platforms. The platforms described above are
academic initiatives and are funded primarily by charities. In order to expand, the programmes must attract industry funding, though such investment will require evidence that molecular screening will ultimately result in a more efficient drug development process and improved patient outcomes. Collaboration between academia and industry will be pivotal to the implementation of future platforms; however, this partnership presents challenges, such as obtaining agreement on data sharing and intellectual property rights (IPR). The optimal balance between centralisation and local empowerment must also be considered; motivation can be an issue if all services are centralised, particularly for pathologists who play a key role in the molecular screening programmes. Nevertheless, there is a need for processes to be standardised to ensure quality control. The reproducibility of multiplex technology must also be evaluated with care, since a large proportion of tumour heterogeneity can be due to variations in tissue handling [32]. A further challenge for molecular screening platforms is that clinicians may need encouragement to include their patients: few patients ultimately take part in a trial (<10 for every 100 patients proposed) yet paperwork must be completed for all potential participants.

Despite the challenges associated with their implementation, molecular screening platforms should be considered to be the way forward for future drug development, and the opportunity to share ideas and experiences (including protocol development) between programmes must be explored to maximise their potential. Clinical trials involving patients with rare mutations (e.g. HER2) are almost impossible to conduct at a national level since they require many thousands of patients to be screened. However, coordination between platforms could enable key centres to be involved in more than one programme, aiding enrolment in such trials and potentially resulting in cost savings by using a common protocol. Coordination between platforms may also help to promote the concept of molecular screening platforms to external bodies to gain funding.

**Optimising clinical trial design using translational oncology**

The use of smarter, faster and better-targeted phase III clinical trials can reduce cost and molecular screening platforms have the ability to improve the efficiency of trial access. However, in order to maximise the potential of translational oncology, appropriate trial designs must be used [33,34]. Regulators still require new drugs to be tested in patients with and without the alteration in a 2xC2 design, which inevitably requires a large sample size. However, a number of novel trial designs for assessing targeted treatments using biomarkers have been proposed, which may avoid the need for a 2xC2 design (Fig. 4) [33]. Whatever study design is used, investigators must ensure that trials are sufficiently powered at the beginning for the question being asked, as sample sizes vary considerably depending on the prevalence of the marker and the hazard ratio required. Moreover, if assessment of the marker is biased due to poor assay sensitivity or specificity, even greater sample sizes are needed [33].

Trialists setting up future studies will need to consider the most appropriate strata to use carefully in order for credible estimates of treatment effects to be made. Increasing knowledge of the inter-patient, inter-tumour and intra-tumour heterogeneity of cancer will continue to separate eligible populations, though clinical trials can only be undertaken on the basis of aggregation of sufficiently similar classes. A further challenge for the design of trials for targeted agents is that regulators require such studies to show an increase in OS, yet this is a demanding endpoint, and indirect means of demonstrating improvement in OS are now needed. Gaining regulatory approval for targeted agents for rare mutations

![Diagram](image_url)
is particularly challenging since many patients must be screened to gain sufficient numbers for a phase II trial, ethically no comparator arm can be included and the sample sizes needed for a phase III trial are prohibitive. Demonstration of a good response in two separate phase II trials followed by a randomised phase II study versus chemotherapy may be a strategy that can overcome this issue and may be acceptable to regulatory authorities. Consideration should also be given to the use of ‘basket’ trials involving patients with the same mutation in different tumour types. For tumours such as breast cancer and CRC where patients respond to chemotherapy, the use of patient-reported outcomes to demonstrate additional benefit from novel agents should be explored. In addition, it is possible that translational research may lead to the development of new endpoints (e.g. CTCs and molecular imaging) that can measure response early in the course of treatment, though prospective validation of such endpoints is needed before their adoption in clinical practice. The development of any new translational research techniques should also consider protocol standardisation at an early stage to avoid future problems in their integration into novel trial endpoints.

In recent years, the Food and Drug Administration in the USA has used breakthrough designation status to expedite approval of innovative new drugs that demonstrate significant PFS or response rate in a phase II trial. Such status is only granted if there are no good alternative treatments and may be particularly beneficial for the development of targeted agents for rare mutations. The regulator may require evidence that a larger phase III comparative trial is already under way at the time of accelerated approval. Nevertheless, alternative endpoints will need to be considered for approval in this setting, as OS improvement cannot be demonstrated using evidence from a randomised study if the drug is already on the market. A similar early approval process is under discussion at the European Medicines Agency (EMA); however, differences in healthcare funding between the USA and Europe may be an issue in this regard.

Models of collaboration in translational oncology

There is an urgent need for academia, pharmaceutical companies and regulatory authorities to work together in order to maximise the benefits of translational oncology for patients and accelerate progress in drug development. The experiences of existing molecular screening platforms should also be shared in order to identify best practice for future collaborative models. As a first step, oncology centres and networks must ensure that they have standard procedures in place for biospecimen collection and use in clinical trials, such as those recommended by BIG and the North American Breast Cancer Group (NABCG), in order to minimise variability and maximise results [34]. Ideally, central biobanking should be under academic control and independent of industry, but with a steering committee involving all parties in place to determine how samples are used along with an efficient tracking system. Consideration should be given to the collection of blood and tumour tissue from all patients in clinical trials for biomarker discovery, with strict quality control policies being applied to sample collection, including procedures to ensure appropriate storage and transportation [35].

One issue that remains an ongoing challenge to collaborative efforts is ownership of data; negotiation of IPR and contracts in collaborative trials can result in considerable project delays and new policies to manage licensing agreements are required [36]. As part of these discussions, consideration must be given to whether discoveries were part of the original protocol or later research projects, as well as to who has funded these projects. Pharmaceutical companies must also appreciate that there needs to be incentives for academia to be involved in trials. Standardising contracts may help to avoid future IPR issues and ensure that trials are completed in a time-efficient manner, though agreements must include a protocol for what to do with left-over materials and specify the duration of sample storage. Material Transfer Agreements should also be signed before any shipment of samples from the biobank. Whatever the agreement in place, however, researchers and clinicians owe it to society to extract the maximum knowledge from every clinical trial, with data being made available to the entire scientific community. Indeed, as the complexity of the data generated by translational research increases, the pressure for academia and industry to share data has intensified. While open access to data from clinical trials may improve the quality of subsequent publications, it also generates scientific, statistical, ethical and legal concerns, and could demotivate the investigators. Nevertheless, the EMA committed to implementing a policy on proactive publication.
of all clinical trial data in January 2014 [37] and open access has been mandatory in the USA since 2008. Consequently, all clinical trials must move towards transparency, with the ultimate aim of efficiently managing valuable resources and maximising the potential clinical benefit from the data gathered.

While collaborative models may be expected to lead to more efficient use of resources, additional developments may be needed to expedite the drug development process further, including improvements in access to clinical trials, advances in molecular screening, clustering of genomic alterations according to pathways, and collaborative trials between academia and industry that test multiple drugs simultaneously [38].

Summary

Huge strides forward have been made in the understanding of the molecular biology of cancer in recent years as a result of advances in genomic analysis techniques. Progress has also been made in the treatment of the disease, with many targeted therapies becoming available. It is now clear from the results of molecular research that cancer should not be considered as a single entity but as a series of diverse diseases with an increasing number of molecular subtypes within each tumour type. Identification of the patients who will benefit from individual therapies and recruitment of sufficient numbers of individuals with particular tumour subtypes into clinical trials is challenging, and will require collaborative efforts from research groups and industry in order to accelerate progress. A number of molecular screening platforms have already been initiated across Europe. It is hoped that the experiences gained from these networks can be used to identify best practice for future collaborative models. This will benefit not only patients but also society due to a reduction in costs as a result of more efficient use of resources.

Conflict of interest statement

Pierre Laurent-Puig has received honoraria from Amgen, Merck Serono, Sanofi and Boehringer Ingelheim. Josep Tabernero has acted as a consultant and has participated in advisory boards on behalf of Amgen, Imclone, Lilly, Merck Serono, Millennium, Novartis, Roche, Sanofi, Celgene, Chugai and Taiho. Hidetumei Tejpar has received speaker honoraria from Merck Serono, Amgen and Sanofi. Eric Van Cutsem has received research funding from Amgen, Bayer, Boehringer Ingelheim, Lilly, Merck Serono, Roche and Sanofi. All remaining authors have declared no conflicts of interest.

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