

The future of clinical research in oncology: where are we heading to?

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Abstract: Despite considerable investment in oncological research, the rate of improvement in cancer treatments remains frustratingly slow and the attrition rate in anticancer drug development has reached exasperatingly high levels. New skills are required to expand upon platforms to integrate clinical, biological and imaging data in the decision making process so that we can control the attrition rate of new drugs and/or determine tumor molecular sub-entities which will ultimately benefit new therapeutic strategies. Furthermore, modern clinical trials will be unable to generate reliable and robust evidence if they are not quality assured. Decreasing the number of poorly designed clinical trials through stronger collaboration between industry and academia is a win-win situation and will reduce the current high attrition rate and minimize exposure of patients to ineffective investigational therapies.

Key Words: Attrition rate; biomarker; imaging; oncological research; quality control



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Challenge of cancer drug development

Cancer is a leading cause of death worldwide and accounted for 7.6 million deaths (13% of all deaths) in 2008 (1). Despite heavy investment in cancer Research & Development, the improvement in cancer treatments remains frustratingly slow, and the attrition rate in anticancer drug development is high. In a recent analysis, 95% of potential anticancer drugs entering clinical development failed compared with an average of 90% for compounds in all therapeutic areas (2). The reasons for the high attrition rate are complex, frequently interrelated, and exacerbated by such factors as the choice of the compound's biochemical target, the use of inadequate preclinical models, an incomplete understanding of resistance mechanisms, and incorrect design and execution of clinical trials (3).

An example demonstrating the importance of clinical trial design is the development of vatalanib, a small molecule tyrosine kinase inhibitor against vascular endothelial growth factor (VEGF) receptor, for metastatic

colorectal cancer. Based on the results of phase I trials which showed a reduction of tumor blood supply measured with dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) (4,5), two phase III trials were launched to investigate the efficacy of vatalanib combined with FOLFOX in patients with colorectal cancer. Both of these trials, CONFIRM 1 and CONFIRM 2, were large multicenter phase III trials which accrued a combined total of 2,023 patients. However, the size of the benefit observed in both trials was too small to justify the use of vatalanib instead of standard regimens (6,7). Moreover, due to the non-negligible added toxicity, these phase III trials results did not support the clinical use of this drug.

Several reasons may account for the failure of the vatalanib development. First of all, the path to large phase III trials was only supported by phase I data. In the absence of sound early clinical and biological data obtained from intended typical phase III schedule, the rationale is not secured.

Secondly, the combined chemotherapy with FOLFOX

might not have been appropriate. There was a randomized, double blind, phase III study compared FOLFOX with or without cediranib (8,9), a multikinase VEGF receptor inhibitor, and this study was similar to the results of CONFIRM 1 and 2.

Finally, the once-daily schedule of vatalanib seems to be inappropriate in terms of the half-life of vatalanib (4-6 hours) (10).

Decreasing the number of poorly designed clinical trials could help to reduce the current high attrition rate and minimize futile exposure of patients to ineffective investigational therapies (11). A recent analysis by the Centre for Medicines Research in the UK has concluded that since 2008, the failure rate for drugs in phase II and III clinical trials has been rising (12,13). At the phase III stage, 66% failed due to lack of efficacy, and 21% failed because of safety concerns (13). In order to overcome this situation, drug development should be based on methodologically robust clinical trials testing drugs selected on the grounds of convincing pre-clinical evidence. Treatment efficacy can only be improved if the biological mechanisms underlying the disease are understood.

Paradigm changes in cancer clinical research

Traditionally, patients with the same disease diagnosis are considered to suffer from the same pathology, and they also receive the same treatments, although clinical experience shows that is only the case in limited circumstances. In practice, patient diagnosed with the same disease may have various causes and respond very differently to the same treatment. Treatment, therefore, should be optimized on a case by case basis.

The concept of personalized medicine is increasingly influencing health care. According to the President's Council of Advisors on Science and Technology, personalized medicine "refers to the tailoring of medical treatment to the individual characteristics of each patient; to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment so that preventive or therapeutic intervention can then be concentrated on those who will benefit, sparing expense and side effects for those who will not". In the future, disease will no longer be classified based on symptoms or according to the organ system, rather, they will be based on the underlying mechanisms at the molecular biological level. The molecular method could facilitate personalized medicine through the use

of various biomarker tests on gene expression, proteins, and metabolism. A companion diagnostic test, especially a biomarker test, allows knowledge based decisions in therapeutic drug development and could help improve the safety and efficacy of the drug. Ideally, basic biomarker research should start at least two or four years prior to first-in-man clinical trials, and once having embarked on the clinical trials route, it is advisable to continue the biomarker research in parallel with the clinical development program (14).

While the understanding of molecular biology evolves, it has become increasingly critical to model clinical research methodology and drug development approaches to take into account the role of the molecular discriminates, whether they are host or tumor related, to predict activity and/or toxicity. This is best achieved through the incorporation of translation medicine in the design of clinical trials with the ultimate goal of treating the patient and tumor at the right time with the right agent. Taken together, these parameters advance us towards the era of personalized medicine.

This paradigm change also includes societal challenges in addition to the medical. For example, a new paradigm, P4, has emerged: Predictive, Preventive, Personalized and Participatory" (15). The P4 medicine uses scientific, well-organized and wellness strategies, so that patients can access personalized medicine and realize improved cost-effectiveness in the health care system. These changes will have profound effects on the design and conduct of modern clinical research.

Drugs should be approved for their effectiveness and the real benefits they bring to the society. Strong translational research should be part of all clinical investigations. Only with well-conceived and justified clinical trials and taking advantage of non-invasive monitoring techniques such as molecular imaging, can we decrease drug attrition rates, the drug development expenditures, and ultimately the cost of health care.

Implementation of translational research and imaging sciences in clinical trials

Complex clinical trials with a strong targeted translational research component enable fundamental advances in the understanding of particular cancer types and directly contribute to defining new tailored standards of patient care. Using proper designs, these clinical trials will investigate new drugs or combinations of drugs in multiple cancer entities and involve the exploration and qualification of biomarker(s), lead to an improved understanding of

the biology of the disease, and incorporate molecular characterization of tumors which could be predictive of activity or toxicity.

When a biological question is integrated into the study design, it is regarded as integral translational research. For example, if a biomarker is a part of eligibility criteria or stratification criteria, then granting access to the biological material/images would become mandatory for patients participating in the trial.

The development of Gefitinib is a prime example. Epidermal growth factor receptor (EGFR) is a cell surface receptor, and the inactivation/inhibition of EGFR induces apoptosis (cell death) and reduces angiogenesis and metastasis of cancer cells. AstraZeneca developed gefitinib by screening 1,500 EGFR inhibitors. Since almost all cells have EGFRs, gefitinib not only inhibits the growth of cancer cells but also inhibits normal cells, particularly those in recovering tissues which have more epidermal growth factor. The low levels of EGFR have been shown to induce lung toxicity, severe bleeding and delayed wound healing in both animal and human studies (16,17). Results from a large trial failed to show a significant overall survival but did show relatively high toxicity. This led to restrictions in the use of gefitinib by the US Food and Drug Administration (FDA) and caused AstraZeneca to withdraw the marketing authorization application which was under review in Europe (18). Later on, EGFR mutation was used as a stratification criteria, and it was demonstrated that EGFR mutated patients responded much better to gefitinib. The discovery of EGFR mutation status as a predictive marker for response led to an approval by the European Medicines Agency (EMA) in June 2009 for the use of gefitinib in patients with activating mutations of EGFR-tyrosine kinase (19). This predictive biomarker helps in selecting patients and to avoid exposing patients to toxicity when they are not expected to benefit. Additionally, such use of a biomarker can decrease overall health care costs and enhance quality of life for patients. If the mechanism of gefitinib were well-known and the stratification for EGFR mutation were integrated at the beginning of the trial, the whole process could have saved the company both time and money.

As opposed to integral translation research, correlative translational research in clinical trials is usually a component of exploratory or companion studies. They may be considered optional for the project, and the implementation of a correlative biomarker in a clinical trial can prove the hypothesis of its predictive or prognostic values. *c-Kit* is a type III receptor tyrosine kinase, and

oncogenic mutations involving Kit exon 11 have been found in a subset of gastrointestinal stromal tumors (GISTs). Based on these basic research results, Kit exon 11 mutations were tested for their prognostic values in clinical trials, and studies showed that GISTs with Kit exon 11 mutations were typically higher grade or associated with poorer outcome (20,21). Later, imatinib was approved for the treatment for patients with Kit-positive GIST. Imatinib binds to the Kit receptor and prevents growth signals from being sent thereby causing tumor cell death. Correlative translation research continued to test the predictive value of KIT mutations in GISTs, and studies demonstrated that KIT mutational status seems to be a more important predictive factor for imatinib-sensitivity/resistance than biological/clinical parameters (22). The use of imaging biomarkers to assess drug therapies has become more common during the past several years. Non-invasive imaging enables associations to be made between therapy and effect and provides continuous, structural and functional assessments. In 1992, the FDA added provisions for accelerated approval for drugs intended for serious or life-threatening disease with enactment of the FDA Modernization Act of 1997: "a drug has an effect on a clinical endpoint or on a surrogate endpoint that is reasonably like to predict clinical benefit." Of the 71 cancer drugs approved from 1990-2002, 53 had clinical trials with surrogate endpoints, and the most common one was the change in tumor size typically measured by MRI or CT (23). Assessment of tumor burden and time to the development of disease progress is of importance in clinical evaluation of cancer therapy. However, with increasing use of cytostatic over cytotoxic targeted agents, response evaluation with conventional technical assessment is difficult, and it usually takes more than two or three months to detect the response.

So, the question remains whether it is time to move from anatomic assessment of tumor burden towards functional assessment. When using morphological assessment by CT or MRI to determine tumor size for the purpose of evaluating the effectiveness of Imatinib on GIST, earlier changes in tumor size are seldom significant. However, it was shown that when using FDG-PET as an indicator of tumor metabolism, response could be detected as early as eight days following the start of treatment and was also associated with a longer progression-free survival (PFS) (24).

Early assessment can also be done by advanced MR techniques, including

(I) ADC as an imaging biomarker of diffusion MRI: may

reflect cell death/apoptosis (25);

(II) dynamic contrast enhanced MRI or CT may detect early changes of micro-vascularization in tumors (26);

(II) MR spectroscopy may show biochemical changes in the tumor tissue (27).

The new challenge in cancer drug development is not only to prove the safety and efficacy of the drug, but also to determine how to achieve this in a rapid and cost-effective manner, and functional imaging may play an important role in early assessment.

Clinical trials are the most expensive part of Research & Development consuming approximately 50% of total investment. Currently, major gaps are insufficient implementation of translational and imaging research in early phase clinical trials which would lead to optimally designed phase III trials and address the so critical drug attrition rate. Biomarkers may enhance the efficacy of new drug development trials, and smaller or shorter clinical trials may reduce drug development cost by investing more in earlier research aimed at identifying key biomarkers and the relevant target sub-groups of patient population (28).

Unmet need of validated biomarkers in clinical trials

The implementation of translational research and imaging, whether integrated in the design or correlative to the conduct of trials, requires access to human biological materials and/or complex imaging modalities which bring new challenges to multi-center clinical trials with regards to quality assurance and standardization. A research project will not be able to generate reliable and robust evidence if not quality assured; ensuring the quality of the research is crucial. Current practices for biomarker assessment vary widely from one institution to another, between countries, as well as from one assay to another, and this can depend on the role of the biomarker within the clinical trial (29-31). This presents significant hurdles in decision making and implementation of biomarker assays in multicenter European clinical trials for logistical, financial and quality assurance (QA) reasons. As opposed to the United States, there is no clear European consensus on the criteria or level of QA, the assay validation (including analytical and performance requirements, reproducibility, robustness, laboratory accreditation, etc.) required for different types of biomarker assay, nor the selection of appropriate laboratories to perform the task in multicenter clinical trials. To overcome this, a multidisciplinary effort should be supported to

establish common principles and guidelines for appropriate levels of QA for biomarker assays that are being used in clinical trials, harmonize standard operating procedures for biomarker assays, cross-validate multicenter trials, and develop appropriate quality assured infrastructures (laboratories).

New skills are required to build new platforms integrating clinical, biological and imaging data in the decision making process so as to control attrition rate of new drugs and/or decide on tumor molecular sub-entities which will ultimately benefit from new therapeutic strategies. Efforts should foster the development of large tissue and data collections for use in pharmacogenomics research projects. Such projects could identify and/or validate biomarkers expressed in tumor samples that may determine disease outcomes or tumor resistance and sensitivity to specific drugs and toxicities. These projects should ultimately lead to the identification of companion tests and the optimization of therapy with an eye towards the realization of “personalized medicine”. During treatment, tissues should be analyzed using whole genome sequencing and gene expression approaches in order to identify tumor somatic mutations and gene expression changes. The inter-relationship between germline allele and somatic mutation could also be studied. The relation between the identified genes and the clinical outcomes should be investigated using robust and discriminative bio-informatics methods. Analyses should go beyond gene association studies. Subsequently, the prognostic and predictive value of the new biomarkers should be confirmed in adequately designed prospective clinical trials.

Imaging biomarkers are facing the same challenge, very few imaging biomarkers are widely considered adequate to provide unambiguous assessment of response or sufficient enough for making decisions to stop or continue the drug development process. The quality and validity of an imaging marker depends on the standardized procedure and an understanding of the molecular imaging mechanism. However, imaging is performed in the presence of patients, while biospecimen biomarkers are commonly quantitated by an *in vitro* diagnostic device. Therefore, validating imaging biomarkers in a multicenter setting must also consider the technical performance characteristics of the instrumentation and the procedures for measuring the imaging biomarker. To qualify an imaging biomarker involves a number of activities including starting with proper study design, following robust and standardized procedures, correlating with pathology/outcome, testing reproducibility and

optimal timing of observation, and having sufficient statistical power (32).

The availability of good quality biological materials and related clinical data are paramount for the advance of biomedical science. However, there is an unmet need of validated biomarkers for clinical trials. Lack of long term vision and funding from industry for implementing and supporting translational research and developing and validating biomarkers is of high concern. New models of collaboration should be developed which allow academic and industry partnerships, so that the industrial partner would be encouraged to collaborate with academic researchers and support a new infrastructure. The Innovative Medicines Initiative (IMI) is Europe's largest public-private initiative, a Joint Undertaking between the European Union and European Federation of Pharmaceutical Industries and Associations (EFPIA). The QuIC-ConCePT (Quantitative Imaging in Oncology: Connecting Cellular Processes to Therapy) consortium has been created under IMI to qualify three imaging biomarker, and its vision is that drug developers can incorporate these imaging biomarkers to detect non-response therapies in early phase I trials, confident that the biomarkers are technically validated, faithfully reflect the imaging biomarker changes in the underlying tumor pathology, and that the imaging biomarkers can be readily used in multiple cancer centers in a robust, consistent and cost-effective way (32). QuIC-ConCePT is a model for future biomarker qualification.

Recommendations for future clinical research in oncology

We are transitioning from an empirical approach (large trials comparing treatments) to a tailored approach (trials asking biologically relevant questions). To be successful in this transition, we need a profound restructuring of clinical research methodology and infrastructure so that we can better understand the biology of the disease and the mechanism of action of new agents, develop new methodological approaches, and document molecular determinants whether host or tumor related predictive of toxicity or activity. Modern clinical trials will investigate new drugs or combinations of drugs in multiple cancer entities and involve the implementation of translation research and imaging with the support of new bio-informatics platforms.

These paradigm changes in cancer clinical research bring opportunities but also challenges: quality assurance and

standardization of new bio-technologies will play a key role in ensuring high quality research. Therefore, prior assay validation is needed for integrating biological tests. The availability/quality of material is also crucial for biomarker test, and screening platforms are required with large tissue and data collections. Performing high quality clinical and translational research requests a large investment in terms of resources and know-how, and this requires time and funding before projects are secured. The concept of personalized medicine could potentially reduce the use of drugs in non-responders, but, it may increase diagnostic budgets by requiring the testing of a whole patient population in order to identify groups of responders, and only smaller groups of eligible patients might benefit; it therefore leads to higher unit prices.

Considering the cost-benefit for sub-populations, is a tailored approach sustainable? Studies of cost-effectiveness of personalized medicine are still on the way, but promising results have been demonstrated (33). The evaluation of cost-effectiveness is not easy to describe, but at least it has a huge potential to reduce the cost resulting from side effects, to improve compliance and persistence, and improve patient quality of life.

Good communication between drugs developers, academia, regulatory agencies and payers is important. Identifying biomarkers is a collaborative effect. It is time consuming, costly and difficult to identify and validate biomarkers, because it requires adequate evidence of clinical utility, testing in a multicenter setting and across different cohorts. Public-Private partnership should be encouraged so that the pharmaceutical industry and academia can join forces and generate high-value clinical data in a pre-competitive setting. Academic organizations can contribute with scientific advice and incorporate additional translational research projects, and industries could support the infrastructures of screening platforms and/or patient derived translation research platforms. Such platforms set up by academic networks can secure efficient public-commercial cooperation and avoid duplication of costly screening initiatives by multiple companies. Adaptation of industry-academia interactions is necessary to enable a quick, cost-effective and safe development of new personalized drugs. Decreasing the number of poorly-designed clinical trials through stronger collaboration between industry and academia will result in a win-win situation for industry and academia, reduce the current high drug attrition rate and minimize exposure of patients to ineffective investigational therapies.

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